X-ray phase-contrast tomosynthesis for improved breast tissue discrimination

Abstract

Purpose

Attenuation-based tomosynthesis has proven to successfully resolve the glandular tissue overlap present in mammography. However, the ability of tomosynthesis to differentiate tumorous and glandular tissue remains limited, due to the small differences in X-ray attenuation in breast tissue. One possibility to overcome this limitation and to further increase the diagnostic value of tomosynthesis exams, is the application of recently developed grating-based phase-contrast methods, which provide complementary information on the phase shift and the local scattering power of the sample. In this study, we report on first phase-contrast breast tomosynthesis results of a mastectomy sample slice with an invasive ductal carcinoma.

Material and Methods

A slice of a mastectomy sample with histologically proven invasive ductal cancer was imaged at the synchrotron radiation source ESRF (Grenoble, France). We used a two-grating interferometer setup at the ninth fractional Talbot distance and with an X-ray energy of 23 keV. In grating interferometry absorption, differential phase, and scattering images are recorded simultaneously. The tomosynthesis scan comprises 61 projections. Multimodal tomosynthesis results were reconstructed using a standard filtered back-projection approach. Our findings are supported by a comparison of tomographic views to histopathology.

Results

Phase-contrast tomosynthesis combines the advantage of improved soft-tissue discrimination

in phase-contrast imaging with the ability of tomosynthesis to provide a third dimension so that improved feature visibility is not hampered by superposition artifacts. Our results indicate superior diagnostic value due to the depth resolution supplied in tomosynthesis imaging; a region of necrotic tissue that is obscured in a projection image can clearly be depicted in one single tomosynthesis slice. Compared to absorption tomosynthesis alone, soft tissue contrast is significantly enhanced in phase-contrast tomosynthesis views, where fibrous structures are clearly visible.

Conclusion

In this article we present the first proof-of-principle grating-based phase-contrast tomosynthesis of a mastectomy sample section. A comparison of conventional attenuation with phase-contrast and dark-field tomosynthesis indicates that complementary information from three signals yields an increase in diagnostic value, which is verified in a comparison of our results to histological sections of the sample. As grating-based phase-contrast mammography efficiently works with conventional lab sources, our benchmark results indicate the potential benefit of translating phase-contrast tomosynthesis into a clinical setting.

Keywords: X-ray phase contrast, mammography, breast imaging, grating interferometer, tomosynthesis

I. Introduction:

Breast cancer is the most frequently diagnosed cancer and the second leading cause of death among women both in developed and developing countries. Mammography is currently the standard imaging approach for breast cancer screening and has proven to decrease mortality

rates due to early cancer detection [1]. The technique is unmet in its ability to depict micro calcifications, which are an indication in about 30 % of breast tumors. Due to the limited contrast between glandular and tumorous tissue, mass detection in mammography relies mainly on the discrimination of structural disorders, which can be significantly hindered by fibro-glandular tissue overlap in a 2D projection technique. This so-called ’anatomical noise’ is a severe problem especially in dense breasts where summation effects can both lead to obscuration of tumors in mammograms and false positive diagnosis [2], accounting for the often-cited low specificity and high number of missed cancers in dense breast mammography. Currently different approaches are used to supply depth resolution in follow up diagnostic breast imaging, namely ultrasound and contrast enhanced MRI. Compared to X-ray imaging, MRI has the clear advantage of avoiding ionizing radiation with the drawback of lower spatial resolution, which hinders the detection of micro calcifications, the use of contrast agents, considerable time and effort required, and a low specificity. Ultrasound is highly time-consuming, depends on the operator’s experience and thus results are only partly reproducible [3].

In the field of X-ray imaging both breast CT and tomosynthesis are investigated as possible diagnostic and breast cancer screening modalities, where in the latter case the techniques have to compete with mammography in terms of sensitivity, specificity, interpretability, dose compatibility and cost efficiency. Compared to CT, tomosynthesis uses only a sparse number of projection angles to produce a quasi 3-D aspect of the object. It is currently applied in addition to conventional mammography to reduce the masking of tumors by superposition artifacts [4]. In breast CT measurements the trade off between resolution and dose hinders a clear depiction of micro calcifications [5], while overlying soft-tissue structures are successfully resolved leading to a superior performance in detecting masses compared to mammography [2, 6]. Contrast-enhanced breast CT showed an improved conspicuity of malignant lesions [7]. Tomosynthesis slices of the breast are reconstructed from a set of 10 to

25 projection images taken over an angular range of often less than 40°, where exact acquisition parameters are part of ongoing research [8]. Due to the incomplete angular sampling the technique does not supply the isotropic 3D spatial resolution as CT, nevertheless it yields a high spatial resolution in in-plane views comparable to mammography and superior to CT. The advantages of tomosynthesis compared to standard mammography comprise a better visibility and delineation of masses [9, 10], important for the discrimination of benign and malignant tumors, as well as of superposition artifacts and real existing mass lesions. Furthermore, the technique offers more accurate 3D localization of masses potentially helpful in biopsy guidance and operation planning. A recent study has demonstrated that the combined use of mammography and tomosynthesis leads to a decrease in false positive diagnosis and a significant increase in cancer detection rate especially in dense breasts [11]. The detection of micro calcifications in tomosynthesis is different from mammography due to the possibility that slices of micro calcification clusters are visualized instead of projections of the entire cluster which are well established in mammography readings [8]. To circumvent this issue and possibly omit the mammography exam, the use of synthetic projection images, which are calculated from the tomosynthesis dataset, is currently discussed and studies are under way to investigate sensitivity and specificity when using tomosynthesis alone - as compared to tomosynthesis in addition to conventional mammography - in breast cancer screening. However, one has to keep in mind that unlike the well established clinical procedure of mammography, in tomosynthesis, studies on acquisition parameters, special training on image interpretation, and image post processing are still developing.

One possibility to further increase the diagnostic value of tomosynthesis exams and to overcome the problem of limited soft-tissue contrast inherent to attenuation-based breast imaging is the application of X-ray phase-contrast techniques. In phase-contrast imaging the phase shift of the X-ray wavefront in the sample under investigation is measured in addition to the attenuation. This comprises an effect orders of magnitude higher in soft tissues

compared to X-ray attenuation [12]. Several methods have been developed to measure this phase shift and promising results in breast imaging have been achieved with free space propagation techniques [13] including a first clinical trial of synchrotron phase-contrast mammography [14]. Also analyzer-based imaging [15], where dose compatible results of breast phase-contrast CT have recently been reported [16], and interferometer-based methods [17, 18] are available. Grating interferometry is often described as one of the most promising phase-contrast technique for a clinical implementation as it has been proven to work with conventional laboratory X-ray sources [19]. This is due to its toleration of divergent, polychromatic X-ray beams and large X-ray source sizes; properties inevitable for sources which yield high enough flux to result in clinically tolerable exposure times. Grating-based phase-contrast CT measurements of breast tumor tissue revealed improved soft tissue contrast and a better differentiation of tumor types as compared to conventional attenuation-based CT [20], leading to the assumption that this improvement in tissue discrimination can be translated to tomosynthesis measurements. Furthermore, the grating-interferometer supplies the so-called dark-field signal, which is related to ultrasmall-angle scattering in the sample and has shown to improve tumor detection in breast tissue [21]. Only few reports on phase-contrast tomosynthesis experiments can be found in the literature, including experiments based on free-space propagation [22], analyzer-based methods [23, 24] and grating interferometry [25]. In these studies mostly phantoms have been measured demonstrating the possibility to separate superimposed objects and the complementarity of phase and attenuation images [26].

In this paper we show the first grating-based phase-contrast tomosynthesis results of a human breast specimen, demonstrating the ability of phase-contrast tomosynthesis to resolve overlapping tissue in the breast. A comparison with registered histological sections of the specimen shows a gain in diagnostic information due to improved tissue discrimination in the phase-contrast and dark-field tomosynthesis reconstruction.

II. Material and Methods:

Grating Interferometer setup at ID19

The grating-interferometer setup at ESRF beamline ID19 comprises two X-ray optical gratings and a detector [27]. A silicon π phase shift grating with 4.8 μm pitch (design energy 23 keV, fabricated at the Laboratory for Micro- and Nanotechnology, Paul Scherrer Institut, Villingen, Switzerland) and a gold absorption grating with 2.4 μm pitch (gold thickness 74 μm, fabricated at the Institute for Microstructure Technology and Karlsruhe Nano Micro Facility, Karlsruhe Institute of Technology, Germany) were used at the ninth fractional Talbot distance, corresponding to an inter-grating distance of 481 mm. A double-crystal monochromator selects X-rays of the desired energy and approximately 10^{-4} bandwidth from the wiggler spectrum. The grating interferometer is placed at 150 m distance from the wiggler source. The tomosynthesis dataset consists of 61 equally spaced projections where the breast sample was rotated from −30° to +30°. 12 projections each comprising a field of view of 373 x 1376 pixel^2 (corresponding to 12 mm x 41 mm) were recorded to cover the entire breast sample, where each projection consists of a phase-stepping scan of the phase grating with respect to the absorption grating, over one grating period using four steps. The exposure time for each phase step was 0.1 seconds when the sample was inserted and 0.05 seconds for the flat-field projections to avoid detector saturation. All images were recorded using a FReLoN CCD camera E2V-SN42 with a 125 μm thick LuAG:Ce scintillator (Crytur, Czech Republic) and nominal 30 μm pixel size. Dark frames were collected prior to the tomosynthesis scans.

Data processing and reconstruction

All raw phase-stepping detector frames were dark current corrected. Subsequently we used Fourier analysis to extract the relative transmission, differential-phase contrast (DPC) and dark-field image [28]. Twelve projections were stitched together to cover the entire sample by using a linear ramp function in the overlapping regions. Phase-contrast projections were further corrected by subtracting a linear phase ramp. Sinograms comprising 61 projection

angles were reconstructed using a filtered-backprojection algorithm (FBP). A Ram-Lak filter was used to reconstruct attenuation and dark-field data and a Hilbert filter in the case of phase-contrast tomosynthesis [30]. To find a cutting plane in the 3D tomosynthesis volume that matches the histological sections shown in Fig. 4 (A-D) manual alignment was performed using the 3D visualization software VGStudio MAX.

Sample preparation and histology

The study was conducted in accordance with the Declaration of Helsinki, was approved by the local ethics committee and written informed patient consent was obtained. We analyzed a mastectomy specimen containing an invasive ductal cancer from a 66-year-old woman. One representative sagittally orientated, 9 mm thick slice was chosen for tomosynthesis examination and fixed in 4 % neutral-buffered formaldehyde solution. After image acquisition had been completed the breast slice was manually cut into 4 pieces of comparable size, suitable for further post-processing. Since the tissue sections exceeded the size used for standard staining procedures, they were manually enwrapped in a blotting-paper for further processing and staining. All slices were 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 hematoxylin and eosin using standard protocols.

III. Results:

A slice of a human mastectomy sample, fixated in formalin (Fig. 1a), was measured with a two-grating interferometer setup at an X-ray energy of 23 keV at beamline ID19 of the European Synchrotron Radiation Facility (ESRF, Grenoble, France) [27]. During a phase-stepping scan of the phase grating with respect to the position of the absorption grating an intensity variation is recorded in each pixel. Fourier analysis is used to extract the attenuation image, the differential phase image and dark-field image [28]. Due to the limited field of view

of the beam comprising 12 mm x 41 mm, 12 projections of the breast were stitched together to cover the entire sample. Fig. 1 shows one projection of the breast sample in all three modalities indicating a complementarity in information. Regions that appear homogeneous in the transmission image show various substructures in both the differential phase-contrast and the dark-field projections. To record a tomosynthesis dataset 61 projections covering an angular range of ±30° were recorded by rotating the sample. Reconstruction was performed using a filtered-backprojection algorithm with a Ram-Lak filter in the case of attenuation and dark-field data and a Hilbert filter in case of the differential phase signal. A central in-plane slice of the reconstructed 3D volume is presented in Fig. 2. The complementarity seen in the projection images is also evident here. A comparison of the zoomed regions (dotted red rectangles Fig. 2) shows that many tissue features are only visible in the phase and dark-field images. Furthermore, the contrast in the phase reconstruction appears to be less compromised by noise as compared to the attenuation image. This is in accordance with literature where small pixel sizes are discussed as being advantageous in grating based phase-contrast CT [29]. Moreover, the small nominal pixel size of 30 μm used in this experiment is in the range of pixel sizes used in standard clinical tomosynthesis. A movie through in plane reconstructed slices of the phase-contrast tomosynthesis volume is provided (see video, Supplementary Digital Content 1, which shows how different features in the sample are in, and go out of focus when moving through tomosynthesis slices). Attenuation, phase-contrast and dark-field tomosynthesis slices of the entire sample at different depths can be found as Supplementary Digital Content (see FIG. SDC 2-4, Supplementary Digital Content, which demonstrates the complementarity found in the three reconstructed signals). In Fig. 3, a zoom of the in-plane reconstructed slices is shown with an in depth separation of 2 mm. In a comparison of a differential phase projection (Fig. 3 A) with reconstructed tomosynthesis slices at different depths in the sample the information gain becomes obvious. While going through the slices different features of the sample come in and out of focus. The marked parenchymal necrosis

(green arrow) is visible most prominently in Fig. 3 E, while in the other reconstructed slices, structures below and above the parenchymal necrosis are in focus. Furthermore, the fiber structures seen in the differential phase projection 3 A (red arrow) can clearly be localized within a limited depth in the sample. Attenuation, phase and dark-field tomosynthesis datasets were manually reoriented using the 3D visualization software VGStudio MAX to best match the histological sections shown in Fig. 4. The following prominent histological features (see Fig. 4 C,D) can be clearly differentiated in phase contrast and dark-field but not as well in attenuation contrast: dermal fibrosis (1), parenchymal necrosis (2), a region containing tumorous tissue (3) and necrotic tissue with an adjacent tumor spread (4) exhibit more contrast in the phase-contrast tomosynthesis slice compared to the attenuation-based slice. Especially feature (2), a parenchymal necrosis, is not visible in the attenuation tomosynthesis dataset due to the limited difference in soft-tissue attenuation.

IV. Discussion and Conclusion:

In this article we describe the results of a grating-based phase-contrast tomosynthesis measurements of a human mastectomy sample section recorded at a synchrotron facility. Our results indicate superior diagnostic value due to the depth resolution supplied in tomosynthesis imaging: a region of necrotic tissue that is obscured in the projection image can clearly be depicted in one single tomosynthesis slice and fibrous structures visible in the differential-phase contrast projection can be attributed to a certain depth location in the sample.

Discerning tissue superposition artifacts from pathological structures is one of the challenges in diagnostic mammography. Phase-contrast tomosynthesis combines the advantage of improved soft-tissue discrimination in phase-contrast imaging with the ability of tomosynthesis to provide a third dimension so that the effect of improved visibility is not hampered by superposition artifacts. A comparison of conventional attenuation with phase-

contrast and dark-field tomosynthesis demonstrates the complementarity of all three signals and an increase in diagnostic value is illustrated by using corresponding histological sections as a reference.

For supplying depth resolution in phase-contrast breast imaging we focused on tomosynthesis rather than breast CT as attenuation-based tomosynthesis is already successfully applied in both research studies and diagnostic clinical breast imaging. The reconstructed tomosynthesis views of the breast and the in-plane resolution are comparable to mammography views.

In this first proof-of-principle study we chose the well-established filtered-backprojection algorithm (FBP) to reconstruct the tomosynthesis dataset. A Ram-Lak filter was used to reconstruct the attenuation and dark-field signal and a Hilbert filter was applied in the case of phase-contrast data [30]. There certainly is room for improvement of our reconstruction results either by using dedicated tomosynthesis filter designs or iterative reconstruction techniques as the benefit of both methods is well established in conventional attenuation-based tomosynthesis [8]. With respect to the noisy appearance of the attenuation tomosynthesis results we would like to point out that there exist dedicated post-processing algorithms to improve attenuation-based mammography images. We did not apply any post-processing in this study and we expect that attenuation as well as phase-contrast and dark-field tomosynthesis images would improve significantly.

In this study we focused on diagnostic improvements arising from the use of phase-contrast rather than dark-field tomosynthesis. As dark-field projections have proven superior to the attenuation signal in the detection of micro calcifications [17,21], a thorough investigation of the former in the context of tomosynthesis will be the objective of further investigations.

The setup and procedure of this benchmark synchrotron based experiment was not optimized with respect to dose applied to the sample. The total dose was not prospectively evaluated, however, the estimated dose is significantly higher than the dose applied in clinical mammography. Nevertheless the phase interaction of X-rays with matter exceeds the

attenuation-based contrast by several orders of magnitude, which theoretically enables phase-contrast measurements at lower dose compared to conventional mammography. First dose compatible results in phase-contrast breast imaging support this assumption [16]. Further investigations will thus focus on a translation of phase-contrast tomosynthesis to conventional X-ray tubes and the optimization of experimental setup, data processing and reconstruction routines to achieve dose compatible results.

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Figure captions:

Fig. 1. Photograph of the 9 mm thick breast mastectomy slice (A). Projection images of the breast sample resulting from 12 frames that were stitched together to cover the entire sample. In the transmission image, glandular tissue (bright structures) containing a widespread carcinoma and fatty tissue (darker structures) are discriminated nicely (B). In the differential phase-contrast projection (C) and in the dark-field image (D) fibrous structures appear more clearly. Moreover, regions that appear homogeneous in the attenuation image show substructures in the differential phase and the dark-field images (the scale bar corresponds to 5 mm).

Fig. 2. Central slice of the reconstructed tomosynthesis dataset of the breast showing: conventional attenuation signal (A) phase-contrast signal (B), and dark-field signal (C). Dotted rectangles in the images indicate two regions that are shown in magnified views in all three modalities. The images are scaled to provide maximum detail visibility (the scale bar corresponds to 5 mm).

Fig. 3. DPC projection of a 28.5 mm by 20.7 mm zoom of the breast (A). Images (B)-(F) display different phase-contrast tomosynthesis slices of the corresponding section of the sample with 2 mm separation each. Structures that are superimposed in the DPC projection (A) can clearly be attributed to a certain tomosynthesis slice. Fibrous structures visible in the lower right part of the DPC projection (red arrow) are only depicted in tomosynthesis slice (D) and (E). A parenchymal necrosis (green arrow, histological comparison in Fig. 4) is only depicted in slice (E) and not visible in the DPC projection image (A) (the scale bar corresponds to 5 mm).

Fig. 4. Histological section zoom on a nodular necrosis with adjacent tumor extension (A). Zoom on dermal fibrosis (B). Histological section showing a parenchymal necrosis (2) a region containing tumorous tissue (3) and necrotic tissue with an adjacent tumor extension (4) (C). Histological section showing dermal fibrosis (1) (D). Cut through the 3D reconstructed volume that has been manually aligned to best match the histological slice showing attenuation (E), phase-contrast (F) and dark-field result (G). All features (1-4) are more clearly depicted in the phase-contrast and the dark-field tomosynthesis.

Video SDC 1. The movie shows 400 adjacent in-plane views of the reconstructed phase-contrast tomosynthesis volume.

Fig. SDC 2. Reconstructed tomosynthesis slices with a difference of $\Delta z = 2.5$ mm displaying attenuation signal on a linear grayscale (the scale bar corresponds to 5 mm).

Fig. SDC 3. Reconstructed tomosynthesis slices with a difference of $\Delta z = 2.5$ mm displaying phase signal on a linear grayscale (the scale bar corresponds to 5 mm).

Fig. SDC 4. Reconstructed tomosynthesis slices with a difference of $\Delta z = 2.5$ mm displaying dark-field signal on a linear grayscale (the scale bar corresponds to 5 mm).

List of Supplemental digital content:

Supplemental Digital Content 1.

Video that shows a sequence of reconstructed phase contrast tomosynthesis slices.

Supplemental Digital Content 2.

Figure that shows three attenuation tomosynthesis slices of the entire sample

Supplemental Digital Content 3.

Figure that shows three phase-contrast tomosynthesis slices of the entire sample

Supplemental Digital Content 4.

Figure that shows three dark-field tomosynthesis slices of the entire sample