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Intra-Operative Assessment of Cancer with X-Ray Phase Contrast Computed Tomography

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ABSTRACT

X-ray Phase-Contrast Computed Tomography (PC-CT) increases contrast in weakly attenuating samples, such as soft tissues. In Edge-Illumination (EI) PC-CT, phase effects are accessed from amplitude modulation of the x-ray beam using alternating transmitting and attenuating masks placed prior to the sample and detector. A large field of view PC-CT scanner using this technique was applied to two areas of cancer assessment, namely excised breast and esophageal tissue. For the breast tissue, Wide Local Excisions (WLEs) were studied intra-operatively using PC-CT for the evaluation of tumor removal in breast conservation surgery. Images were acquired in 10 minutes without compromising on image quality, showing this can be used in a clinical setting. Longer, higher resolution PC-CT images were also taken, with analysis showing previously undetected thinning of tumor strands. This would allow a second use of the system for "virtual histopathology", outside of surgery. For the esophagus samples, tissues were taken from esophagectomy surgery, where the lower part of the esophagus is removed, and the stomach relocated. For the assessment of ongoing therapy, accurate staging of tumors in the removed esophagus is essential, with the current gold standard provided by histopathology. PC-CT images were acquired on several samples and compare well with histopathology, with both modalities showing similar features. Examples are shown where staging of tumor penetration is possible with PC-CT images alone, which is hoped will be an important step in performing the imaging and staging intra-operatively.

Keywords: Phase Contrast, Computed Tomography, Breast Conserving Surgery, Wide Local Excisions, Esophagus Tumor Staging

1. INTRODUCTION

Breast cancer is the most common cancer worldwide accounting for 12.5% of all cases [1]. For early-stage breast cancer, Breast Conserving Surgery (BCS) followed by adjuvant therapy is the preferred treatment. Ensuring clear margins is a primary objective in BCS and currently relies on histopathology [2,3], a time-consuming process that means results are

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not available for several days. Cancerous tissue found in the margin of the excised tissue can lead to recurrence and possibly to a further operation. Re-operations are stressful for patients and costly to the healthcare service; their incidence rate was shown to have a median value of 17% [2]. A 3D technique capable of assessing the margins intra-operatively with the reliability of histopathology would thus be hugely beneficial, so the significant interest in x-ray Phase Contrast-Computed Tomography (PC-CT) at synchrotron facilities [4-6] and translation into lab settings is hardly surprising [7-9].

Cancer of the esophagus is the 7th most common worldwide [10], and its prevalence has risen over the past 30 years [11]. 5-year survival rates have improved from around 4% (1970) to 16% (2010) [11], with new therapies increasingly available [12]. Staging is the most accurate reflection of prognosis, guiding therapy and as a survival reference point. It is based on a number of methods including any combination of endoscopic ultrasound, computed tomography (CT), ultrasound, positron emission tomography and laparoscopy. While several studies have looked at the effectiveness of these techniques individually [13-15], a meta-analysis of T2N0 staging involving a combination of techniques showed an accuracy of T&N staging of just 19 ± 4 %, and T staging accuracy of 29 ± 5% [16]. An intra-operative technique with the dependability of histopathology would again be a significant step forward and follows on from attempts to image esophagus tissue with x-ray phase contrast methods at synchrotron facilities [17].

Conventional CT contrast is generated by differences in attenuation between tissue types. Soft tissues, including muscle, fat, milk ducts, esophagus submucosa and mucosa, along with tumors, have similar attenuation properties. This leads to poor differentiation between tissue layers and tumor, resulting in the inability to determine margins in BCS and inaccurate clinical staging in esophageal cancer. Here, we use Phase Contrast-Computed Tomography (PC-CT), often explained by means of the complex refractive index, $n = 1 - \delta + i\beta$, where β describes attenuation and δ phase [18]. Interest in phase imaging is driven by δ being generally greater than β (in some cases 1000 times), particularly for low Z materials. This means that contrast between soft tissues may be greatly improved, allowing the assessment of tumor layer penetration with greater accuracy. In this study, PC-CT scans are applied to excess tissue from BCS, namely Wide Local Excisions (WLEs) and to esophagectomies, and the images assessed vs. the current gold standard in both fields, histopathology, as has been shown in previous works with phase contrast imaging on various soft-tissue types [19-22].

2. METHODOLOGY

WLE specimens from breast surgery were collected fresh following ethical approval. Samples were typically 30 mm superior to inferior,15-20 mm medial to lateral and 10 mm anterior to posterior. As per standard protocols, these were inked and weighed and fixed in 10% saline for 24 hours prior to scans. Samples were placed in plastic pots for the CT scanning without further processing. After imaging, specimens were sent for histopathological examination based on standard protocols.

Following ethical approval, ~10 esophagectomy specimens were obtained, including both squamous and adenocarcinomas. Samples were fixed in formalin overnight and dried in graded ethanol prior to imaging. After PC-CT scans, the samples were sent for histopathology as usual.

This work uses edge-illumination (EI) to generate x-ray phase contrast, where apertured masks are placed before and after the sample. The pre-sample mask splits the incoming x-rays into beamlets. When a sample is introduced between the signal arriving at the detector depending on the phase change. Prior to scanning, an illumination curve is acquired without a sample present by moving the position of the sample mask. The shape of the illumination curve is described by a Gaussian, and subsequent deviations caused by the introduction of a sample can also be fitted as a Gaussian, with attenuation described by a reduction in integral and phase by a shift of the center. The EI imaging system, built by Nikon X-TEK systems (Tring, United Kingdom), used a rotating anode molybdenum source (Rigaku 007-HF Micro Max, Rigaku, Japan), operated at 40kVp and 24 mA. The detector was a flat panel detector (C9732DK-11, Hamamatsu, Japan. The system employs two gold masks manufactured by Microworks GmbH (Karlsruhe, Germany) by electroplating a layer of gold ~120 µm thick on a 1 mm thick graphite substrate. Pre-sample and detector masks were 9 x 9 and 11.5 x 11.5 cm^2 with aperture sizes of 12 and 20 µm, respectively. Projections were collected while the sample stage was continuously rotated. For the breast tissue, 10-minute scans were acquired with 1500 projections at a rotation speed of 0.6°s^{-1} and 0.4 s exposure time, while for esophagus samples an exposure time of 0.6 s was used with example parameters for 2/10-hour scans are 12000/60000 projections acquired at rotation speeds of 0.05°s^{-1}/0.01°s^{-1}.

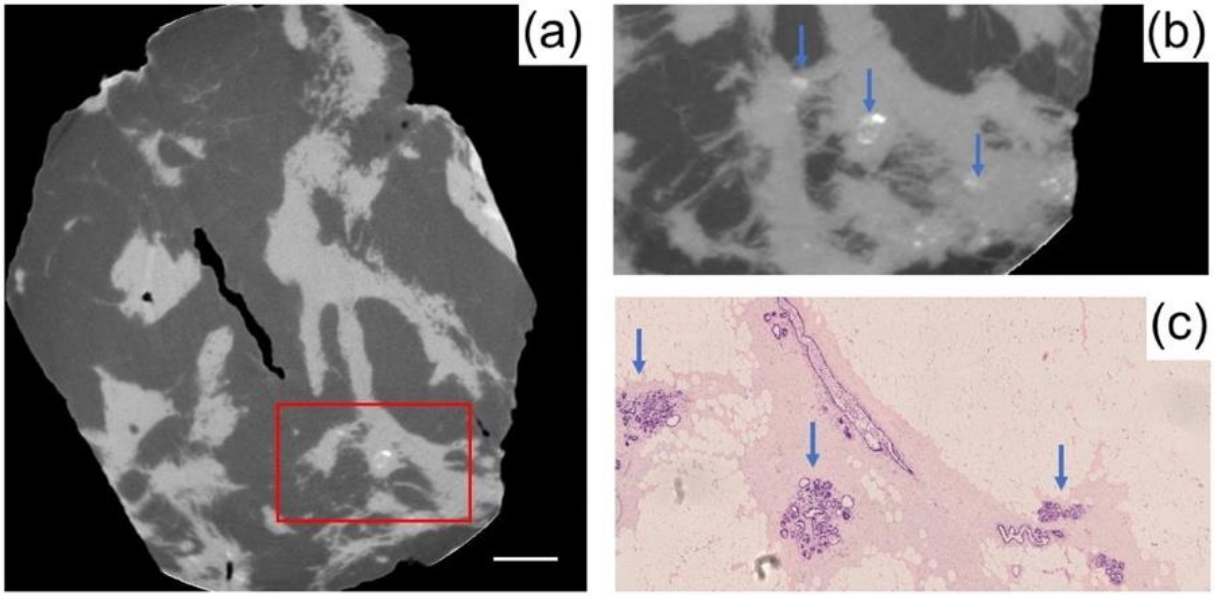

Figure 1.(a): Example of image quality obtained with the UCL scanner (scale bar 3 mm). A maximum intensity projection of the area in the red rectangle is shown in (b), allowing a clear visualization of microcalcification clusters, validated by histopathology in (c).

Phase retrieval was performed using the single shot method [23] implemented on custom Nikon software, so retrieved images are a mix of both attenuation and phase. This allows for all acquisitions to be taken at just one position of the illumination curve, typically the half height position where sensitivity to refraction effects is greatest. CT reconstruction used the filtered back projection method, again on Nikon developed software. CT ring removal was applied to all scans by transferring to polar co-ordinates and median filtering.

3. RESULTS

Initial scans on the breast work used surplus tissue from diagnostic WLEs to assess the ability of phase contrast to assist margin detection. For this part of the study, an imaging system based at UCL was used, conceptually identical to the Nikon one apart from smaller masks (5.5 x 2 and 6 x 2.5 cm^2). Phase retrieved and CT reconstructed images were assessed by radiologists to consider if lesion was observed in the margin, with a distance of less than 1 mm considered a positive margin, as specified by clinical protocols. The samples were then sent for histopathology, the results of which were used as the ground truth. 101 specimens were scanned, 99 of which were also scanned using a conventional system (Bioptics

Core Vision, Bioptics Inc, Tucson, AZ). Of the 101, histopathology determined that 47 had cancer at margins and 54 did not. Out of the 47 positive margins, PC-CT classified 39 and 8 as having affected and unaffected margins, respectively. Out of the 55 negative margins, 9 and 45 were classified as having affected and unaffected margins, respectively. This corresponds to sensitivity and specificity values of 83% (95% CI 69–92%) and 83% (95% CI 70–92%), respectively. Out of the 99 examined with the conventional system, 43/56 had affected/unaffected margins according to histopathology. Of the affected 43, the conventional system detected 14 as affected and 29 as unaffected, while of the unaffected 56, it detected 8 as affected and 48 as unaffected. This corresponds to sensitivity and specificity values of 32% (95% CI 20–49%) and 86% (95% CI 73–93%), respectively. This part of the study allowed us to conclude that PC-CT has a specificity comparable to the conventional system, but a significantly higher sensitivity – a key point as it suggests improved capability to detect cancer at margins, and therefore to prevent re-operations.

An example image from this part of the study is shown in figure 1, highlighting how well PC-CT compares against histopathology [24]. Following the success of this initial study, the larger field-of-view pre-commercial system built by Nikon was used to image 15 fresh WLE specimens straight from BCS. This successfully demonstrated that the technology could cope with a range of larger samples and scan them in acceptable times (see example in Fig 2), i.e., that it can be seamlessly integrated in the clinical workflow [24].

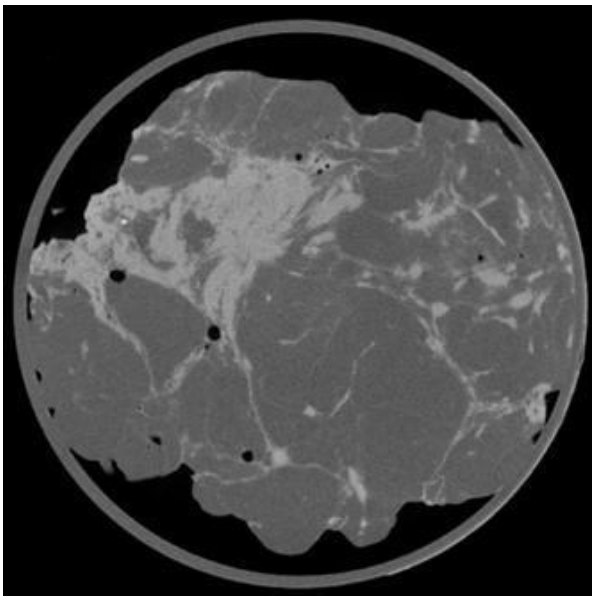

Figure 2. An example mixed attenuation and phase image of a fresh WLE scanned immediately after the operation. The sample diameter is approximately 5.5 cm, the total scan time was 10 minutes.

Finally, we investigated a different use of the same machine, which exploits the fact that the ultimate resolution provided by the sample is determined by the size of the apertures in the pre-sample mask [25], independently from focal spot and detector pixel size. Achieving this enhanced resolution level requires either the sample or the mask to be stepped laterally at each CT projection, which lengthens the scan making the approach incompatible with intra-operative use. However, this imaging mode could be used during surgery downtime as an aide/possible replacement to histopathology [26]. An example of this alternative higher resolution use is provided in Fig. 3.

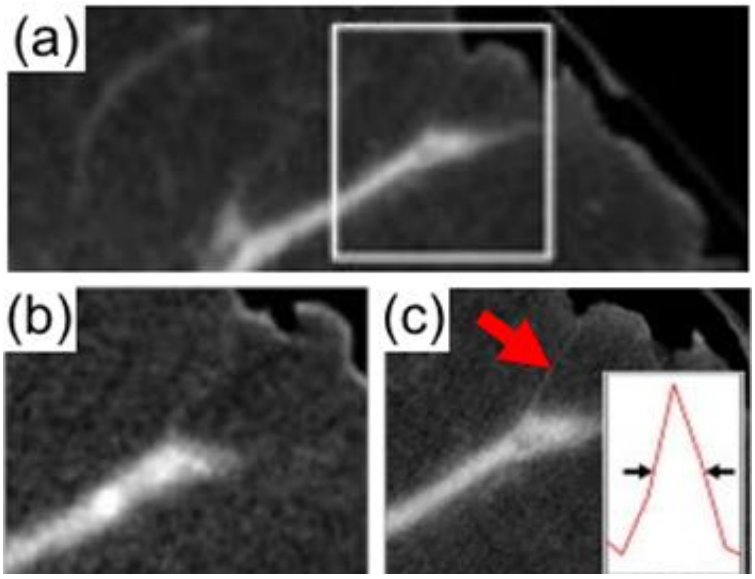

Figure 3. (a) Example scan showing a tumor strand extending towards the edge of a WLE. This image was acquired with the "standard" use of the scanner, which has a resolution of ~100 μm. (b) zoom-in of the area highlighted by the rectangle in (a). The sample was re-scanned in higher resolution mode (c). The width of the strand highlighted by the red arrow (actually reaching the sample's margin) was measured to be approximately 30 μm (profile in the inset). All images are mixed attenuation and phase.

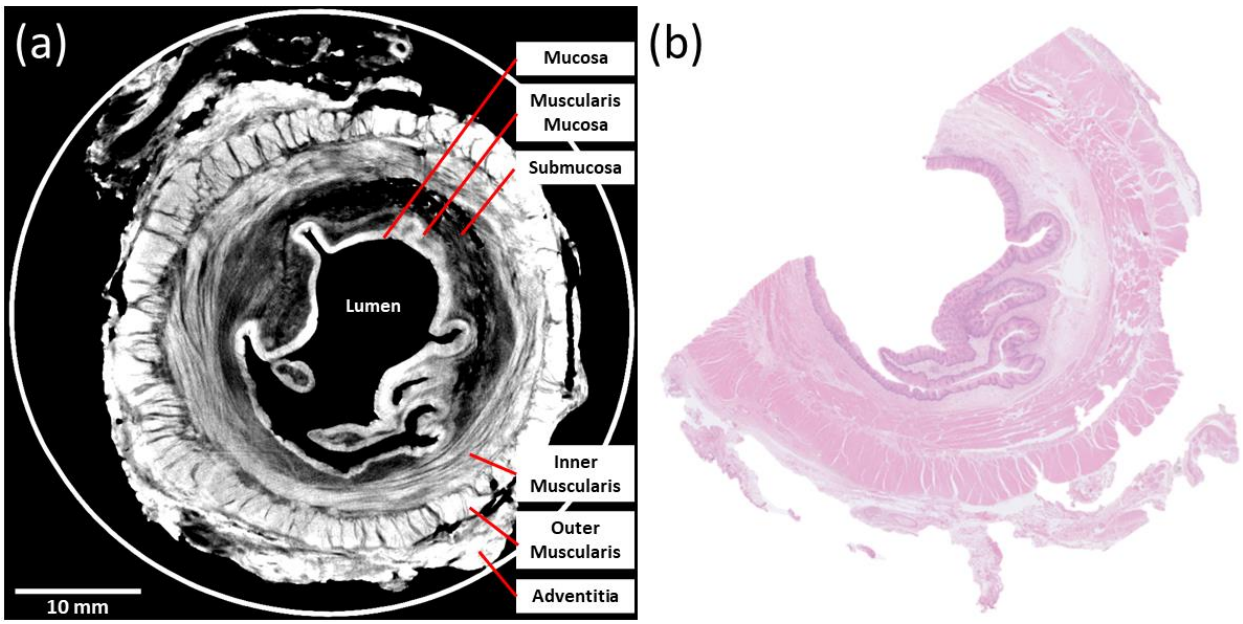

Figure 4. Mixed attenuation and phase PC-CT image slice of a cancer-free esophagus (a), demonstrating that the high soft tissue sensitivity of PC-CT allows recognizing all esophageal layers (see labels in (a)), while providing a match with histopathology (b).

The same pre-commercial scanner was employed to study esophageal tissue from esophagectomy surgeries. Example results are shown in figure 4, demonstrating that PC-CT allows distinguishing all esophageal layers, while providing a good match with histopathology.

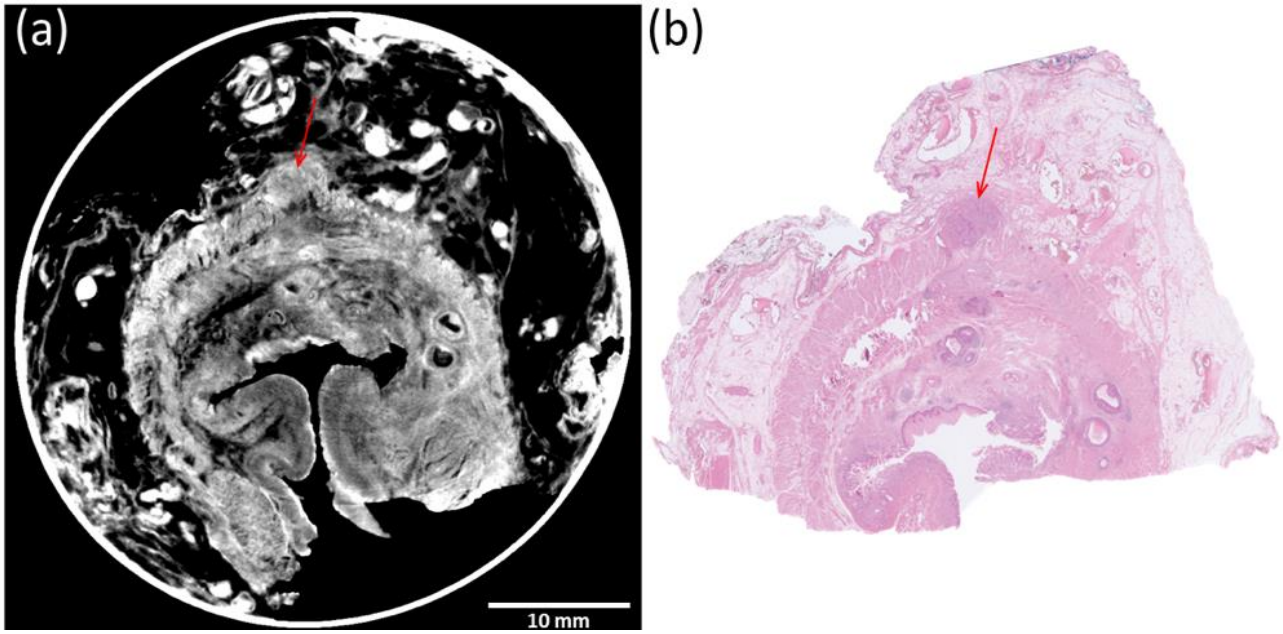

Figure 5. (a) PC-CT mixed attenuation and phase scan and (b) matching histopathology, for a sample with T3 stage cancer. The red arrow highlights the area where the tumor is pushing through the muscle layers into the adventitia, characteristic of a T3 cancer. The arrow was independently placed by radiologists and histopathologists for (a) and (b), respectively.

4. CONCLUSION

PC-CT was shown to offer a significant improvement in sensitivity when compared to standard specimen imaging alone for WLE like tissue from BCS. Based on this, a large field-of-view pre-commercial system was designed for intra-operative work and was shown to be able to acquire high quality images in 10 minutes, making it compatible with intra-operative use. The same scanner can also be employed in a high-resolution mode which, while taking longer to scan, can provide more detailed images for use as a digital histopathology. This would offer a secondary use of the system in a clinical setting outside of intra-operative surgery. The same system was also applied to samples from esophagectomy surgery. For both breast imaging and esophageal tissue, it was shown that PC-CT images compare well against histopathology, with all key features present in both modalities. Esophageal tumors were examined at different stages of intrusion, and independent staging by radiologists and histopathologists provided matching results. In both breast and esophagus tissues the full 3D volume extracted from PC-CT scans was shown to offer enhanced capability for diagnosis than slices alone, indicating the potential of this technology to assist if not replace histopathology in clinical settings.

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