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James E. Montgomery
Michal J. Wesolowski
Bailey Wolkowski
Rajni Chibbar
Elisabeth C. R. Snead
Jaswant Singh
Murray Pettitt
Pritpal S. Malhi
Trinita Barboza
Gregg Adams

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James E. Montgomery,^{a,*} Michal J. Wesolowski,^b Bailey Wolkowski,^c Rajni Chibbar,^d Elisabeth C. R. Snead,^e Jaswant Singh,^f Murray Pettitt,^c Pritpal S. Malhi,^g Trinita Barboza,^h and Gregg Adams^e

^aUniversity of Saskatchewan, College of Medicine, 107 Wiggins Road, Saskatoon, Saskatchewan S7N 5E5, Canada

^bUniversity of Saskatchewan, Department of Medical Imaging, College of Medicine, 107 Wiggins Road, Saskatoon, Saskatchewan S7N 5E5, Canada

^cUniversity of Saskatchewan, Department of Animal and Poultry Science, College of Agriculture and Bioresources, 51 Campus Drive, Saskatoon, Saskatchewan S7N 5A8, Canada

^dUniversity of Saskatchewan, Department of Pathology and Laboratory Medicine, College of Medicine, 107 Wiggins Road, Saskatoon, Saskatchewan S7N 5E5, Canada

^eUniversity of Saskatchewan, Department of Small Animal Clinical Sciences, Western College of Veterinary Medicine, 52 Campus Drive, Saskatoon, Saskatchewan S7N 5B4, Canada

^fUniversity of Saskatchewan, Department of Veterinary Biomedical Sciences, Western College of Veterinary Medicine, 52 Campus Drive, Saskatoon, Saskatchewan S7N 5B4, Canada

^gPrairie Diagnostic Services, 52 Campus Drive, Saskatoon, Saskatchewan S7N 5B4, Canada

^hUniversity of Saskatchewan, Western College of Veterinary Medicine, 52 Campus Drive, Saskatoon, Saskatchewan S7N 5B4, Canada

Abstract. Prostatic urethral transitional cell carcinoma with prostatic invasion in a dog was imaged with abdominal radiography and abdominal ultrasonography antemortem. Synchrotron in-line x-ray phase contrast imaging computed tomography (XPCI-CT) was performed on the prostate *ex vivo* at the Canadian Light Source Synchrotron and compared to histology. XPCI-CT imaging provides greater soft tissue contrast than conventional absorption-based x-ray imaging modalities, permitting visualization of regions of inflammatory cell infiltration, differentiation of invasive versus noninvasive tumor regions, and areas of necrosis and mineralization. This represents the first report of XPCI-CT images of an invasive prostatic urothelial neoplasm in a dog. © 2016 Society of Photo-Optical Instrumentation Engineers (SPIE) [DOI: [10.1117/1.JMI.3.1.015504](https://doi.org/10.1117/1.JMI.3.1.015504)]

Keywords: prostate cancer; x-ray phase contrast imaging; computed tomography; transitional cell carcinoma; synchrotron imaging.
Paper 15197RR received Oct. 10, 2015; accepted for publication Feb. 25, 2016; published online Mar. 14, 2016.

1 Introduction

The basic principles of conventional absorption-based x-ray imaging have not changed dramatically since the first clinical radiographs were acquired in 1896. Image contrast in conventional x-ray imaging techniques depends on the absorption of the x-rays as they pass through tissues with differing linear attenuation coefficients. Soft tissues are difficult to visualize and distinguish from one another in traditional radiographs because they all have similarly low x-ray attenuation coefficients, i.e., they are relatively transparent to x-rays in the diagnostic range, typically 10 to 200 keV.^{1,2} Lower-energy x-rays improve contrast in soft tissues, but result in increased absorbed doses of radiation to the patient. Conversely, higher-energy x-rays more readily pass through soft tissues (i.e., reduced absorbed dose), but provide less image contrast.

Unlike conventional absorption radiography, where image contrast is formed mainly by the absorption of a portion of the x-rays passing through the tissue, x-ray phase contrast imaging (XPCI) exploits the refraction that x-rays undergo as they pass through matter. Visualizing this phase shift can increase the

overall image contrast and permit detection of details that are classically considered x-ray transparent, such as the interfaces between soft tissues.^{3,4} The simplest implementation of XPCI, called in-line or propagation-based XPCI, has become one of the most used imaging methods in preclinical research.⁵ The technique involves the propagation of an x-ray beam with high spatial coherence through a sample. Phase contrast imaging may be one of the most important advances in x-ray imaging since the invention of computed tomography (CT).^{1,5–8}

Animal models of prostate cancer are well established, though most of these models use rodents.⁹ These models use induced rather than spontaneous disease and genetically inbred species, rather than more genetically outbred species, such as the dog, which also has spontaneously occurring prostate cancer.^{10,11} The dog is a unique animal model for the study of the pathogenesis of human prostatic disease because it is the only animal in addition to humans that is known to spontaneously develop benign prostatic hyperplasia and prostate cancer with advancing age.¹²

In this report, in-line XPCI-CT was used to image an invasive prostatic transitional cell carcinoma in a dog and compared to

*Address all correspondence to: James E. Montgomery, E-mail: james.montgomery@usask.ca

results from histology to explore its potential as a diagnostic imaging modality.

2 Methods

2.1 Case Data

A 12-year-old, castrated male, Nova Scotia Duck Tolling Retriever was presented to the Western College of Veterinary Medicine Veterinary Medical Centre with a one-week history of stranguria and tenesmus, and a single episode of vomiting the morning prior to presentation. Physical examination revealed a palpable abdominal mass at the pelvic inlet. Digital rectal examination identified a symmetrically enlarged prostate that was nonpainful. The most common differential diagnosis for stranguria, tenesmus, and prostatomegaly is prostatic neoplasia (transitional cell carcinoma or adenocarcinoma), with prostatitis, prostatic abscess, and para-prostatic cyst considered less likely. The clinical findings were considered consistent with metastatic prostatic neoplasia. The owners elected to have the dog euthanized. With the owner's consent, a postmortem examination was done and tissue samples were taken for additional imaging and histopathology. Use of the prostate for biomedical imaging at the Canadian Light Source Synchrotron was approved by the University of Saskatchewan Animal Care Committee in accordance with the Guidelines of the Canadian Council on Animal Care.

2.2 Clinical Analysis

A physical examination, complete blood count, serum biochemistry, free catch urine, and urine cytology were performed as part of a standard clinical workup. Based on preliminary findings, survey abdominal and thoracic radiographs (Agfa CR 30-X, Agfa Healthcare Corporation, Greenville, South Carolina), and abdominal ultrasonography (Philips iU22, curvilinear 5 to 8 MHz probe, Philips Healthcare, Markham, Ontario, Canada) were performed. Following euthanasia a necropsy was performed by Prairie Diagnostic Services. The prostate was excised and formalin-fixed for histological analysis and XPCI imaging. Unstained sections of the formalin-fixed, paraffin-embedded prostate tissues were also submitted to the Diagnostic Center for Population and Animal Health (DCPAH) at Michigan State University for immunohistochemistry for detection of cytokeratin 7 (CK7) and prostatic acid phosphatase (PAP).

2.3 X-Ray Phase Contrast Imaging Methodology

An ~3-mm-thick transverse slice of the fixed prostate (stored in 10% buffered formalin solution) was acquired for XPCI-CT

imaging. The specimen was suspended in Knox Gelatine (Knox Gelatine, Associated Brands LP, Toronto, Ontario) within a plastic specimen tube and imaged at the Biomedical Imaging and Therapy Bending Magnet (BMIT-BM) beamline at the Canadian Light Source Synchrotron.¹³ The experimental setup and imaging protocol for XPCI-CT were as previously described in Ref. 14. Briefly, the samples were positioned 25 m from the 30 keV monochromatic synchrotron x-ray source, allowing for an effective parallel beam geometry, on a rotating stage and a Photonic Science VHR-90 x-ray detector (Photonic Science Ltd., Millham, Mountfield, United Kingdom) with a detector pixel size of $18.7 \mu\text{m}^2$ was positioned 5 m downstream from the sample as illustrated in Fig. 1. XPCI-CT was performed with an image slice thickness of 3.1 mm and 3751 projections were acquired over 180 deg. Images were calibrated for flat and dark field noise using a plug-in algorithm of the software ImageJ (ImageJ, version 1.46r, Wayne Rasband, National Institutes of Health). The calibrated image data were reconstructed using the Feldkamp algorithm, which is a cone beam geometry algorithm available in NRecon (NRecon, version 1.6.8.0, 2011, SkyScan Bruker-Microct, Kontich, Belgium), a freeware program for the reconstruction of volumetric datasets. Given that our experimental setup provides parallel beam geometry, this is not an ideal reconstruction method and could impact the final reconstructed image resolution. In future work, we plan to use customized reconstruction software to maximize image quality. Following XPCI-CT, the same prostate slice was embedded in paraffin and corresponding $4 \mu\text{m}$ thick histological sections were obtained for comparison to the XPCI-CT images. The reconstructed XPCI-CT images were evaluated alongside the corresponding histology section and were reviewed by a pathologist (RC) and a veterinary radiologist (JM).

3 Results

3.1 Clinical Findings

A complete blood count revealed evidence of mild chronic inflammation. The serum biochemistry panel was unremarkable. A free-catch urine sample was cloudy and yellow, with a specific gravity of 1.025. Urine cytology revealed numerous clumps of epithelial cells (12 to 20/hpf; reference interval: 0 to 5/hpf) with dysplastic cytomorphologic features. A tentative diagnosis of prostatic, urinary bladder, or urethral neoplasia was made.

Survey abdominal radiographs (Agfa CR 30-X, Agfa Healthcare Corporation) revealed prostatomegaly with subtle evidence of mineralization. Prostatomegaly with mineralization in a neutered dog is highly suggestive of neoplasia with a reported sensitivity of 84% and specificity of 100%.¹⁵

Fig. 1 Diagram of a top-down view of the XPCI-CT experimental setup illustrating the relative position of the sample and detector within the monochromatic x-ray beam in the BMIT-BM imaging hutch.

Thoracic radiography demonstrated numerous small, ill-defined soft tissue opacity, interstitial nodules consistent with pulmonary metastases. Abdominal ultrasonographic (Philips iU22, curvilinear 5 to 8 MHz probe, Philips Healthcare) findings included an enlarged (3.6 cm × 3.4 cm), smoothly margined, heterogeneous prostate with numerous hyperechoic foci consistent with areas of mineralization, and a moderately thickened, prostatic urethra. In addition, there were numerous hypoechoic nodules within the liver. Differential diagnoses for the hepatic nodules included metastatic foci or nodular hyperplasia. Multifocal pulmonary nodules were seen in the caudal lung lobes using a transdiaphragmatic ultrasonographic window.

At necropsy, the prostate was asymmetrically enlarged and had raised tan nodules of variable sizes. The cut surface revealed multiple, tan nodules present within the prostatic parenchyma and relatively darker, cavitory areas indicating loss of tissue or necrosis.

Histologically, the prostatic urothelium showed high-grade dysplasia and the surrounding prostatic parenchyma was replaced by an infiltrative epithelial tumor. Neoplastic tissue consisted of islands, nests, and sheets of round to cuboidal to polyhedral cells within fibrovascular connective tissue. Neoplastic cells had indistinct or distinct cell borders, scant

to moderate eosinophilic cytoplasm, high nuclear to cytoplasmic ratio, centric or eccentric round to oblong nuclei, stippled to vesiculated chromatin, and one to three nucleoli. Anisokaryosis and anisocytosis were moderate. Mitotic figures were 0 to 4 per 40× objective field. Neoplastic cells frequently had a single large vacuole within the cytoplasm and the nucleus was present at the periphery (signet ring cells). Neoplastic cells also formed acini with a central lumen or micropapillary structures. Coagulative necrosis was present centrally in the majority of tumor nests. There were also multiple foci of mineralization. Infiltrates of neutrophils, plasma cells, small lymphocytes, and hemosiderophages were present within the neoplastic tissue. A narrow zone of fibrovascular connective tissue was present around the mass, which contained smooth muscle, nerve bundles, ganglionic cells, infiltrates of lymphocytes admixed with plasma cells, and a few lymphoid nodules.

Unstained sections of the formalin-fixed, paraffin-embedded tissues were submitted to the Diagnostic Center for Population and Animal Health at Michigan State University for immunohistochemistry for detection of CK7 and PAP. The neoplastic cells were immunopositive for CK7 and negative for PAP. The histological features and immunoprofile were consistent with a urothelial carcinoma.

Fig. 2 (a) An H&E stained whole mount section of the prostate and (b) the corresponding XPCI-CT image at the same level as the histology section. In the XPCI-CT image, regions of lymphocytic infiltration are seen as darker, irregularly margined regions in the peripheral zone of the prostate (black arrows) surrounded by the regions of brighter prostatic stroma. Large zones of necrosis (asterisks) are present within areas of prostatic tumor, and with XPCI-CT, this is seen as a thin margin of hypointense cells encapsulating a central region of fluid with a brighter intensity. (c) and (d) Magnifications of the regions of lymphocytic infiltrate (black arrows) and adjacent zone of necrosis (asterisks).

3.2 X-Ray Phase Contrast Imaging Computed Tomography

When the x-ray wavefront is refracted at the interface of different structures within the sample, it subsequently interferes with the unperturbed x-ray beam, resulting in an interference pattern that is recorded by a detector placed downstream from the sample.^{6,16,17} When the interference is constructive, there are resulting higher-intensity fringes at the margins of structures where the wave amplitude (and hence intensity) are increased causing edge enhancement. Conversely, where destructive interference occurs, there is decreased wave amplitude and, therefore, decreased signal intensity.¹⁸ Interfaces in in-line XPCI images are characterized by pairs of fringes, one bright (hyperintense) and one dark (hypointense) relative to a reference structure when describing the image findings.

On comparing the histology to XPCI-CT, the imaging plane and the histological sectioning plane were not perfectly parallel, though good co-localization of features within the tissue was

maintained (Figs. 2–5). While the detector pixel size was 18.7 microns, based on known pixel dimensions, the reconstructed XPCI image resolution was calculated to be 80 μm . This degradation in image resolution could potentially be due to the reconstruction method. The neoplastic tissue was characterized by central areas of necrosis, which are generally large, roughly circular structures [Figs. 2(a) and 2(b), asterisks] with thin margins of darker cells encapsulating a central region of fluid, which was brighter relative to the wall. Aggregates of lymphocytes visible at the periphery of the tumor by histology were recognized near the periprostatic adipose tissue in the XPCI-CT image [Fig. 2(b)] as darker, irregularly margined regions in the peripheral zone of the prostate surrounded by regions of brighter prostatic stroma.

With histology, a sharp distinction between dysplastic urothelium and adjacent prostatic parenchyma was evident [Fig. 3(a), small black arrows]. With XPCI-CT, a linear hypointense thickened band was apparent along the urothelial margin

Fig. 3 (a) Corresponding histology and (b) XPCI-CT images. A sharp distinction between urothelial carcinoma and adjacent prostatic parenchyma is evident [small black arrows in (a)]. In the corresponding XPCI-CT image [Fig. 3(b)], a linear hypointense thickened band is seen along the urothelial margin (small black arrows) compatible with the region of urothelial carcinoma *in situ* seen in the histology image. Extension of the neoplastic cells into the adjacent prostatic ducts is noted with histology (large black arrows), but is not well visualized in (b). Also seen are nests of invasive urothelial carcinoma (large white arrows) with extensive regions of necrosis (asterisks). There is distinction between invasive carcinoma foci and surrounding inflammatory infiltrates.

Fig. 4 (a) Same canine prostate with histology preparation and (b) XPCI-CT. Areas of dystrophic calcification (black arrows) associated with necrotic debris in the center of dilated tumor nests, which correspond to hyperintense foci seen in the same regions in the corresponding XPCI-CT image. Additionally, (a) the histology image shows a distinct vertically oriented central shearing defect crossing the middle of the image where there is clear disruption of the tissue. This same region is seen in (b) the XPCI-CT image and no tearing of the tissue is present as the prostate was intact while being imaged.

Fig. 5 Same image as Fig. 3 showing line signal intensity profiles made over the region of invasive tumor (1) and on the region of noninvasive tumor (2); the resulting plot of signal intensity shows distinct signal peaks at the tumor boundary in 2 (red arrows, also indicating the level of the peaks in the XPCI-CT image), but no change in the line profile in (a) where the tumor has invaded into the surrounding parenchyma.

[Fig. 3(b), small black arrows] compatible with the region of urothelial carcinoma seen in the histologic images. At one edge, extension of the neoplastic cells into the adjacent prostatic ducts was evident with histology [Fig. 3(a), large black arrows], but was not well visualized in the same region in the corresponding XPCI-CT image [Fig. 3(b), large black arrows]. Also seen are nests of invasive urothelial carcinoma (large white arrows) and regions of necrosis (asterisks). As well, there are areas of dystrophic calcification associated with necrotic debris in the center of dilated tumor nests, which correspond to hyperintense foci seen in the same regions in the corresponding XPCI-CT image (Fig. 4, black arrows).

An interesting feature was the hyper- and hypointense bands evident along the margin of the urothelium by XPCI-CT. This was seen only along the margin of the noninvasive portion of the urothelial carcinoma and was not evident in the regions of invasive tumor, where, with histology, invasion of the carcinoma cells beyond the margins of the urothelium is evident. Figure 5 is the same image as Fig. 3, but shows a line intensity profile made over the region of invasive tumor (line 1) and on the region of noninvasive tumor (line 2). The result shows distinct signal peaks at the tumor boundary in 2 (arrows), but no change in the signal intensity profile in 1 over the region where the tumor has invaded into the surrounding parenchyma and no defined boundary between the tumor and surrounding tissue exists.

Limitations of the current XPCI-CT setup included our inability to recognize the uninvolved neurovascular bundles present in the extraprostatic tissue, or the extraprostatic extension of disease visible at the microscopic level, which may be due to insufficient sensitivity or resolution. Additionally, individual cell types were not visible as were seen with microscopy (Fig. 3). Without microscopic visualization, it was not possible to assess the characteristics of malignancy at the cellular level, but other features consistent with malignancy were evident, such as the presence of mineral foci, loss of organized tissue architecture, which was replaced with irregularly spaced nests of glandular tissue, and the heterogeneous fibrous stroma.

4 Discussion

Conventional radiographic modalities consist of absorption-based images generated using a polychromatic x-ray source. Contrast in conventional radiographic images is produced by variations in the degree of x-ray photon absorption of various tissues along the beam path. The image is, therefore, a composite of varying radiographic opacities/transparencies that provides contrast among bone, soft tissue, fat, gas, and mineral elements.¹⁹ Because soft tissues have similar x-ray attenuation properties, variations in density or characteristics of soft tissues cannot be readily discerned using conventional radiography. In addition to absorption, a fundamental characteristic of x-ray photons as they pass through tissue is refraction.

Potentially valuable information provided in the refractive characteristics of soft tissue is not accessible when using conventional radiography.

For x-rays in the 10 to 100 keV energy range, phase shifts between different tissues are much greater than the difference in projected linear attenuation coefficients.²⁰ Thus, XPCI-CT imaging increases the contrast of soft tissues that otherwise have very similar linear attenuation coefficients and greatly improves visualization of features within soft tissues in a noninvasive manner. While soft tissue visualization and contrast is dramatically improved over clinically available diagnostic imaging modalities, the equipment for XPCI-CT currently available at the Canadian Light Source does not provide sufficient resolution to identify biological structures at the microscopic level; however, with improvements in x-ray detector technology, this may one day be possible. The edge enhancement provided within soft tissues with our XPCI-CT setup allowed for increased soft tissue contrast, with the ability to resolve structures with a diameter of 80 μm in the prostate studied herein. This resolution is compared to 0.6 mm for clinical CT, and up to 0.25 mm for 3T MRI.^{21,22} Based on images obtained in this report, the hyperintense fringe [Figs. 3(b) and 5(b)] provided by phase contrast at discrete tissue feature margins warrants further investigation as this may provide a quantifiable parameter in determining whether regions of tumor are contained within anatomic margins or have become invasive.

Histopathology is currently, and is likely to remain for some time, the gold standard for cancer diagnosis. However, aside from the obvious invasive nature of removing tissue from the body for histopathology, there are inherent artifacts in tissue preparation—both physical and biochemical. Physical disruption of the tissue architecture occurs while obtaining the biopsy sample and during sectioning. Biochemical changes to the tissue vary depending on the method of fixation, embedding, and histologic staining. Figure 4(a) shows a distinct central shearing artifact crossing the middle of the image from top to bottom, where there is clear disruption of the tissue. This same region is seen by XPCI in Fig. 4(b) with no shearing of the tissue present. Two hyperintense mineral foci are seen near the bottom margin of the XPCI-CT image (black arrow). These correspond to the two mineral foci seen in the histological section (black arrow). Additional mineral foci are evident in the XPCI-CT image, which were lost in the histologic preparation as they were situated in the region of tissue that was torn during sectioning. The lack of preparation-based tissue artifacts is an advantage that volumetric imaging such as XPCI-CT has over traditional histology. In the future, it is hoped XPCI-CT will offer the opportunity to obtain information traditionally acquired with histology in a noninvasive, antemortem procedure.

The use of synchrotron radiation has the potential to offer considerable improvements in many techniques currently used in diagnostic imaging. Coronary angiography, bronchography, mammography, multiple-energy CT, and microbeam radiotherapy are several examples of current uses of synchrotron radiation in medical imaging and radiation therapy.⁷ Applied in a clinical setting, the improvements in soft tissue contrast provided by XPCI-CT would provide the radiologist with an entirely new tool set with the potential for greatly improved sensitivity and specificity in disease detection, and improved accuracy in making diagnoses. Live animal imaging is feasible and is in the early stages of research, though is currently not practical for clinical practice due to limited availability of synchrotron

facilities. Additional research is also needed to decrease the image acquisition time at BMIT-BM (with the current protocol 45 min per 3 mm slice of tissue), which will also reduce radiation exposure. Further challenges with high-resolution *in vivo* imaging will arise from motion artifacts secondary to respiratory motion and pulsation from the vasculature, and gating techniques may need to be employed. This report represents the first published images of synchrotron XPCI-CT of a canine urothelial carcinoma with prostatic invasion.

The use of XPCI-CT represents an opportunity to image the prostate gland with greater detail than is currently possible with clinically available diagnostic tomographic imaging modalities such as CT and MRI. In this case, XPCI-CT was not able to influence the outcome of the patient as the disease state was well advanced at the time of diagnosis. With future research, it is hoped that XPCI-CT may be able to provide early detection and staging of disease in a noninvasive manner. Additional prospective work is needed to document and discriminate normal from various disease states, with the goal of developing a reliable diagnostic test with high sensitivity and specificity. While the current imaging study focuses on the prostate, there are a myriad of potential future clinical applications of XPCI-CT. As the technology evolves, there is no reason the XPCI-CT technique would be limited to any specific body system, whether soft tissue or bone, and would have similar clinical applications as the other tomographic imaging modalities.

Acknowledgments

The University of Saskatchewan Prostate Research team gratefully acknowledges funding received from the Saskatchewan Health Research Fund and Motorcycle Ride For Dad—Saskatoon Chapter. The research described in this paper was performed at the Canadian Light Source, which is funded by the Canada Foundation for Innovation, the Natural Sciences and Engineering Research Council of Canada, the National Research Council Canada, the Canadian Institutes of Health Research, the Government of Saskatchewan, Western Economic Diversification Canada, and the University of Saskatchewan.

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Biographies for the authors are not available.