University of Victoria

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To the members of the Lung Ambition Awards review committee,

The XCITE (X-ray Cancer Imaging and Therapy Experimental) lab at the University of Victoria seeks support for developing photon-counting-based imaging techniques to detect lung abnormalities as indicators of early-stage lung cancer. As lung cancer remains the leading cause of cancer-related deaths in Canada, early diagnosis is critical to improve patient survival rates by treating cancer at early stages. Photon-counting technology holds promise for improving diagnostic imaging quality at lower radiation doses. We are requesting $50,000 over one year to conduct this project. To be eligible for this funding, The proposal has not been sent to any other agencies, and no other support apart from the NSERC Alliance Missions with different non-clinical goals has been applied for or received.

In our study, we will develop advanced techniques for photon-counting computed tomography (PCCT) to enable more precise identification and localization of angiogenesis in early-stage lung cancer. The ability of photon-counting detectors to differentiate multiple energy levels and colorize the X-ray spectrum offers significant advantages over traditional dual-energy CT, especially in low-dose settings.

The XCITE lab, led by Dr. Magdalena Bazalova-Carter (co-PI), is uniquely equipped for this study with a state-of-the-art table-top PCD-CT system featuring photon-counting detectors developed by Redlen Technologies (Saanichton, BC, Canada), a subsidiary of Canon Medical Systems Canada. Our preliminary experiments have demonstrated the system's capability to detect iodine contrast at low radiation doses in phantoms with lung-like structures. Additionally, we have demonstrated an imaging method that enhances soft tissue contrast without the aid of contrast-enhancing agents such as iodine. The study will be primarily conducted by two other co-investigators, post-doctoral fellows Dr. James Day and Dr. Xinchen (Alison) Deng, who bring extensive experience in photon-counting detector imaging and AI techniques to optimize angiogenesis detection in screening and diagnostic lung cancer imaging.

This study is structured into two stages. The first stage focuses on iodine contrast imaging for angiogenesis, aiming to detect early vascular changes associated with lung cancer development. The second stage of the study aims to minimize iodine contrast agent concentration while maintaining diagnostic accuracy. We will conduct the study on an anthropomorphic lung phantom with 3D printed lung inserts to mimic structures with different anatomic noises in lungs and ex vivo lung models.

We are confident that this project will have the potential to provide more affordable and effective lung cancer screening methods and contribute to the ongoing efforts to reduce lung cancer mortality through early detection.

Thank you for considering our proposal.

Sincerely,

James Day and Xinchen Deng

LOOPHOLE: LOw dOse PHoton-cOunting for detecting nodules in early Lung cancEr

Lung cancer is the leading cause of cancer deaths worldwide, constituting over a quarter of cancer cases [1]. For all cancers, the **early diagnosis of cancer is key for survivability**. While the cancer is still in stage 1 and has not spread outside the lung, the typical five-year survival rate is 60%; however, only 1 in 5 people are caught in this stage, with over half found in stage 4 [3] leading to medical assistance in death (MAID) requests at over twice the rate of any other cancer type [4]. **Low-dose computed tomography** (CT) is the primary method of lung cancer screening and is responsible for a **reduction in mortality** rates by up to 24% [5]. While reduction in mortality using current techniques is a positive outcome, the detection of early lung cancer can be improved using more advanced imaging techniques and **color x-ray imagers known as photon-counting detectors** to detect these tumors at earlier stages.

The first FDA-approved **photon-counting detector CT** (PCD-CT) scanner, developed by Siemens Healthineers in September 2021, generated unprecedented interest in the medical community due to its groundbreaking potential in disease diagnosis. By offering improved spatial resolution, enhanced contrast-to-noise ratio, and reduced radiation dose, PCD-CT was hailed as “a quantum leap in disease diagnosis” and “redefining CT.” If applied to contrast enhanced low-dose CT or even standard chest radiography, photon-counting technology may pave the way to new and more affordable lung cancer screening.

The key advantage of these detectors is the ability to **colorize the X-ray spectrum** and utilize this to separate materials from one another, creating **material-specific images**. One such use of these detectors is in the field of breast imaging, where minor nodules (7mm diameter) can be detected with an iodine concentration of less than 1mg/ml [6]. When applied to low-dose CT, PCDs have exhibited prominent iodine contrast and excellent resolution when performing iodine specific imaging in Figure 1A to Figure 1D. In this project we plan to extend the application of PCDs to early lung cancer imaging.

The detectability of abnormalities in early lung cancer is dependent on the **vascularization (angiogenesis) of nodules**, creating regions of internal bleeding for the iodine to pool into. Angiogenesis typically occurs during the early stages of solid tumor growth when the tumor's diameter reaches about 2 mm. During this process, many poor-quality blood vessels are formed, leading to areas of internal bleeding. In lung cancer cases, approximately 80% to 90% of nodules exhibit angiogenesis. These regions are typically well **highlighted by iodine** showing higher contrast in comparison to the surrounding tissue [7]. However, iodine is not always available for screening purposes due to a **global shortage** [8]. Recently, our lab has explored material-specific imaging using the effective atomic number of soft tissues such as muscle, lung, fat, and water shown in Figure 2A to Figure 2D. Using a brute-force photon-counting approach, the tissues showed improved delineation between these materials and superior accuracy compared to an approach using conventional systems [9]. This innovative method could **enhance sensitivity to iodine** and potentially address the need for iodine in some imaging scenarios.

One of the primary objectives of the proposed study is to **develop advanced techniques for PCD-CT** to enable more precise identification and **localization of abnormalities in early-stage lung cancer**, such as bleeding points and nodules. A key component of this effort is material decomposition, a process that separates a CT image into its constituent materials, allowing for improved tissue characterization and differentiation between structures with similar attenuation properties, as demonstrated in prior research [9]. By leveraging the multi-energy capabilities of PCD-CT, material decomposition can facilitate **better**

contrast between soft tissue, lung parenchyma, blood, and calcifications, which is critical for early lung cancer detection and staging.

This study is structured into two stages. The **first stage** focuses on iodine contrast imaging for angiogenesis, aiming to **detect early vascular changes** associated with lung cancer development. Tumor angiogenesis, a hallmark of malignancy, results in abnormal vascular proliferation and increased perfusion, which can be potentially visualized using iodine-based contrast agents in PCD-CT. By employing **spectral material decomposition**, we aim to use iodine contrast and quantify perfusion patterns, allowing for more accurate differentiation between malignant and benign nodules. This approach could improve early-stage lung cancer diagnostic performance and provide quantitative imaging biomarkers for risk assessment.

The **second stage** of the study aims to **minimize** the needed concentration of **iodine contrast** agents while maintaining diagnostic accuracy. **Artificial intelligence** (AI), including convolutional neural networks (CNNs) and physics-guided models, have shown significant promise in denoising images, correcting artifacts, and enhancing spatial resolution [10, 11]. Our approach will leverage AI techniques to reconstruct high-quality iodine contrast images from low-dose scans, enabling low-concentration iodine imaging without compromising diagnostic performance. **The goal of this study is to determine if iodine-less or iodine-free imaging of angiogenesis is possible** in complex structures such as the lung allowing for effective material decomposition imaging **in lung screening**.

In this project, we will utilize an **anthropomorphic lung model** designed at the XCITE lab, with 3D printing lung inserts to mimic structures with different anatomic noises in lungs. XCITE lab has developed a similar breathing anthropomorphic thorax phantom, nicknamed "Casper" (as shown in Figure 3), which simulates the attenuation properties of a human lung. An **ex vivo lung model** (excised pig lungs) will also be used in this study. as they closely resemble human lungs in both anatomy and physiology, making them ideal for studying lung mechanics, diseases, and therapeutic interventions. The lung structures in the 3D printed phantom and **excised pig lungs** will be perfused using a solution such as Krebs-Henseleit buffer and **ventilated by a mechanical ventilator**.

The **X-ray Cancer Imaging and Therapy Experimental (XCITE)** lab, led by **co-principal investigator (co-PI)** Dr. Magdalena Bazalova-Carter at the University of Victoria, is at the forefront of photon-counting CT research using their **state-of-the-art table-top PCD-CT system**. This system features two advanced photon-counting detectors manufactured by Redline Technologies (Saanichton, BC, a subsidiary of Canon Medical Systems Canada) and a small focal-spot X-ray tube that enables high-resolution, low-dose, contrast-enhanced (HR) PCD-CT imaging. Two **co-investigators** performed the proof-of-concept experiments for this project, post-doctoral fellows **Dr. James Day** and **Dr. Xinchen (Alison) Deng**, who have ample experience in photon-counting detectors. This project will be guided by Dr. Magdalena Bazalova-Carter as the main co-PI; the other two co-investigators, Dr. James Day and Dr. Xinchen (Alison) Deng, will design experiments and mentor students/interns to conduct experiments.

APPENDIX

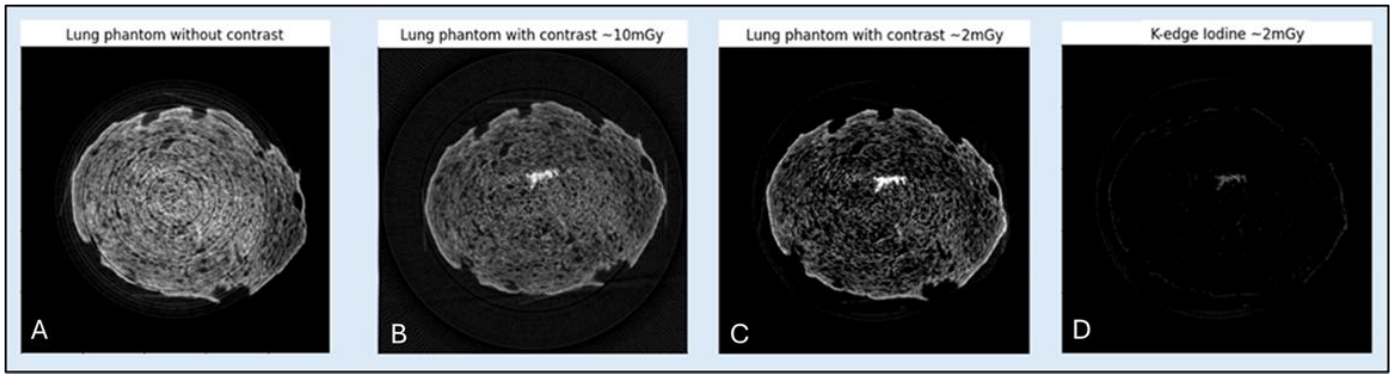

Figure 1: (1) Sourdough used as a lung imaging demo. (A) is without contrast agent B) and C) are with 0.2ml of injected iodine with 10ml/mg concentration D) is produced through weighted log subtraction. The scale of the images is 10cm by 10cm.

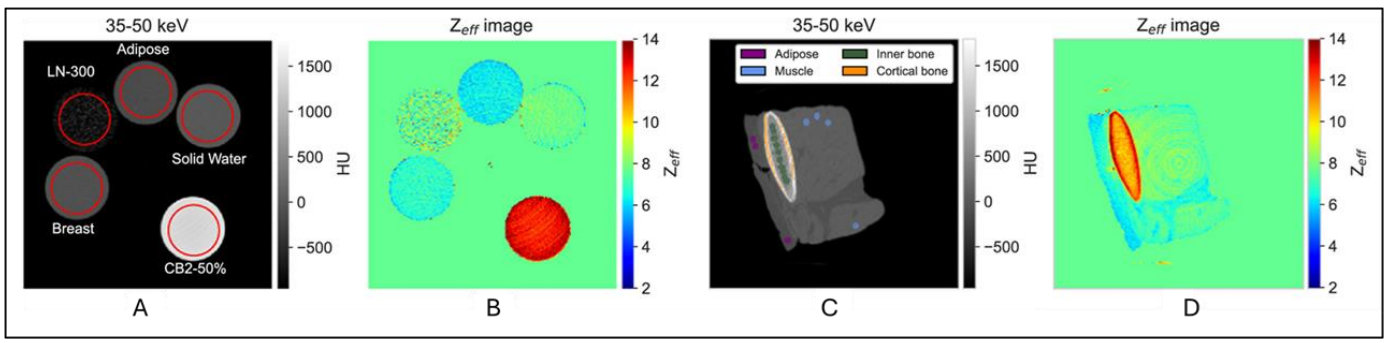

Figure 2: Z-effective imaging on phantom and beef short ribs (A) CT image of phantom inserts for different materials (B) Z-effective image for phantom inserts (C) CT image of beef short ribs with material decomposition (D) Z-effective image of beef short ribs

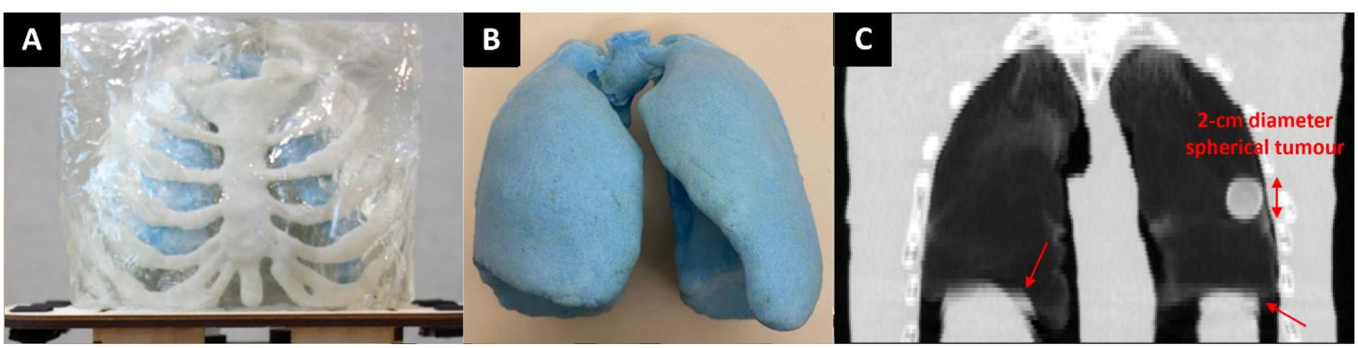

Figure 3: Images of the anthropomorphic thorax phantom designed at the University of Victoria. **A**: Photograph of the assembled thorax phantom. B: Photograph of a pair of foam lungs. **C**: CT images with breathing motion activated: motion artifacts are visible and indicated by red arrows and the spherical tumour has an oval shape.

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LOOPHOLE: LOw dOse PHoton-cOunting for detecting nodules in early Lung cancEr

Lung cancer is currently the deadliest cancer, even exceeding breast cancer mortality. Cancer survival is dependent on the stage of the cancer when diagnosed. Currently, only 1 in 5 people diagnosed with lung cancer are fortunate enough to receive a stage 1 cancer diagnosis and a 60% survival rate while 50% receive a stage 4 diagnosis and a 4% survival rate. Currently lung cancer cases receive twice as many medical assistances in death (MAID) requests than any other cancer type. For most people, detection of lung cancer depends on palpable symptoms such as coughing up blood, clubbed fingers, and unusual lymph nodes rather than regular screening. However, 90% of lung cancers develop irregular structures of poorly formed blood vessels early in their development through angiogenesis. These blood vessels can be highlighted using iodine. However, due to a world-wide iodine shortage, the use of iodine is restricted from being used for screening purposes.

This research is aimed at imaging these blood vessel structures using a low dose photon-counting CT system in two phases. The first phase is to reduce the amount of iodine needed to image angiogenesis in the lung. The second phase is to optimize the soft tissue contrast through effective atomic number imaging to increase the effectiveness of lung cancer screening with low dose CT.

Scientific basis: Recently photon counting detectors have been used in CT for the quantification of angiogenesis. This was performed using a type of material decomposition known as effective atomic number imaging. Paired with and iodine contrast agent angiogenesis can be quantified but the sensitivity is unknown. Effective atomic number imaging can be pushed further to increase soft tissue resolution in CT. This was demonstrated by a study from our lab which managed to distinguish between water, muscle and fat also showing that photon counting has higher precision with this type of imaging than conventional imaging techniques.

Potential impact on the research field: Assessing the limits of visibility of photon-counting detectors for lung imaging in low-dose CT can lead to increases in the detection of early-stage lung cancers. Increasing the sensitivity of low dose CT to iodine, less iodine can be used to achieve the same or better results reducing the impact on the iodine supply freeing up more of this contrast agent for other applications. Additionally pairing artificial intelligence with photon counting low dose CT can increase the soft tissue contrast through effective atomic number imaging improving the effectiveness of screening. This project could revolutionize lung cancer screening by increasing the number of stage 1 lung cancer diagnoses further improving survival.

Since photon counting CT systems are clinically available the findings of this research effort and imaging technique could be implemented on current scan without the need for extra imaging. In the medium term as these detectors become more available these imaging techniques can impact the stage at which the lung cancer is discovered resulting in earlier stages being diagnoses more often.

Impact Statement

Reduction in healthcare burden: Increasing detector sensitivity to finding angiogenesis increases the chance of finding early-stage cancer. Finding more early-stage cancers can range between a quarter and a half of the treatment cost of later-stage diagnoses.

The power of photon-counting imaging is the ability to see the colors/energies of X-ray light in a single exposure, and it is not limited to only two energies. Using CT images from multiple energy bins, specific materials can be isolated for direct visualization. This is particularly effective with contrast agents, as they are designed to stand out. These contrast agents can be used to detect very minor bleeds and early-stage tumor vascularization.

Reduction in lung cancer incidence and mortality: This project could significantly reduce the incidence of late-stage diagnoses by enabling earlier detection of lung cancer, particularly before symptoms like hemoptysis arise. Early detection would lead to more timely interventions, reducing the overall mortality rate. Furthermore, if photon-counting technology can be adapted to low-dose chest X-ray imaging, it could democratize access to effective lung cancer screening, especially in resource-limited settings where low-cost solutions are critical.

Improvement in patient quality of life: The earlier lung cancer is detected, the less aggressive the treatment required, which can lead to better patient outcomes and quality of life. This project could ultimately reduce the burden of late-stage cancer treatments, such as chemotherapy and radiation, which are often associated with severe side effects and. With the potential for more widespread screening and earlier diagnosis, patients could benefit from less invasive treatments, improved survival rates, and overall better health outcomes resulting in fewer MAID requests.

Public non-scientific summary

LOOPHOLE: LOw dOse PHoton-cOunting for detecting nodules in early Lung cancEr

Lung cancer is the leading cause of cancer-related deaths in Canada, responsible for 25% of all cancer fatalities—more than breast, prostate, and colorectal cancers combined. In 2023, over 30,000 Canadians were expected to be diagnosed with lung cancer, and about 20,000 were projected to die from the disease. This high mortality rate is primarily due to late diagnoses, as lung cancer is often detected at advanced stages when treatment options are limited.

Early detection is key to improving survival rates. **Low-Dose Computed Tomography (LDCT)** is the primary screening tool for lung cancer. With its use in lung cancer screening, mortality has been reduced by 24%. Low-dose CT uses less radiation than standard CT scans but provides similar diagnostic capability. Detecting lung cancer at an early stage is crucial for increasing survival rates. If diagnosed at stage 1, the five-year survival rate is about 60%. Unfortunately, only about 1 in 5 cases are caught this early, partly due to the limited detection capabilities of conventional LDCT screening.

Recent advancements, such as **photon-counting detectors (PCDs)**, are improving the effectiveness of LDCT. Recently approved by the U.S. Food and Drug Administration (FDA), these new detectors can colorize x-ray images. Through these colorized images, PCDs have the potential to make lung cancer screenings even more accurate by dividing materials into separate images.

An essential indicator of early-stage lung cancer is the growth of a network of poorly formed blood vessels, also known as angiogenesis, surrounding a growing tumor. Although not all lung cancers undergo angiogenesis, this occurs in about 90% of cases when a tumor grows past 2mm in diameter. At this point, the cancer signals the growth of new blood vessels. In other studies, it has been shown that using **Iodine can identify these vessels**, showing the extent and location of the cancer. However, a global iodine shortage restricts the use of iodine from screening imaging. With their high sensitivity, photon-counting detectors may further improve the ability to detect small tumors using these contrast agents and, combined with AI techniques, could reduce or eliminate the need for iodine when looking for angiogenesis.

Our recent research has demonstrated the capability of PCDs to colorize tissues of the body and water without iodine; however, applying this to more complicated objects such as the lung will require AI assistance. These advancements in screening technology offer hope for improving early lung cancer detection. More stage 1 diagnoses and fewer stage 4 diagnoses will inevitably increase survivability and survival rates by making screenings more accessible and accurate for patients.

Budget

The total requested budget is $50,000 for 12 months (April 2025 – March 2026). The distribution of funds for HQP and other items is listed below and briefly described in the text proceeding the table.

Item	Justification	Cost
Wages (HQP)		
Co-op student or intern wages (three terms)	CT acquisitions, data analysis, image processing technique development	$ 23,971.50
Phantom		
Casper lung phantom	3D printing of a high-quality phantom with multiple configurations	$ 15,000.00
Pig lung	Pig lung outsourced from local butcher shops	$ 500.00
Mechanical pump	For simulating lung ventilation during CT scans	$ 400.00
Peristaltic pump	For blood flow simulation during CT scans	$ 400.00
Other consumables	Cannulas, tracheal tube, blood substitute solution	$ 700.00
Custom components for the mechanical setup	This covers the expenses of manufacturing custom components for the mechanical setup, such as stands or mounts for the phantom	$ 2,000.00
Iodine Contrast Agent	Contrast media used in CT scans to enhance the visibility of vasculature of the phantom	$ 1,000.00
Software/Hardware		
GPU or cloud platform	Accelerating image processing and analysis	$ 4,000.00
Other expenses		
Conference travel & publications	We intend to publish the results of the project in scientific conferences and peer-reviewed journals.	$ 1,000.00
Miscellaneous cost	General lab supplies	$ 1,028.50
TOTAL :		**$ 50,000.00**

The co-op students and interns will be selected from disciplines with relevant training, such as physics and biomedical engineering. Each undergraduate research assistant will be compensated at $22.83/hour (UVic recommended rate including Mandatory Employment Related Costs) for a total of 350 hours over the 12-month duration of the project. $22.83 x 350 x 3 = $23,971.50. This project is ideal for students to learn about the field of medical physics, and they will also have research responsibilities.

University of Victoria

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February 5, 2025

Lung Cancer Canada
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Dear Lung Ambition Awards Review Committee,

On behalf of the University of Victoria, I am pleased to provide this letter of support for Dr. James Day, Dr. Xinchen Deng and Dr. Magdalena Bazalova-Carter's application entitled LOOPHOLE: LOw dOse PHoton-cOunting for detecting nodules in early Lung cancEr. Upon successful completion of the project, the team will have reduced the amount of iodine needed to quantify angiogenesis in the lung and developed a method of increasing soft tissue delineation to visualize small nodules using current screening methods.

I confirm that the proposed research is feasible to conduct here at the University of Victoria. In the XCITE lab, the investigators have access to resources and equipment that are necessary to carry out this project, such as a photon-counting CT system, 3D-printed phantoms, and a supply of iodine contrast agent. James Day and Xinchen Deng are postdoctoral fellows, supervised by Dr. Bazalova-Carter, in the departments of Physics and Astronomy. Dr. Bazalova-Carter meets all the requirements as a researcher as defined in eligibility criteria for this research grant.

We look forward to a successful outcome.

Sincerely,

Fraser Hof, PhD
Associate Vice President Research
University of Victoria