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To the members of the Geoffrey Ogram Memorial Research Grant 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 hemoptysis as an indicator of early-stage lung cancer. As lung cancer remains the leading cause of cancer-related deaths in Canada and globally, early diagnosis is critical to improve patient survival rates by treating cancer at early stages. Hemoptysis or cough of blood is often an early-stage indicator of lung cancer. Photon-counting technology holds promise for improving diagnostic imaging quality at lower radiation doses. We are requesting $25,000 over one year to conduct this project.

In our study, we will investigate the potential of photon-counting detectors as different screening techniques, including low-dose CT (LDCT), planar radiography, and contrast-enhanced imaging using both iodine and gadolinium contrast agents. 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. M. Bazalova-Carter, 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 in detecting iodine contrast at low radiation doses in phantoms with lung-like structures, and we anticipate further improvement when employing gadolinium. The study will be primarily conducted by post-doctoral fellows Dr. James Day and Dr. Xinchen (Alison) Deng, who bring extensive experience in photon-counting detector imaging.

The study will involve two stages: first, using an anthropomorphic lung phantom developed at the X-ray Cancer Imaging and Therapy Experimental (XCITE) lab at the University of Victoria, and second, using an excised animal lung model. The phantom, nicknamed "Casper," will be modified to include contrast-enhanced regions, while excised pig lungs, known for their anatomical similarity to human lungs, will be used for further investigations.

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 screening for hemoptysis in early Lung cancEr**

Lung cancer is the leading cause of cancer deaths worldwide, constituting over a quarter of cancer cases.[1] Current treatment protocols require several stages of screening for palpable symptoms such as bleeding in the lungs (coughing up blood), clubbing in the fingers, suspicious swelling in the lymph nodes, and long-lasting anemia before diagnostic imaging is performed.[2] 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, since only 1 in 4 people are caught in this stage [3] the actual survival rate is 26.7%. Low-dose CT is the primary method of lung cancer screening. It has been effective in doing so with an 88% sensitivity and a 92% specificity;[4] however, it is restricted to ages 55 to 80 with 30-pack years.[1] Chest radiography is more available and much cheaper than CT; however, the sensitivity is comparably poor for lung cancer detection when using conventional imagers.[4]

Hemoptysis, or bleeding of the lungs, is a common indicator for malignancies constituting 27% of early-stage lung cancer cases. [5] Early detection of hemoptysis is often associated with a diagnosis of lung cancer in the early stages where survival rates are around 60%. Contrast agents, such as iodine, can accumulate in blood pools surrounding tumors, improving tumor visibility. Using photon counting imaging, it is possible to extract the iodine signal from the rest of the tissue, increasing tumor visibility.

Iodine for contrast-enhanced radiography is used for most cancers that display vascularization, as well as in angiography. Angiography, much like lung imaging, uses higher tube voltages in regular imaging practices. Iodine as a contrast agent is not the optimal contrast agent for this type of radiography since the contrast-increasing benefits are underutilized by these spectra, unlike in mammography. Gadolinium has been used as the standard contrast agent for MRI; however, it has also seen some success in pilot studies for angiography with high sensitivities of 87% and specificity of 98%[6] but is not currently used in most angiography cases since it is not significantly beneficial as iodine will yield an 83% sensitivity and a 100% specificity due to the high concentrations used in angiography.[7]

Dual-energy techniques using conventional CT detectors have been employed for contrast-enhanced lung imaging in the past. The study found that dual-energy imaging of iodine corresponded with a sensitivity of 75% and specificity of 76% for iodinated lymph nodes.[8] Since this study, a new class of detectors called photon counting detectors have been used to create CT imaging systems. These detectors can colorize the X-ray spectrum, allowing them to perform multi-energy techniques without the need for kVp switching, a secondary imaging system, or multiple detector layers. These detectors have since seen clinical comparisons to conventional CT detectors, displaying image quality improvement for lung imaging.[9] For low-dose CT, a similar comparison is likely to be observed; however, it is unknown what sort of improvements will be observed when looking at contrast-enhanced imaging. For lung imaging, Gadolinium may lead to an improvement over iodine, considering the already low sensitivity seen with iodine.

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 XCITE lab proposes a study to quantify the potential of photon counting detectors for the detection of hemoptysis in a) low-dose CT (LDCT) and b) for a planar radiograph, and c) contrast-enhanced planar and low-dose CT using Iodine and Gadolinium.

In this project, we propose a two-stage approach. The first stage utilizes an **anthropomorphic lung phantom** designed at the XCITE lab, and the second involves an **ex vivo animal lung model** for further investigation. The XCITE lab has developed a breathing anthropomorphic thorax phantom, nicknamed "Casper" (as shown in Figure 2), which simulates the attenuation properties of a human lung. This model will be modified to include custom lesions enhanced with **iodine and gadolinium contrast agents**. For the second stage, **excised pig lungs** will be used, as they closely resemble human lungs in both anatomy and physiology, making them ideal for studying lung mechanics, diseases, and therapeutic interventions. An ex vivo perfusion and ventilation system will be established, with the lungs perfused using a physiological solution such as Krebs-Henseleit buffer and ventilated by a mechanical ventilator. **Contrast agents** will be administered to the perfusate and circulated through the lungs, enhancing the imaging of pulmonary vasculature.

The **X-ray Cancer Imaging and Therapy Experimental (XCITE)** lab, led by **principal investigator (PI)** 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 Redlen 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. The proof-of-concept experiments were performed by two **co-PIs** for this project, post-doctoral fellows Dr. James Day and Dr. Xinchen (Alison) Deng, who have ample experience in photon-counting detectors. To demonstrate the system's capabilities, we imaged a loaf of sourdough bread, used as a stand-in for lung tissue, before and after injecting it with 0.2 mL of 10 mg/mL iodine contrast agent. Even at the lower doses typical of low-dose CT, the system's resolution remains comparable to that of standard chest CT. Additionally, by properly weighting multi-energy images, the rest of the bread structure is effectively suppressed, allowing the iodine to be clearly visualized, demonstrating the system's capacity for enhanced contrast detection.

APPENDIX

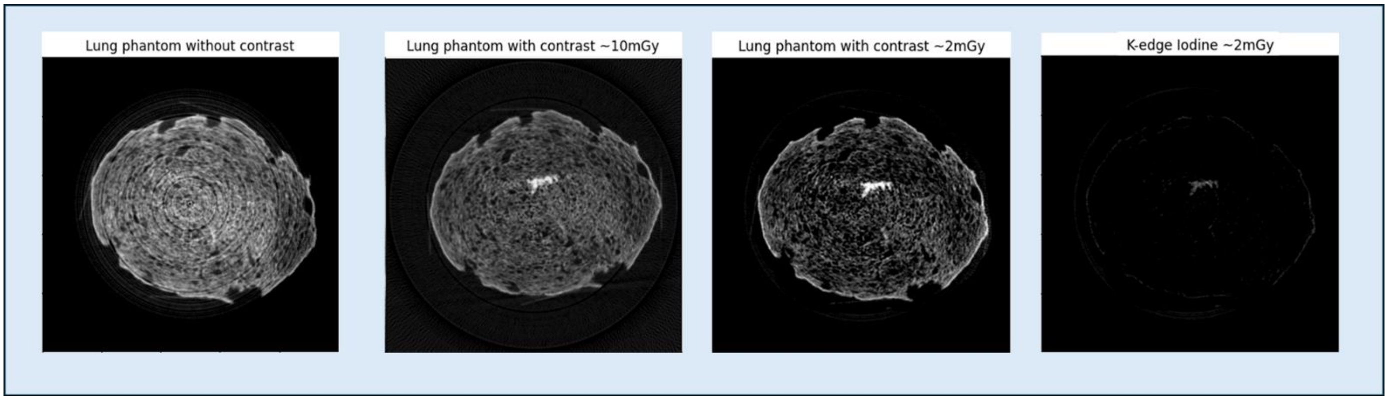

Figure 1: Sourdough used as a lung imaging demo. A) is without contrast agent B) and C) are with 0.2ml of injected iodine with 10ml/mg concentration D) is produced through weighted log subtraction. The scale of the images are 10cm by 10cm.

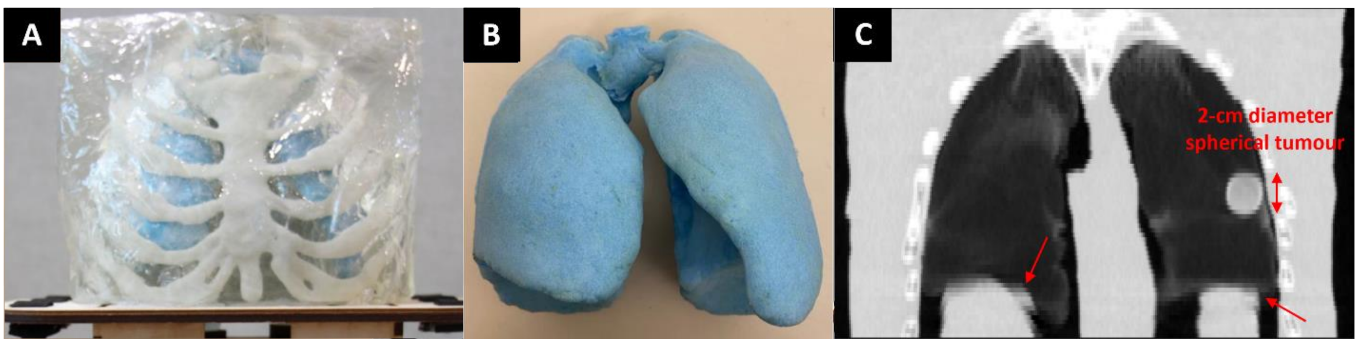

Figure 2: Images of the anthropomorphic thorax phantom designed at the University of Victoria. **A**: Photograph of the assembled thorax phantom. B: Photograph of a pair of foam lungs. **C**: CT images with breathing motion activated: motion artifacts are visible and indicated by red arrows and the spherical tumour has an oval shape.

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Impact Statement

LOOPHOLE: **LOw dOse PHoton-cOunting screening for hemoptysis 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 4 people diagnosed with lung cancer are fortunate enough to receive a stage 1 cancer diagnosis and a 60% survival rate. 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. Regular screening using chest X-rays has been shown to provide limited information. At the same time, low-dose CT is regularly successful at detecting malignancies, although its availability is limited due to much higher costs.

This research is aimed at imaging the minor bleeding of the lungs, which accounted for 27% of cases, using dose contrast-enhanced photon-counting options such as low-dose CT and chest X-ray imaging. Like in other vascular cancers, these bleeds should be traceable with a contrast agent and may be visible in an imaging system before palpable symptoms occur, leading to a stage 1 diagnosis.

Potential impact on the research field: Assessing the limits of visibility of photon-counting detectors for lung imaging in both CT and chest X-rays has the potential to address critical gaps in lung cancer screening technology. By rigorously assessing the limits of visibility of photon-counting detectors, our research could offer a significant advancement in the precision of lung cancer diagnostics, detecting more minor bleeds and using lower radiation doses. This project could revolutionize lung cancer screening by making early detection accessible to a larger population, similar to the impact of mammography in breast cancer screening.

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. 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.

Public non-scientific summary

LOOPHOLE: **LOw dOse PHoton-cOunting screening for hemoptysis 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 largely 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. Screening programs in provinces like Ontario and British Columbia focus on high-risk individuals—current and former smokers aged 55 to 74 who have smoked for at least 20 years. **Low-Dose Computed Tomography (LDCT)** is the primary screening tool for lung cancer. It uses less radiation than standard CT scans, reducing potential harm while still providing detailed images that can detect small nodules or abnormalities before symptoms appear. This early detection allows for more effective treatment and can significantly improve outcomes.

Recent advancements, such as **photon-counting detectors (PCDs)**, are improving the effectiveness of LDCT. These new detectors, recently approved by the U.S. Food and Drug Administration (FDA), produce clearer images while further lowering radiation exposure. PCDs have the potential to make lung cancer screenings even safer and more accurate, improving the balance between image quality and patient safety.

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 4 cases are caught this early, partly due to limited access to LDCT screening. LDCT scans are much better than regular chest X-rays at spotting lung cancer. LDCT can identify cancer in 88% of cases, compared to 78% for chest X-rays (sensitivity). This makes LDCT more effective for finding cancer early. However, because LDCT is very sensitive, it may sometimes result in follow-up tests for findings that turn out not to be cancer, but it still correctly rules out cancer in 92% of cases (specificity).

An important indicator of early-stage lung cancer is **hemoptysis**, or coughing up blood, which occurs in about 25% of cases. This can happen when a tumor grows and causes bleeding in the lungs through malformed blood vessels. **Iodine contrast agents**, commonly used in other cancer screenings like breast cancer, could also be useful for detecting lung cancer by highlighting tumors and showing the extent of the disease. Photon-counting detectors, with their high sensitivity, may further improve the ability to detect small tumors using these contrast agents.

These advancements in screening technology offer hope for improving early lung cancer detection and, in turn, survival rates, by making screenings more accessible, accurate, and safer for high-risk individuals.

Budget

The total requested budget is $25,000 for 9 months (December 2024 – August 2025). The distribution of funds for HQP and other items is listed below and briefly described in the text proceeding the table.

	Item	Justification	Cost
HQP	Co-op student or intern wages	CT acquisitions and data analysis	$12,000
Phantom	Caspr lung phantom	3D printing of a high-quality phantom with multiple configurations	$4,000
Ex vivo lung model	Pig lung	Pig lung outsourced from local butcher shops	$500
	Mechanical pump	For simulating lung ventilation during CT scans	$400
	Peristaltic pump	For blood flow simulation during CT scans	$400
	Other consumables	Cannulas, tracheal tube, blood substitute solution	$700
Machine shop cost	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	$1,000
Contrast agents	Iodine and gadolinium	Contrast media used in CT scans to enhance the visibility of vasculature of the phantom	$2,000
Computing Cost	GPU or cloud platform	Accelerating image processing and analysis	$4,000
	Total		$25,000

Two undergraduate students will be hired to support this project. The students will be selected from disciplines with relevant training, such as physics and biomedical engineering. This project is ideal for students to learn about the field of medical physics, and they will also have research responsibilities.

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September 26, 2024

Lung Cancer Canada
Geoffrey Ogram Memorial Research Grant
133 Richmond St. W., Suite 208
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To the Geoffrey Ogram Memorial Research Grant review committee,

On behalf of the University of Victoria, I am pleased to provide this letter of support for James Day and Xinchen(Alison) Deng's application entitled **LOOPHOLE: LOw dOse PHoton-cOunting screening for hemoptysis in early Lung cancEr**. Upon successful completion of the project, the team will have preliminary evaluation results on using photon counting detectors in imaging techniques for early-stage lung cancer to publish in peer-reviewed journals or conferences.

I confirm that the proposed research is feasible to conduct here at the University of Victoria. James Day and Xinchen(Alison) Deng are postdoctoral fellows, supervised by Magdalena Bazalova-Carter, in the Department of Physics & Astronomy. Magdalena Bazalova-Carter meets all the requirements as a researcher as defined in the eligibility criteria for this research grant.

Magdalena Bazalova-Carter, James Day and Xinchen(Alison) Deng will have full access to facilities and services required to achieve the deliverables of this project within the proposed 1-year study period.

We look forward to a successful outcome.

Sincerely,

Fraser Hof, PhD
Associate Vice President Research
University of Victoria