Title: Review of an initial experience with an experimental spectral photon-counting computed tomography system

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Abstract

Spectral photon-counting CT (SPCCT) is an emerging X-ray imaging technology that extends the scope of available diagnostic imaging tools. The main advantage of photon-counting CT technology is better sampling of the spectral information from the transmitted spectrum in order to benefit from additional physical information being produced during matter interaction, including photo-electric and Compton effects, and the K-edge effect. The K-edge, which is specific for a given element, is the increase in X-ray absorption of the element above the binding energy between its inner electronic shell and the nucleus. Hence, the spectral information contributes to better characterization of tissues and materials of interest, explaining the excitement surrounding this area of X-ray imaging. Other improvements of SPCCT compared with conventional CT, such as higher spatial resolution, lower radiation exposure and lower noise are also expected to provide benefits for diagnostic imaging. In this review, we describe multi-energy CT imaging, from dual energy to photon counting technology, and our initial experience results using a clinical-scale spectral photon counting CT (SPCCT) prototype system *in vitro* and *in vivo*. In addition, possible clinical applications are introduced.

Keywords:

Spectral photon-counting computed tomography, gold nanoparticles, K-edge imaging, contrast agent, dual contrast imaging, clinical applications.

Abbreviations

ASIC: application specific integrated circuit

CNR: contrast-to-noise ratio

CT: Computed tomography

DECT: Dual energy computed tomography

EID: energy integrating detector

HU: Hounsfield units

MRI: magnetic resonance imaging

SPCCT: spectral photon-counting computed tomography

PET: positron emission tomography

PCD: photon-counting detectors

1. Introduction

Computed tomography (CT) is currently one of the key imaging modalities in clinical use. The number of CT scans performed worldwide per year is now numbered in the hundreds of millions (1). It is available in standard and emergency settings nearly everywhere in the world, with applications in the diagnosis of many different conditions and injuries. It provides three-dimensional images of the linear attenuation coefficient distribution within a patient, accurately delineating organs and tissue. However, there are five major limitations to current CT technologies with current contrast agents: 1) Spatial resolution (around 0.5 mm), even if better than other non-invasive technologies such as MRI or PET, is still a limitation for assessment of small structures such as the lumens of coronary arteries and atherosclerotic plaques. 2) Contrast between different tissues or materials is often insufficient, especially for soft tissue, because CT images are not tissue-type specific. Indeed different tissue types often have similar attenuation values. 3) X-ray attenuation measured by CT and expressed in Hounsfield Units (HU) does not allow an absolute quantification of the contrast agent injected, e.g. iodine, since it combines the attenuation of the contrast material to be quantified and the attenuation of the underlying tissue. Furthermore, the attenuation of a material depends on the energy of the X-rays spectrum used. 4) CT scanning is a relatively high radiation-dose procedure. In general, its use is therefore mostly for diagnostic imaging and is limited for screening of large populations or repeated examinations in the presence of a chronic disease. 5) Iodine-based contrast agents currently in use are not specific and thus do not detect or monitor pathologic processes in patients in a targeted fashion. These limitations impair the diagnostic performance of CT in all medical fields where CT is applied.

A recent, notable development in the field of CT is the analysis of spectral information of the X-rays that have passed through the subject. Although this concept has been discussed since

CT was invented (2–4), the technology to accurately record this information has only become available over the past decade. Conventional CT scanners integrate all the signals from the detected transmitted X-ray photons into a single attenuation signal without recording any information on their individual energies (Fig 1A). A variety of systems that are given the term dual-energy CT (DECT) and use energy-integrating detectors (EIDs) have been introduced clinically that begin to exploit the benefits of spectral detection by acquiring two energetically distinct datasets (Fig 1B,C). Nevertheless, DECT systems do not typically have improved spatial resolution compared to single energy CT scanners, which is still limited by the scintillators used to convert photons into light that spread the signal spatially, and by the noise resulting from the signal integration process and the associated detection electronics. Furthermore, DECT systems only perform a two-point analysis of the X-ray attenuation, which improves tissue characterization and allows quite precise iodine quantification, but is insufficient to accurately discriminate between iodine and calcium, especially at low radiation dose. In addition, many DECT systems expose the patient to two energy beams that can result in potentially high radiation exposure, and motion can create issues for aligning the two datasets. Finally, no specific contrast agent has been developed for DECT due to the lack of sensitivity of such systems for specific material imaging (5).

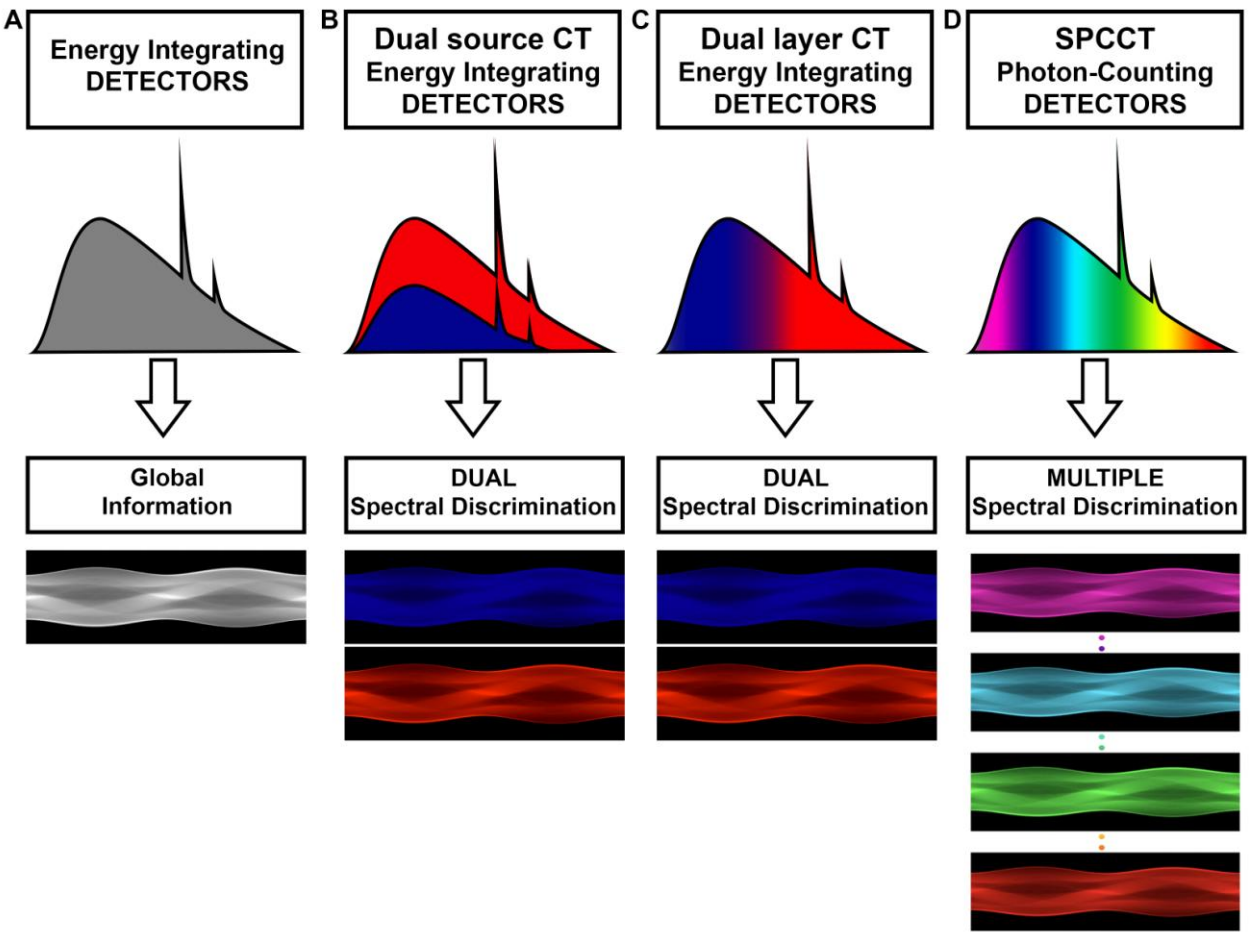


Figure 1. Representation of the information provided by the energy integrating detectors in single energy CT systems (A), dual source DECT systems (B) and dual-layer detector based DECT systems (C), compared to SPCCT systems that allow several datasets to be derived from a transmitted spectrum (D).

Recently, systems based on photon counting detectors (PCDs), termed spectral photon-counting detectors CT (SPCCT) or multicolor SPCCT (6), have been introduced in the field of CT imaging (Fig. 1D). These PCDs are the subject of ongoing research and development in CT systems (5,7–10). They have the capability of energy discrimination based on analysis of the pulse height of each detected photon of the transmitted x-ray spectrum and the count of their

number above different energy thresholds or in multiple energy windows (7). The number of energy bins (windows) depends on the design of the detection chain of the PCDs, and the energy thresholds can be selected depending on the chosen application. Hence, the transmitted spectrum is divided into several energy bins leading to better sampling of the X-ray spectrum than DECT. This characteristic allows detection of K-edges within certain energy windows and to distinguish simultaneously between different attenuation profiles, for instance those specific to different contrast agents, allowing multi-contrast agent imaging (6). In addition, due to their architecture and detection mechanism, PCDs can provide improved spatial resolution and reduced radiation dose compared to conventional CT (11). Although all these advantages have the potential to improve the five intrinsic limitations of the conventional CT imaging described above, SPCCT systems face technical challenges such as handling the high photon flux used in CT (approximately 10^9 counts/sec/mm^2) (5).

SPCCT systems are being investigated for CT applications as the next step to derive more information from transmitted X-ray photons. In this review, we describe the field of clinical imaging using DECT systems and experimental spectral photon counting technology and the results of our initial experience using a pre-clinical spectral photon counting CT (SPCCT) in vitro and in vivo. In addition, possible SPCCT clinical applications are introduced.

2. Multi-energy CT imaging

With single energy CT imaging systems, tissues and materials can have the same attenuation values (i.e. Hounsfield unit values) despite having different compositions, based on their mass density (12), leading to a potential misclassification of pathologies, e.g. in differentiation between hemorrhage and tissue in a kidney cyst, or in separating calcified plaques from the lumen of vessels filled with iodine. Pitfalls such as these have encouraged the development of multi-energy

CT imaging techniques, based on acquiring more than one dataset from energetically distinct X-ray spectra. The first technology based on a multi-energy approach that has been translated to clinical use is DECT imaging. SPCCT is a next generation, multi-energy technology that is being seriously considered for clinical translation, with the first report of SPCCT scans of patients being recently published (13).

2.1. DECT systems

This term is typically used for techniques making use of two datasets that are derived from energetically distinct X-ray spectra in order to differentiate between different materials. Well-known implementations include emission based dual energy CT: dual-source CT (14–16), various implementations of kVp-switching from view-to-view during the CT acquisition (17–19), and detection based dual energy CT: i.e. dual-layer detector CT (20). All these forms of DECT use EIDs. DECT enables two-material basis set decomposition techniques and a number of applications inaccessible to conventional CT. New image types that are often available from DECT systems include basis material images of iodine and water, soft-tissue and bone-images, and virtual mono-energy (MonoE) images (Fig 2) (12,21,22).

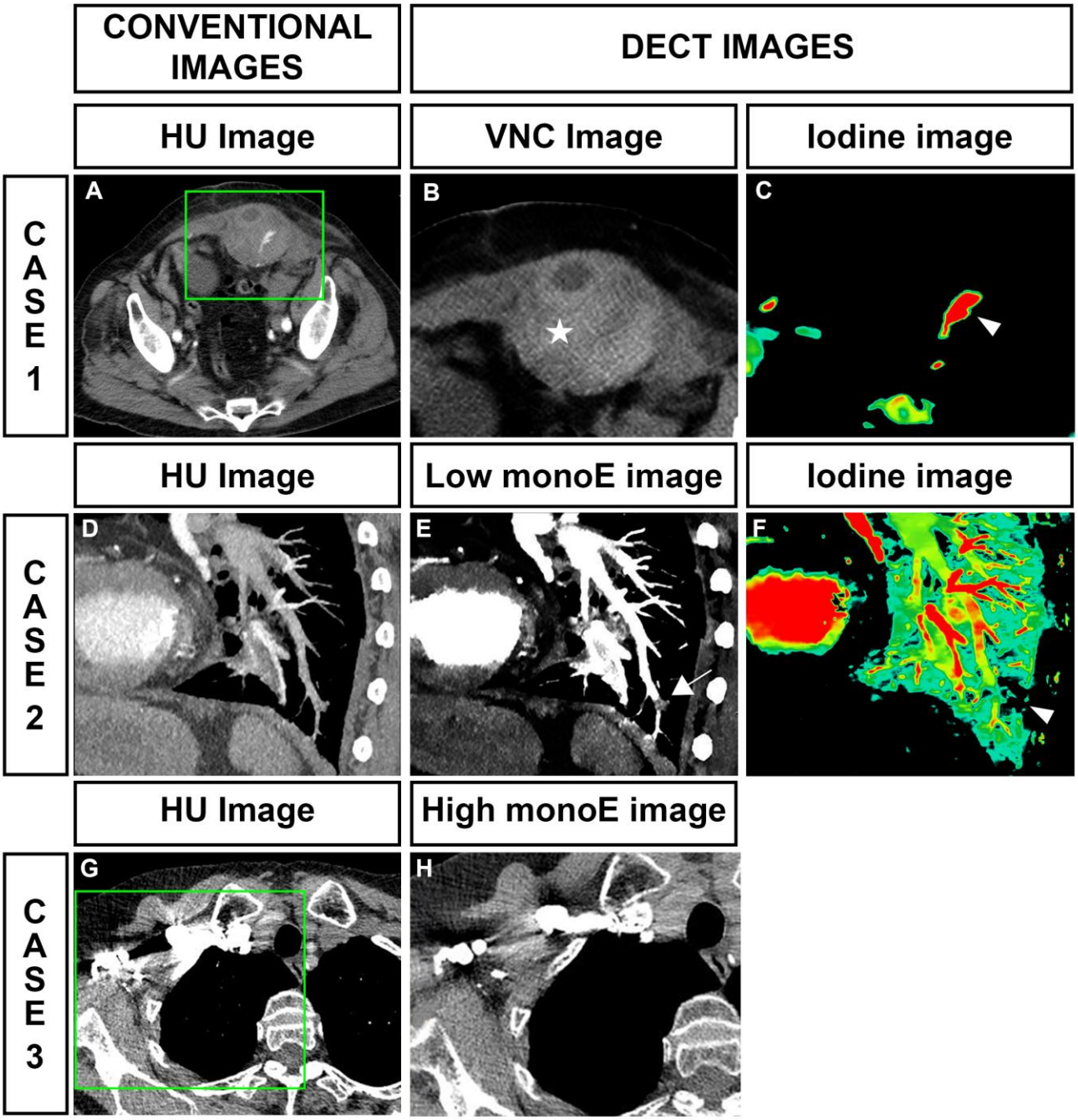


Figure 2. Examples of dual energy CT images. Case 1: In the conventional image (A) iodine cannot be discriminated from blood, but can be in the Virtual non enhanced (VNC) (B) and iodine images (C) where blood is highlighted with a star and iodine suffusion with an arrowhead. Case 2: The conventional image (D) didn't allow the diagnosis of a distal pulmonary artery thrombus due to imperfect opacification of the blood. However, the iodine image (E) revealed a

defect of perfusion in the lung (arrowhead) indicating a pulmonary embolism, confirmed by the low kV (40 kV) monoenergetic images (F) that showed the thrombus due to stronger contrast in the pulmonary arteries (arrow). Case 3: The conventional image (G) has a substantial beam hardening artifact from the opacification of the subclavian vein, whereas the high (140 keV) mono-energetic image allowed a reduction of this artifact (arrowhead).

Iodine/water basis images are better known in the community as iodine maps and virtual-non-contrast images (VNC) (Fig 2A-C). The latter basis pair ideally separates the attenuation caused by atoms with an attenuation behavior like iodine (high atomic number with high photoelectric/Compton ratio) from attenuation caused by tissue material with attenuation behaviors similar to water (low atomic number with low photoelectric/Compton ratio). Nevertheless, current dual energy techniques have two main limitations in the accurate formation of VNC/iodine map image pairs (23): 1) the two energy spectra, emitted and/or detected, have significant overlap and only provide moderate energy resolution; 2) the two energy spectra are not necessarily acquired precisely the same time and/or spatial location (not taken at the same azimuthal or axial position), except for detection based DECT. Another important imperfection of dual-energy iodine maps is contamination with attenuation arising from calcium-rich structures such as bones or calcifications, resulting from the previously mentioned limitations of DECT and the material decomposition technique making calcium shared between iodine and water images due to its intermediate attenuation behavior. In particular, in coronary CT angiography, the issues with differentiation between the contrast agent filled lumen and heavily calcified plaque compromise diagnosis.

In clinical use, the main benefits of iodine/water material decomposition from DECT are currently the possibility to avoid the non-enhanced scan leading to a dose reduction by using

VNC for some applications, and on the other hand to get direct quantification of iodine tissue perfusion independently of the tissue density. This enables many clinical applications such as better and easier pulmonary embolism detection through lung perfusion defect detection (Fig 2D-F), or tumor perfusion quantification for oncology follow-up. Some other material characterization applications already in use include detection of uric acid and calcium for renal stone or gout analysis. Another major imaging functionality enabled by DECT is the display of virtual mono-chromatic CT images, i.e. images of the linear attenuation coefficient $\mu(E)$ at a single energy chosen by the radiologist (Fig 2). This functionality offers the possibility to increase iodine contrast with low energy virtual monoE images, to better detect some lesions or reduce the amount of iodine injected, or to reduce metal artifacts in the images using high energy monoE images (Fig 2G,H), and to reduce beam hardening artifacts (22).

In practice, and for all current dual-energy implementations, the 2D material decomposition from two energetically different measurements constitutes mathematically an ill-conditioned inverse problem in which higher imaging specificity is obtained at the cost of increased image noise (24). This is a well-known and reported problem. Energy-resolving photon-counting detectors will not change the fact that spectral material-decomposition remains a weakly-conditioned inverse problem, but offer the potential to significantly improve the mathematical conditioning, which will result in lower basis material noise (25).

2.2. SPCCT systems

SPCCT can be considered an extension of the detection based dual-energy CT technology (12) (Fig 1C), but with completely different detector technology. In this system, each X-ray photon is absorbed in the sensor and produces a small charge cluster (~2 fC or 10 000 electrons with ~100 μm spread) that can be collected by pixelated electrodes connected to individual

electronic readout channels in an application specific integrated circuit (ASIC). This technique has many advantages over conventional CT detectors, i.e. individual photon counting and photon energy discrimination, the absence of electronic noise (due to the lower threshold discriminating between electronic noise and X-ray pulses), the improved spatial resolution because of small charge cluster size and the absence of electronic noise allowing reduced pixel size, the size compared to scintillator and photodiode conventional CT detectors, the absence of dead space between detectors (26).

Hence, SPCCT technology allows the discrimination of the energies of individual photons enabling advanced material characterization tasks, which are only partially provided by dual-energy techniques. While the number of independent readings per frame and detector pixel in conventional CT, or DECT is limited to one, or two respectively, in SPCCT it is mainly limited by the number of energy thresholds implemented in the ASICs hardware per channel (Fig 1C). In practice the number of thresholds used in SPCCT systems that have been reported range from four to eight (13,27). This, of course, provides the ability to better differentiate between different tissue types, even if the number of thresholds needs to be adapted to the intrinsic energy resolution and low-energy tailing behavior of the spectral detectors. Thus, the biggest advantage of SPCCT over DECT is the improved spectral sampling because of intrinsic energy resolution and energy windowing functionality absent in all DECT (7,12). SPCCT is expected to outperform dual energy techniques because of the following potential benefits: 1) Better spatial resolution, with a higher modulation transfer function in the usual range 0-15 lp/cm and significant strength in the extension to 25 lp/cm because of the smaller pixel size of PCDs. Consequently, this is leading to sharper edges and better delineation of structures in reconstructed images, with the additional value of decreasing the partial volume effects from small objects. 2) Improved contrast-to-noise ratio images due to the reduction of noise at low dose since photon counting

does not have a noise floor from electronics and lower statistical noise due to counting versus integration compared to the EIDs (27). 3) Reduced radiation dose and/or contrast media volume, due to the improved contrast to noise ratio of contrast-enhanced tissues at a given dose.

In addition, SPCCT is expected to present the following new capabilities: 1) The possibility to decompose more than 2 basis materials from multiple energy bins, enabling simultaneous multi-agent imaging. 2) Absolute quantification of specific contrast materials. Indeed, PCDs allow an exact physical representation of pixel values, with quantitative information processed by the SPCCT system from the spectrum transmitted through the subject. This allows measurement of the absolute concentration of targeted or non-targeted contrast media in regions-of-interest. 3) The possibility to map K-edge materials by using specific reconstructed images (7,28,29). Image reconstruction in SPCCT has been a topic of intense research in the last decade, in particular when it was realized that the discrimination of energies of individual photons allows not only to selectively image, but to also quantify the concentrations of contrast agents based on elements with high-atomic numbers. This approach, called K-edge imaging, is based on the detection of the strong attenuation variation due to photoelectric effect at the specific binding energy of the K shell electron of an atom (e.g. 50.2 keV for gadolinium, 80.7 keV for gold). K-edge imaging allows measuring the absolute concentration of the targeted material used.

Lastly, similar to DECT systems, SPCCT allows reconstruction of mono-energetic images at desirable energies leading to an increase of the contrast of high atomic number materials at low kilovoltage due to the photoelectric effect.

However, certain limitations that are intrinsic to this technology have to be considered. Photon-counting detectors cannot function accurately with high count rates. Indeed, high count rates (i.e. high photon flux) can result in frequent instances of 2 photons being absorbed very

close together in time and being incorrectly counted as a single photon with an energy equal to the sum of the energy of both photons. This effect, called electronic pileup, results in reduction of the energy resolution and impacts image quality (5,7,30,31). Hence, it explains the interest in having fast readout electronics and small detector pixels in order to decrease the count rate per pixel. However, reducing the pixel size too much can lead to an increase of another limitation of PCDs that is called charge sharing, i.e. the electron charge cloud caused by photon absorption in the detector being shared between two nearby pixels, also causing distortions in the spectral response. Research teams and manufacturers have made some different technologic choices and compromises (7) in order to build SPCCT systems that are being investigated in the pre-clinical field such as the camera and the MARS spectral scanner (32) and the system developed by Danielsson et al. (9), or in the clinical field (27).

Over the past ten years, the field of SPCCT imaging has been subject of significant research and development. In 2007, Roessl and Proksa demonstrated the additional value of the spectral information using simulated images of an atherosclerotic coronary vessel filled with a gadolinium-based contrast agent (29). In 2008, Shikhaliev showed the first experimental results using SPCCT using x-ray energy weighting to form images that confirmed the improvement of CNR (10) due to the intrinsic architecture of the photon-counting detectors as we discussed above. The same year, Feurlein *et al* demonstrated the potential for improved luminal depiction in vascular imaging with SPCCT using the additional values of the monoenergetic images and the K-edge imaging of gadolinium in vitro (33). Meanwhile, Firsching *et al* demonstrated spectral discrimination of an iodine contrast agent in a small animal CT scanner using the Medipix2 PCD (34) supporting the feasibility of contrast agent imaging using SPCCT. In 2010, Fredenberg *et al* showed that contrast-enhanced spectral mammography was feasible and beneficial by drastically improving the signal noise ratio of breast tissue-like phantom (35). The same year, Cormode *et al*

demonstrated the spectral capabilities of SPCCT by using gold nanoparticles and an iodine contrast agent simultaneously. The gold nanoparticles were targeted to the macrophages of atherosclerotic plaque due to a coating similar to HDL and were well visualized, accumulating in the plaques of a mouse model of atherosclerosis, whereas the iodine contrast agent could be discriminated in the blood and calcified structures also distinguished at the same time (6). This study highlights the use of candidate contrast agents for SPCCT imaging, as Pan *et al* demonstrated with bismuth and ytterbium based nanoparticles (36,37) and as Schirra *et al* confirmed with gold nanoparticles (38). In addition, recently, SPCCT has been tested in vitro for dual contrast colonography using iodine-filled lumen and gadolinium-tagged polyps allowing a potential differentiation between polyps and tagged fecal material (39).

In this context, SPCCT is a promising new tool that could assess lesion characteristics beyond what is currently achievable with conventional CT or MRI, with accurate quantification and the possibility of using targeted contrast agents. Furthermore, the accurate absolute quantification opens the way to functional imaging. Recently, the first patients have been scanned using this technology for abdominal imaging without any use of contrast media (13), endorsing the concept that PCDs have a role to play as a next generation of CT systems.

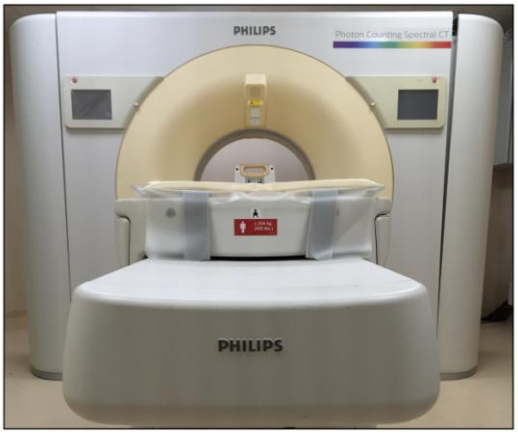
3. Preliminary results using a spectral photon-counting CT prototype system

3.1. Experimental SPCCT prototype

A prototype spectral photon-counting computed tomography system derived from a modified clinical CT with a small field-of-view (FOV) is being tested in our center (Fig 3A). It allows in vivo acquisitions with a temporal resolution of 0.75 second (Fig 3B). For each single acquisition, we reconstructed multiple image types, i.e. images equivalent to conventional CT images, and the

specific material images that we were interested in, such as water, iodine and K-edge gadolinium images with a material decomposition process based on a maximum-likelihood method (28, 29).

A



B

Parameter	Scanner Specifications
Base Platform	iCT
Tube Voltage	80, 100, 120 kVp
Tube Current	10-100 mA
Acquisition Modes	Axial, Step and Shoot, Helical
Z-Coverage	2 mm
FOV	168 mm
Minimum Rotation Time	0.75 sec/rotation

Figure 3 (A) Photograph of the SPCCT system. (B) Characteristics of the current system.

3.2. Contrast agent imaging

SPCCT is expected to require less contrast material to be administered to patients than the currently used amounts due to a better contrast to noise ratio (CNR) (particular at low current dose) (7,42). Importantly, SPCCT provides additional energy information and will allow enhanced contrast of different materials in the body due to material mapping as in current DECT imaging, but with improved signal to noise ratio thanks to the multiple energy bins and less noise.

However, CT contrast agents currently used in clinical procedures are not well suited for SPCCT K-edge imaging. These agents are iodinated small molecules that have very short circulation half-lives and are non-specific. Crucially, since the K-edge of iodine is at 33 keV, K-edge imaging is not possible for this element, as there are too few photons in the transmitted spectrum around 33 keV. However, material decomposition for iodine is possible with SPCCT, but suffers from the same drawbacks as DECT (7,12). Therefore, these agents do not take

advantage of the capability of photon counting technology to perform spectroscopic CT imaging. In order for spectral K-edge imaging to be practical, the element needs a K-edge in the range ~40-100 keV. Contrast agents reported for SPCCT imaging have been based on heavy elements such as the lanthanides (e.g. gadolinium), gold, ytterbium, bismuth, tantalum, whose K-edges lie within the afore-mentioned range (6,7,12,29,36,37,42,43).

A first proof of principle measurement using the scanner described has been performed on a phantom made of Delrin (PTFE, d=1.4 mg/ml, diameter =15 cm) containing multiple test tubes of different dilutions of iodine contrast agent (Iomeron, 400 mg/ml, Bracco) and gadolinium chelate solutions (Multihance, 0.5mmol/ml, Bracco) (from 2.5 to 8 mg/ml of gadolinium and iodine), and phosphate buffered saline (PBS), as shown in Figure 4. The conventional image doesn't allow either the determination of a material or the discrimination of the iodine from the gadolinium. On the contrary, the iodine material decomposition image and the gadolinium K-edge image successfully show only the specific materials, with signal intensity in proportion to the agents' absolute concentrations. There is a suppression of the background in the specific images, e.g. the plastic phantom, improving drastically the signal to background ratio. This stems from the fact that the specific information about the presence of contrast is obtained by a measured difference in attenuation above and below the K-edge feature of the element, e.g. 50.3 keV for gadolinium. In addition, the water image shows not only the solutions due to their water content, but also the plastic since it is made of elements close in atomic number to those that make up water.

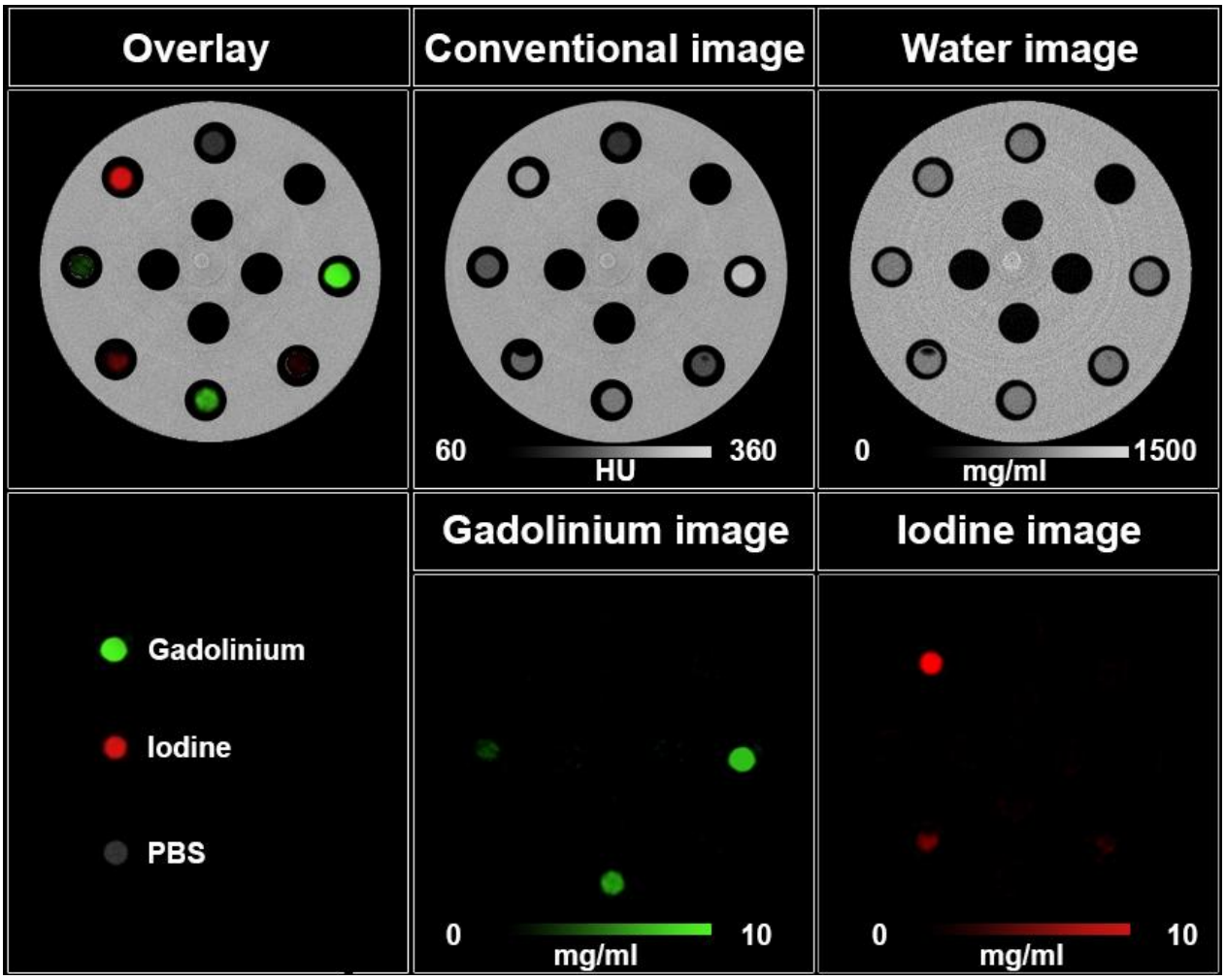


Figure 4. Spectral photon-counting images of a phantom containing multiple test tubes of different dilutions of gadolinium chelate and iodine contrast agent solutions (conventional CT, material decomposition water/iodine, K-edge gadolinium image and an overlay of the material specific images).

In conclusion, new contrast agents could be developed to benefit from the advantages and new possibilities of the SPCCT associated with K-edge detection (44). We expect that future improvements in SPCCT technology and also contrast agents properties will lead to more sensitive K-edge detection. The field of X-ray contrast agents in general is experiencing a

renaissance in recent years, with many publications on new formulations (45,46). Agents capable of sustained blood pool imaging, molecular imaging and cell tracking have been reported (47–52). These developments could improve the imaging of specific physiopathologic phenomena such as organ perfusion, tissue permeability, inflammation, edema, fibrosis and facilitate molecular imaging in the future (6,36,53).

3.3. Potential clinical applications

3.3.1. Stent imaging

Blooming artifacts in standard CT angiography images related to vascular calcifications and metallic stents impair correct visualization of the vascular lumen, reducing the possibility of diagnosis of coronary stenosis or in-stent restenosis. Indeed, blooming artifacts can cause under- or over-estimation of the vessel lumen because of the thicker appearance of highly attenuating materials (54). This limitation necessitates invasive coronary angiography for assessing the vessel diameter. However, invasive coronary angiography can cause complications such as coronary dissection, or a local complication of the needle-puncture site or simple hematoma. Hence, there is a need for decreasing blooming artifacts, which are due mainly to highly attenuating material artifacts and the partial volume averaging effect. The higher spatial resolution inherent to SPCCT systems can decrease the partial volume effect and therefore might be expected to reduce blooming.

We have tested the capability of SPCCT to improve the visualization of stent architecture compared to a standard CT system (Brilliance 64, Philips, Cleveland, USA: B64). The apparent width of the metallic struts was smaller on SPCCT than on the standard CT for the stent. Thus SPCCT enables improved visualization of stent metallic mesh owing to a significant reduction of blooming artifacts due to increased spatial resolution compared to conventional CT.

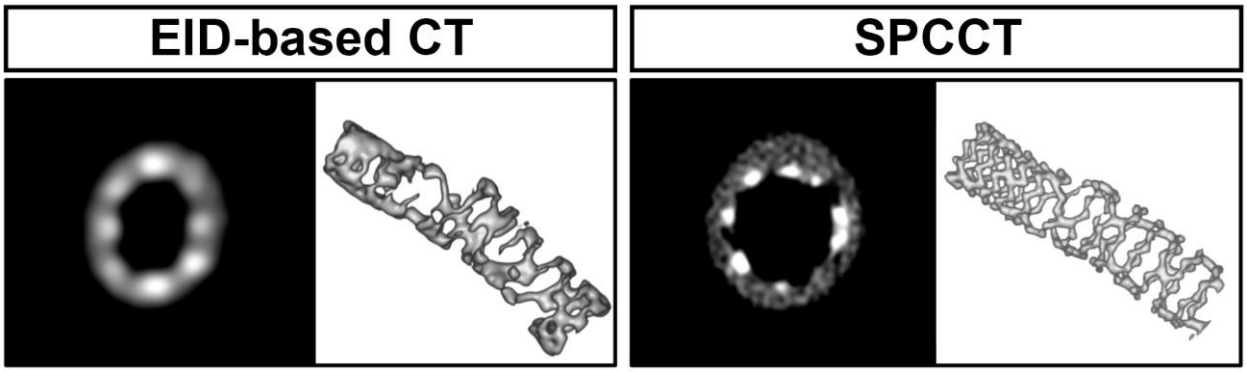


Figure 5. Comparison of conventional and volume rendering CT images of a stent using the same reconstruction and acquisition parameters on an EID-based CT and the SPCCT (voxel size: 0.1*0.1*0.1 mm).

3.3.2. Specific quantitative imaging

With conventional CT systems, the characterization of tissue relies only on the CT attenuation values without and with injection of contrast media at consecutive specific time points, such as the arterial, portal and urinary phase. Despite the fact that multiphase contrast enhanced imaging helps to characterize pathologies, it is undermined by the lack of specific absolute quantitative evaluation of contrast media biodistribution. Indeed, in various pathological findings, the assessment of enhancement is incorrect due to the surrounding tissue, such as in the case of a hemorrhage renal cyst, which has slight inner enhancement. Taking advantage of the specific characterization and quantification of K-edge elements, we performed a study of the renal biodistribution of a gadolinium contrast agent (Multihance, 0.5mmol/ml, Bracco) after intravenous injection into a rabbit. We have shown a higher concentration of gadolinium in the urinary cavity than in the renal cortex during a urinary phase, matching the pharmacokinetics of gadolinium contrast media. This preliminary result supports quantitative characterization of pathologic processes such as ischemic lesion or tumor enhancement.

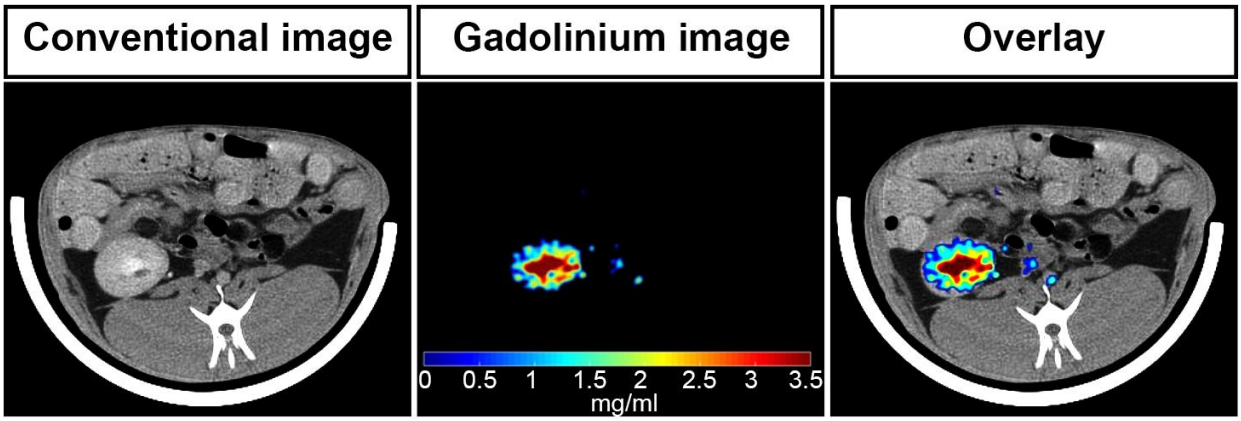


Figure 6. Spectral photon-counting images (conventional, gadolinium K-edge and overlay images) 60 seconds after injection of a gadolinium chelate into a rabbit. Gadolinium K-edge images allow the quantification of gadolinium content, with 2.92 mg/ml in the urinary cavity and 1.63 mg/ml in the renal cortex, for example.

3.3.3. Multiphase imaging

One of the main advantages of SPCCT is to image multiple contrast agents simultaneously due to specific discrimination, using their K-edge signatures and/or material decomposition. Indeed, by dividing the spectrum into well-chosen energy-based datasets, it would be possible to detect multiple elements such as gadolinium, gold, bismuth, ytterbium, tantalum, whose K-edges are in the relevant energy range of the x-ray spectrum used, this latter being ~40-100 keV. Note that while the X-rays used in SPCCT range between ~25-120 keV, K-edge imaging requires sufficient number of photons above and below the K-edge, therefore excluding elements whose K-edges are much below 40 or over 100 keV. This will potentially permit a new form of functional imaging, where multiple contrast agents with different pharmacokinetics are used simultaneously in the same biological system. For example, with the

use of different contrast agents in the vascular system injected sequentially, within a single scan we would be able to image multiple uptake phases of a given tissue/organ (Fig. 7); or the use of a combination of one non-specific and one specific contrast agent for the simultaneous imaging of the vascular lumen and vascular wall in pathologies such as atherosclerosis (6); or for the simultaneous imaging of the different biodistributions of two contrast agents, such as gold nanoparticles and iodine contrast agents, to probe different biological processes and diseases in a single scan (Fig. 8). Note that gold nanoparticles are a good candidate for K-edge imaging, as has been shown previously (6,55,56). In addition, they have the potential to circulate longer than iodinated contrast agents for improved blood pool imaging and possessing high biocompatibility (52,57).

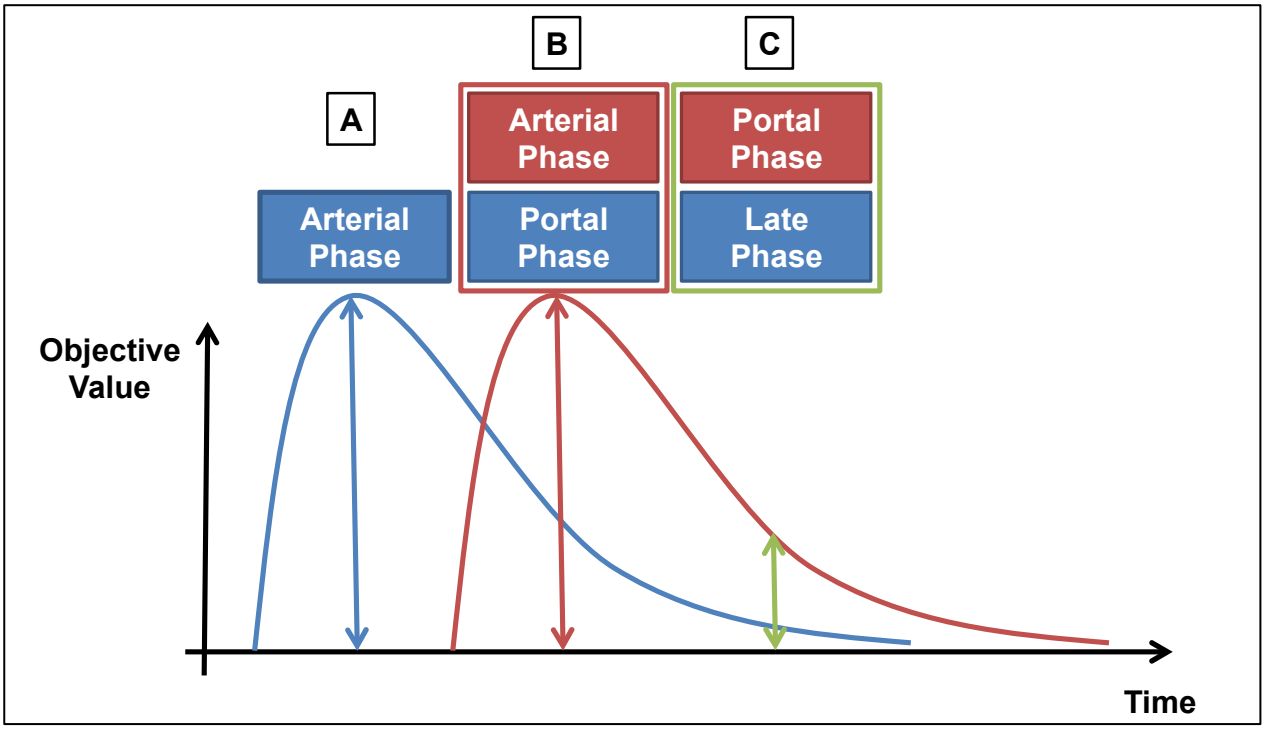


Figure 7. Graph depicting one phase imaging per acquisition using a single contrast agent (blue curve – scan at timeA to get arterial phase, time B to get portal phase and time C to get late phase) compared to the potential of SPCCT multiphase imaging per acquisition using dual

contrast discrimination which allows, with delayed injection of a second contrast agent (red curve), simultaneous arterial and portal phase imaging (scan at time B), or portal and late phase imaging (scan at time C).

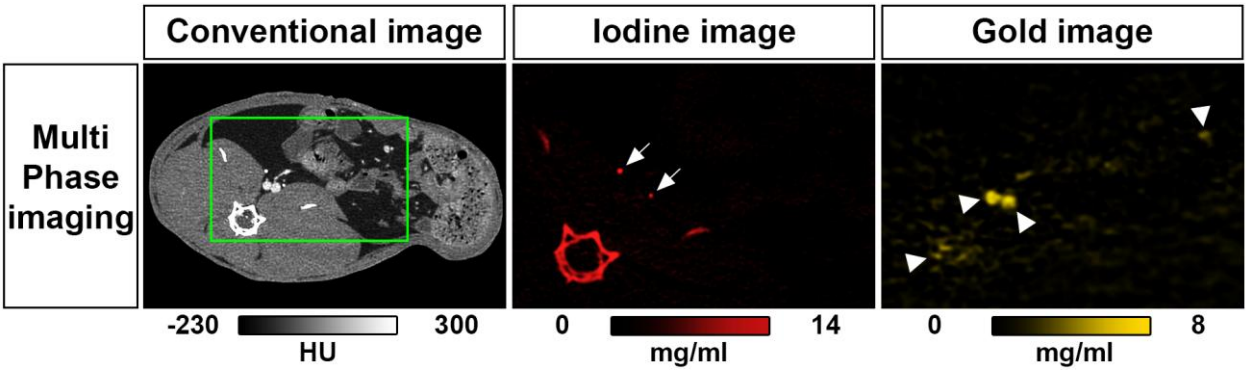


Figure 8. Spectral photon-counting images (conventional, iodine, gold K-edge) showing wash out of iodine in the ureters (arrow) and blood vessels (head arrow) filled with a blood pool based gold nanoparticles in favor of dual phase dual contrast imaging. Note that the vertebral vessels are better visualized on the gold specific image than on the conventional image since the CNR increased due to the suppression of the background.

Using SPCCT with multiple contrast agents would have the benefit of 100% spatial registration for all reconstructed images without any registration technique in contrast to the current multiple phase acquisitions with dual-source CT and kVp-switching, where image registration remains a limiting factor (58). Moreover, successfully imaging multiple uptake phases in a single scan could significantly lower patient radiation exposure while at the same time providing important diagnostic capabilities.

4. Conclusion

In conclusion, spectral photon-counting CT imaging represents an emerging field of CT, already existing for clinical use with the dual energy CT systems, and being investigated with the photon-counting CT systems. Our preliminary results show the spectral possibilities that the photon-counting technology offers, demonstrating potentially very compelling applications for cardiovascular diseases, organ perfusion and molecular imaging. Moreover, these findings point to preclinical and clinical applications using multiple types of contrast agents, and also for multi-phase imaging in a single scan. In addition, it highlights the need to develop SPCCT specific contrast agents, which could expand the field of CT-based molecular imaging and create new paradigms in diagnostic imaging.

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Highlights

- Reviewing our initial experience using a spectral photon counting CT is proposed.
- SPCCT represents a new imaging modality in the X-ray imaging field.
- SPCCT allows analysis of the energy composition of the transmitted x-ray spectrum.
- SPCCT K-edge imaging allows specific spectral discrimination of a contrast agent.
- SPCCT could expand the field of CT-based molecular imaging.

Nuclear Instruments and Methods in Physics Research

Dear Mats Danielsson,

We are happy to submit our manuscript as a review, entitled: “Review of an initial experience with an experimental spectral photon-counting computed tomography system” (authors: Salim Si-Mohamed, Daniel Bar-Ness, Monica Sigovan, David P. Cormode, Philippe Coulon, Emmanuel Coche, Alain Vlassenbroek, Gabrielle Normand, Loic Boussel and Philippe Douek), to your journal.

The X-ray imaging field is currently undergoing a period of rapid technological innovation in diagnostic imaging equipment. An important recent development is the advent of new x-ray detectors, i.e. photon-counting detectors, which have been introduced in experimental computed tomography systems. These systems represent a new imaging modality, since they allow analysis of the energy composition of the transmitted x-ray spectrum. By dividing the spectrum into well-chosen energy-based datasets, ‘multicolor’ imaging of specific materials (e.g. water, contrast media, etc), also known as K-edge imaging, is possible with such systems. Based on Philips research and development and a first experience on a proof of concept prototype, a small field of view animal SPCCT system was built and transferred in May 2015 to the University of Lyon collaborators for medical experiments as a small animal Scanner in the context of an european project funded by the Horizon 2020 grant.

In this review, we describe multi-energy CT imaging, from dual energy to photon counting technology, and our initial experience results using this clinical-scale spectral photon counting CT (SPCCT) prototype system *in vitro* and *in vivo*. We introduce also possible clinical applications. For example, we have demonstrated the spectral capabilities of SPCCT, such as the specific K-edge imaging of a gadolinated contrast agent in the kidney with the possibility of an absolute quantitative analysis of the concentrations, or the differentiation between gold nanoparticles and an iodinated contrast agent within the same compartment. We have also demonstrated the impact of the improved spatial resolution on the visualization of the coronary stent which can change the management of coronary in-stent restenosis. In addition, we have shown the potential for performing a multi-phase imaging with the use of

dual contrast agents in a single scan, which could significantly lower patient radiation exposure while at the same time providing important diagnostic capabilities.

Hence, we believe that our manuscript is of interest to the readership of Nuclear Instruments and Methods in Physics Research, as it demonstrates a new capability in the field of x-ray CT imaging, and also because SPCCT is promised to be the next-generation of clinical CT scanner. We sincerely hope that you will consider our manuscript for publication in your journal.

Sincerely yours,

Philippe C. Douek, M.D., Ph.D.
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