LETTER

Imaging of $^{99m}$Tc-DMSA and $^{18}$F-FDG in humans using a Si/CdTe Compton camera

Takashi Nakano 1,*, Makoto Sakai 1, Kota Torikai 2, Yoshiyuki Suzuki 3, Shin’ichiro Takeda 4, Shin-ei Noda 5, Mitsutaka Yamaguchi 6, Yuto Nagao 6, Mikiko Kikuchi 7, Hirokazu Odaka 8, Tomihiro Kamiya 9, Naoki Kawachi 9, Shin Watanabe 9, Kazuo Arakawa 10 and Tadayuki Takahashi 10

1 Heavy Ion Medical Center, Gunma University, Maebashi, Japan
2 System Integration Center, Gunma University Hospital, Maebashi, Japan
3 Department of Radiation Oncology, School of Medicine, Fukushima Medical University, Fukushima, Japan
4 Kavli Institute for the Physics and Mathematics of the Universe (WPI), The University of Tokyo Institutes for Advanced Study, The University of Tokyo, Kashiwa, Japan
5 Department of Radiation Oncology, Comprehensive Cancer Center, Saitama Medical University International Medical Center, Hidaka, Japan
6 Takasaki Advanced Radiation Research Institute, National Institutes for Quantum and Radiological Science and Technology, Takasaki, Japan
7 Department of Physics, The University of Tokyo, Tokyo, Japan
8 Graduate School of Science and Technology, Gunma University, Kiryu, Japan
9 Institute of Space and Astronautical Science, Japan Aerospace Exploration Agency, Sagamihara, Japan
10 Author to whom any correspondence should be addressed.

E-mail: tnakano@gunma-u.ac.jp

Keywords: $^{18}$F, $^{99m}$Tc, Compton camera, human imaging, simultaneous imaging

Supplementary material for this article is available online

Abstract

The Compton camera can simultaneously acquire images of multiple isotopes injected in a body; therefore, it has the potential to introduce a new subfield in the field of biomedical imaging applications. The objective of this study is to assess the ability of a prototype semiconductor-based silicon/cadmium telluride (Si/CdTe) Compton camera to simultaneously image the distributions of technetium ($^{99m}$Tc)-dimercaptosuccinic acid (DMSA) (141 keV emission) and $^{18}$F-fluorodeoxyglucose (FDG) (511 keV emission) injected into a human volunteer. $^{99m}$Tc-DMSA and $^{18}$F-FDG were injected intravenously into a 25-year-old male volunteer. The distributions of $^{99m}$Tc-DMSA and $^{18}$F-FDG were simultaneously made visible by setting a specified energy window for each radioisotope. The images of these radiopharmaceuticals acquired using the prototype Compton camera were superimposed onto computed tomography images for reference.

The reconstructed image showed that $^{99m}$Tc-DMSA had accumulated in both kidneys, which is consistent with the well-known diagnostic distribution determined by clinical imaging via single-photon emission computed tomography. In the $^{18}$F-FDG image, there is broad distribution around the liver and kidneys, which was expected based on routine clinical positron emission tomography imaging.

The current study demonstrated for the first time that the Si/CdTe Compton camera was capable of simultaneously imaging the distributions of two radiopharmaceuticals, $^{99m}$Tc-DMSA and $^{18}$F-FDG, in a human body. These results suggest that the Si/CdTe Compton camera has the potential to become a novel modality for nuclear medical diagnoses enabling multi-probe simultaneous tracking.

1. Introduction

In recent times, the use of Compton cameras has been widely investigated for medical applications, such as scintigraphy, single-photon emission computed tomography (SPECT) (Nakamura et al. 2016, Vernekoohl et al. 2016, Fontana et al. 2017, Muñoz et al. 2017, 2018), and range verification in hadron therapy (Ortega et al. 2015, Hilaire et al. 2016, Solevi et al. 2016, Rohling et al. 2017, Draeger et al. 2018, Huang et al. 2018, Parajuli et al. 2019). Compton cameras reconstruct the distributions of gamma-ray-emitting radioisotopes (RI) based on Compton scattering information recorded by a detector. Figure 1(a) shows a schematic diagram of the working
principle of a Compton camera. Because Compton interaction primarily occurs in the energy band ranging from 100 keV to 1–2 MeV, Compton cameras can be used in this wide energy band. Compton cameras have the potential for application in dual-energy or multi-energy RI tomography, which remains a challenging task among conventional nuclear imaging modalities, such as positron emission tomography (PET) and single photon emission computed tomography (SPECT). However, only recently has a Compton camera with sufficient angular resolution and energy resolution been developed to be suitable for the abovementioned applications.

A silicon/cadmium telluride (Si/CdTe) Compton camera was recently developed based on high-resolution CdTe semiconductor imaging devices (Takahashi et al. 2004, 2012, Watanabe et al. 2005, 2014, Takeda et al. 2012). The Si/CdTe Compton camera can simultaneously detect technetium (99mTc), the most frequently used RI in nuclear medicine diagnosis, as well as positron emitters, such as 18F and 11C. Compton cameras are capable of using multiple RIs, which allows simultaneous imaging and shortens medical examination times by removing the need to wait for the elimination of RIs used for previous a diagnosis to avoid crosstalk. Furthermore, using the Compton camera, the reciprocal actions and metabolism of several related substances can be analyzed over time in vivo.

Multi-tracer imaging is still challenging, but it has the potential for clinical and molecular applications. For example, hypoxia is an important factor for tumor treatment. If blood flow could be observed simultaneously with hypoxia, the detection would be more precise (Lehtiö et al. 2003). Multi-tracer SPECT is helpful in the differential diagnosis of parkinsonism (O’Brien et al. 2014). To investigate the metabolism, a multi-tracer screening system incorporating a Compton camera has been developed (Kanayama et al. 2005). Thus, the clinical application of Compton cameras is a promising advancement in nuclear diagnostic medicine. Nevertheless, several issues need to be addressed before clinically applicable Compton images can be routinely used.

The objective of the current study was to assess the efficacy of the Compton camera to simultaneously capture the distributions of 99mTc-dimercaptosuccinic acid (DMSA) (141 keV emission) and 18F-fluorodeoxyglucose (FDG) (511 keV emission) injected into a human volunteer. This study was performed using a purpose-built prototype Si/CdTe Compton camera.

2. Materials and methods

2.1. Si/CdTe Compton camera

Figure 1(b) shows a photograph of the Compton camera used in our study. The camera consists of one layer of Si double-sided strip detectors (DSDs) and three layers of CdTe-DSDs stacked with a pitch of 4 mm. The geometry of the strip, which is orthogonally implanted on both sides of a detector with a pitch of 250 µm, enables 2D coordinate measurements for gamma rays. The active area of these detectors is 32 mm × 32 mm, and the thicknesses of the Si-DSDs and CdTe-DSDs are 0.5 mm and 0.75 mm, respectively.

Compton events, which refer to the scattering of incoming gamma rays in Si followed by their absorption in CdTe, were recorded by the Compton camera. The locations of the sources can then be determined by accumulating many Compton cones obtained by solving the Compton equation (Takahashi et al. 2004, 2012, Watanabe et al. 2005, 2014, Sakai et al. 2018).

The angular resolution of the Compton camera, which is typically defined by the angular resolution measure (ARM), was determined to be 11.4° (full width at half maximum (FWHM)) for 122 keV photons, and 4.2°
(FWHM) for 511 keV photons. The efficiency of the Compton camera was $3.4 \times 10^{-6}$ for 122 keV photons and $1.3 \times 10^{-6}$ for 511 keV photons for a point source placed 10 cm away from the camera surface.

2.2. Volunteer and RIs

A healthy 25-year-old male volunteered for our study, and his participation was approved by the Institutional Review Board of Gunma University Hospital (UMIN000014452). He provided written informed consent on 11 June 2014. $^{99m}$Tc-DMSA and $^{18}$F-FDG, which are commonly used for SPECT and PET in routine clinical practice, were used in this study. Based on previous phantom experiments, dosages of 30 MBq (0.43 MBq kg$^{-1}$) for $^{99m}$Tc-DMSA and 150 MBq (2.16 MBq kg$^{-1}$) for $^{18}$F-FDG were deemed suitable for the type of human imaging that was undertaken in the study.

2.3. Imaging conditions

A Compton camera was placed under the right side of the volunteer’s body to simultaneously detect RIs from the coronal views of the liver and kidney (figure 2(a)). Because the field of view was limited to the abdominal region by a lead shield, the bladder and most of the heart were not included in the imaging area. The estimated distance between the kidney and the Compton camera surface was 300 mm.

On the first day of the human study, computed tomography (CT) images around the liver and kidneys were acquired. Reference positions were marked on the subject’s body for comparison of the CT images with the Compton images. Then, on the second day, the volunteer was simultaneously injected with $^{99m}$Tc-DMSA (30 MBq, Nihon Medi+Physics) and $^{18}$F-FDG (150 MBq, Nihon Medi+Physics); thereafter, four cyclic sequences involving 45 min of data acquisition and 15 min of rest were performed.

2.4. Image reconstruction method

List mode data consisting of channel IDs, pulse heights, and trigger timing, among other parameters, were recorded by the Compton camera. Based on the event selection method discussed in a previous study (Watanabe et al 2014), full-energy deposited Compton events were recorded within the energy window (e.g. 135–150 keV for $^{99m}$Tc and 480–525 keV for $^{18}$F). In particular, the Compton events are back-projected onto an image plane parallel to the camera surface using a near-field back projection technique based on the method described in a previous study (Takeda et al 2012) with the value of the weighting parameter $w$ set to 0. This projection is used to estimate the source flux at the projected plane based on the changes in flux due to the different distances of the detector from each point on the Compton cone. It should be noted that no likelihood estimation or deconvolution algorithms were included in the current study.

3. Results

The energy spectrum was processed from the detected events over a 35 min period from the 54 min to 89 min marks after RI injection; the spectrum is shown in figure 2(b). As can be seen from the figure, the energy peaks from both $^{99m}$Tc-DMSA (141 keV) and $^{18}$F-FDG (511 keV) were clearly detected. Using the methods described in the previous section, the full-energy deposited Compton events were captured within the energy window (hatched region), and a total of 6741 and 4895 Compton events were extracted for $^{99m}$Tc-DMSA and $^{18}$F-FDG, respectively. The events were back-projected onto the image plane placed 300 mm away from the camera surface, where the liver and kidneys were located.

The accumulation of $^{99m}$Tc-DMSA is represented using a color contour map in figure 2(c); this map is overlapped by a reference CT image. As can be observed from the figure, two strong concentration areas of $^{99m}$Tc-DMSA were clearly detected. Based on the reference CT images, these concentrations seemed to appear at the left and right kidneys. This assessment is supported by the well-known observation that $^{99m}$Tc-DMSA tends to accumulate in healthy kidneys (Lin et al 2000, Sheehy et al 2009). In addition, we confirmed this result using a human abdomen phantom with plastic right and left kidneys filled with liquid $^{99m}$Tc-DMSA with a radioactivity of 12 MBq; two intense concentrations of the isotope originating from the phantom kidneys were also clearly made visible, which firmly corroborated the abovementioned result. Conversely, $^{18}$F-FDG (figure 2(d)) was observed to be broadly distributed over regions that indicated the liver and kidneys, depicting a similar morphological structure when compared with the imaging results of $^{18}$F-FDG using PET-CT in routine clinical practice (Cheng et al 2013, Heusch et al 2013). Thus, the differences in kinetic and static behaviors inside the human body between the two radiopharmaceuticals $^{99m}$Tc-DMSA and $^{18}$F-FDG were confirmed using Compton camera imaging.

4. Discussion

The objective of this study was to investigate the potential of a Si/CdTe Compton camera for simultaneous imaging of two radiopharmaceuticals ($^{99m}$Tc-DMSA and $^{18}$F-FDG) in the human body. Via our imaging experiments, we
successfully demonstrated that the Compton camera was able to capture images of the distributions of $^{99m}$Tc-DMSA and $^{18}$F-FDG, using specific 141 keV ($^{99m}$Tc) and 511 keV ($^{18}$F) gamma rays in one exposure.

In this study, we conducted human imaging using $^{99m}$Tc-DMSA and $^{18}$F-FDG. It is clear that other radioactive tracers attached to the same RI can be imaged by our Compton camera. In addition, the energy of $^{99m}$Tc is low, whereas $^{18}$F generates higher energy gamma rays than a SPECT agent. Thus, the ability of simultaneous imaging to use $^{99m}$Tc and $^{18}$F indicates that any SPECT tracers emitting 141–511 keV gamma rays (i.e. $^{123}$I, $^{111}$In) can be imaged by our Compton camera.

The gamma rays from both $^{99m}$Tc and $^{18}$F were scattered in the body. The reduction ratio of the 141 keV gamma ray was estimated at 80%, considering the attenuation coefficient and the body thickness. In addition, some scattered gamma rays from $^{18}$F may have contaminated the data of $^{99m}$Tc. However, our Compton camera was able to clearly image the kidneys because the cross-talk effect on the Compton imaging is relatively small in comparison to SPECT (Sakai et al. 2018). This capability results from the Compton camera having excellent energy resolution, so the peaks of $^{99m}$Tc and back-scattered gamma rays of $^{18}$F could be distinguished.

The contour of the liver was unfortunately indistinct in the image of $^{18}$F-FDG, in contrast to the contour of kidneys in the image of $^{99m}$Tc-DMSA. This is because the $^{18}$F-FDG was distributed in other organs due to the absence of fasting, so spatial and contrast resolution of Compton camera was not sufficient. Though the imaging resolution of the prototype Si/CdTe Compton camera used in this study is not sufficient for clinical use and does not surpass that of SPECT and PET, the results of our study indicate high potential for the application of Compton cameras in the field of multi-energy RI tomography in the future.

The spatial resolution of a Compton camera is proportional to the distance from the detector to the source. In this study, the distance was 300 mm, but that distance can be reduced. Moving the Compton camera closer to the patient would improve the spatial resolution.

Compared with conventional SPECT, which suffers from count loss due to absorption in the collimator, overall efficiencies of Compton cameras are expected to improve in the future, enabling relatively shorter medical examination times than when SPECT is used.

The dosages of RIs administered in this study (30 MBq $^{99m}$Tc-DMSA and 150 MBq $^{18}$F-FDG), which were sufficient to obtain clinically useful human images in 35 min, are already below the regulatory limits. Furthermore, a Si/CdTe Compton camera recently developed for applications in space (Schelbert et al. 2002) has significantly improved efficiency. Thus, in the near future, it may surpass that of clinical SPECT. In a typical SPECT diagnosis,
the injected dose of $^{99m}$Tc-DMSA is 74–222 MBq (Veenboer et al. 2015, Blaufox et al. 2018), the efficiency is 0.01% to 0.1% (Van Audenhaye et al. 2015, Slomka et al. 2015), spatial resolution is approximately 10 mm (Van Audenhaye et al. 2015, Slomka et al. 2015), and the acquired time is 3–20 min (Maryse et al. 2017, Freeman et al. 2018, Fujiwara et al. 2019).

Hence, the use of an advanced Compton camera as described herein has the potential to reduce human exposure to gamma rays from RIs during nuclear diagnosis in the future.

In this study, one Compton camera was placed underneath the body. Thus, the captured information was limited to a single angle of projection; therefore, the images obtained were limited to a 2D space. We have already successfully reconstructed the 2D and 3D distributions of different RIs in a rat by moving the camera around the rat to gather multi-angle data (Suzuki et al. 2013, Sakai et al. 2018). In the future, we will apply this monitoring technique to pre-clinical and clinical imaging in human.

In addition to its capacity for multi-probe tracking, we confirmed that the Si/CdTe Compton camera has other various advantageous characteristics, such as the potential to reduce examination time, a wide energy band, high energy resolution, and portability. In conclusion, our results indicate that the Si/CdTe Compton camera has great potential for various clinical applications in the future, and may facilitate new nuclear diagnostic procedures. Further improvements in its detection efficiency, spatial resolution, and image reconstruction algorithms are ongoing.

Acknowledgments

This work was supported by Grants-in-Aid from the Program for Leading Graduate Schools from the Japan Society for the Promotion of Science and for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan. The authors thank Dr Aiko Yamaguchi, Madoka Fujisaki, Dr Daisuke Irie, and Takayoshi Ishii for their assistance with the preparation of the manuscript. The authors have confirmed that any identifiable participants in this study have given their consent for publication.

ORCID iDs

Makoto Sakai https://orcid.org/0000-0001-9928-2375
Kota Torikai https://orcid.org/0000-0003-3051-1613
Mitsutaka Yamaguchi https://orcid.org/0000-0002-3412-4066
Naoki Kawachi https://orcid.org/0000-0002-3991-5035

References

Blaufox M D et al. 2018 The SNMMI and EANM practice guideline for renal scintigraphy in adults Eur. J. Nucl. Med. Mol. Imaging 45 2218–28
Cheng G, Alavi A, Lim E, Werner T J, Del Bello C V and Akers S R 2013 Dynamic changes of FDG uptake and clearance in normal tissues Mol. Imaging Biol. 15 345
Draeger E, Mackin D, Peterson S, Chen H, Avery S, Beddar S and Pelof J C 2013 3D prompt gamma imaging for proton beam range verification Phys. Med. Biol. 63 35019
Fontana M, Davergne D, Letang J M, Ley J L and Testa E 2017 Compton camera study for high efficiency SPECT and benchmark with Anger system Phys. Med. Biol. 62 8794
Freeman C W et al. 2018 Unenhanced MRI as an alternative to $^{99m}$Tc-labeled dimercaptosuccinic acid scintigraphy in the detection of pediatric renal scarring AJR Am. J. Roentgenol. 210 869–75
Fujiwara T et al. 2019 Investigation of the relation between administered dose and image quality for pediatric, $^{99m}$Tc-DMSA renal scintigraphy: clinical study applying the JSNM (Japanese Society of Nuclear Medicine) pediatric dosage card Ann. Nucl. Med. 33 153–9
Heusch P et al. 2013 Standardized uptake values for $^{18}$F FDG in normal organ tissues: comparison of whole-body PET/CT and PET/MRI Eur. J. Radiol. 82 870
Hilaire E, Sarrut D, Peyrin F and Maxim V 2016 Proton therapy monitoring by Compton imaging: influence of the large energy spectrum of the prompt $\gamma$-radiation Phys. Med. Biol. 61 3127
Huang H M, Liu C C, Jan M L and Lee M W 2018 A low-count reconstruction algorithm for Compton-based prompt gamma imaging Phys. Med. Biol. 63 085013
Kanayama Y, Tsuji T, Enomoto S and Amano R 2005 Multitracer screening: brain delivery of trace elements by eight different administration methods Biometals 18 553–65
Lehtio K et al. 2003 Quantifying tumour hypoxia with fluorine-18 fluoroerythronitrimidazole ($^{18}$FETNIM) and PET using the tumour to plasma ratio Eur. J. Nucl. Med. Mol. Imaging 30 101–8
Lin E et al. 2000 Reproducibility of renal length measurements with $^{99m}$Tc-DMSA SPECT J. Nucl. Med. 41 1632
Maryse M G et al. 2017 Dimercaptosuccinic acid scintigraphy versus ultrasound for renal parenchymal defects in children Can. Urol. Assoc. J. 11 260–4
Muñoz E, Barrio J, Bernabéu J, Etxebesta A, Lacasta C, Llosa G, Ros A, Roser J and Oliver J F 2018 Study and comparison of different sensitivity models for a two-plane Compton camera Phys. Med. Biol. 63 135004
Muñoz E, Barrio J, Etxebesta A, Ortega P G, Lacasta C, Oliver J F, Solaz C and Llosa G 2017 Performance evaluation of MACACO: a multilayer Compton camera Phys. Med. Biol. 62 7321
Nakamura Y, Shimazoe K, Takahashi H, Yoshimura S, Seto Y, Kato S, Takahashi M and Momose T 2016 Development of a novel handheld intra-operative laparoscopic Compton camera for 18F-Fluoro-2-deoxy-2-D-glucose-guided surgery Phys. Med. Biol. 61 5837
O’Brien J T et al 2014 18F-FDG PET and perfusion SPECT in the diagnosis of Alzheimer and Lewy body dementias J. Nucl. Med. 55 1959–65
Ortega P G et al 2015 Noise evaluation of compton camera imaging for proton therapy Phys. Med. Biol. 60 1845
Parajuli R K et al 2019 Annihilation gamma imaging for carbon ion beam range monitoring using Si/CdTe Compton camera Phys. Med. Biol. 64 055003
Rohling H, Priegnitz M, Schoene S, Schumann A, Enghardt W, Huseo-González F, Pausch G and Fiedler F 2017 Requirements for a Compton camera for in vivo range verification of proton therapy Phys. Med. Biol. 62 2795
Sakai M et al 2018 In vivo simultaneous imaging with 99mTc and 18F using a Compton camera Phys. Med. Biol. 63 205006
Schelbert H R 2002 18F-deoxyglucose and the assessment of myocardial viability Semin. Nucl. Med. 32 60
Sheehy N, Tetrault T A, Zurakowski D, Vija A H, Fahey F H and Treves S T 2009 Pediatric 99mTc-DMSA SPECT performed by using iterative reconstruction with isotropic resolution recovery: improved image quality and reduced radiopharmaceutical activity Radiology 251 511
Slomka P J et al 2015 Advances in SPECT and PET hardware Prog. Cardiovasc. Dis. 57 566–78
Solevi P et al 2016 Performance of MACACO Compton telescope for ion-beam therapy monitoring: first test with proton beams Phys. Med. Biol. 61 5149
Suzuki Y et al 2013 Three-dimensional and multienergy gamma-ray simultaneous imaging by using a Si/CdTe Compton camera Radiology 267 941
Takahashi T et al 2004 Hard x-ray and gamma-ray detectors for the NEXT mission New Astron. Rev. 48 269
Takahashi T, Watanabe S, Ishikawa S, Sato G and Takeda S 2012 High-resolution CdTe detectors and their application to gamma-ray imaging Biological and Medical Sensor Technology ed K Iniewski (Boca Raton, FL: CRC Press)
Takeda S, Odaka H, Ishikawa S, Watanabe S, Aono H and Takahashi T 2012 Demonstration of in vivo multi-probe tracker based on a Si/CdTe semiconductor Compton camera IEEE Trans. Nucl. Sci. 59 70
Van Audenhæge K et al 2015 Review of SPECT collimator selection, optimization, and fabrication for clinical and preclinical imaging Med. Phys. 42 4796–813
Veenboer P W et al 2015 Diagnostic accuracy of Tc-99m DMSA scintigraphy and renal ultrasonography for detecting renal scarring and relative function in patients with spinal dysraphism Neurourol. Urodyn. 34 513–8
Veenboer P W et al 2016 feasibility study of Compton cameras for x-ray fluorescence computed tomography with humans Phys. Med. Biol. 61 8521
Watanabe S et al 2005 A Si/CdTe semiconductor Compton camera IEEE Trans. Nucl. Sci. 52 2045
Watanabe S et al 2014 The Si/CdTe semiconductor Compton camera of the ASTRO-H soft gamma-ray detector (SDG) NIM A 765 192