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High-resolution clustered pinhole ^{131}Iodine SPECT imaging in mice

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ABSTRACT

Introduction: High-resolution pre-clinical ^{131}I SPECT can facilitate development of new radioiodine therapies for cancer. To this end, it is important to limit resolution-degrading effects of pinhole edge penetration by the high-energy γ-photons of iodine. Here we introduce, optimize and validate ^{131}I SPECT performed with a dedicated high-energy clustered multi-pinhole collimator.
Methods: A SPECT–CT system (VECTor/CT) with stationary gamma-detectors was equipped with a tungsten collimator with clustered pinholes. Images were reconstructed with pixel-based OSEM, using a dedicated ^{131}I system matrix that models the distance- and energy-dependent resolution and sensitivity of each pinhole, as well as the intrinsic detector blurring and variable depth of interaction in the detector. The system performance was characterized with phantoms and *in vivo* static and dynamic ^{131}I-NaI scans of mice.
Results: Reconstructed image resolution reached 0.6 mm, while quantitative accuracy measured with a ^{131}I filled syringe reaches an accuracy of $+3.6 \pm 3.5\%$ of the gold standard value. *In vivo* mice scans illustrated a clear shape of the thyroid and biodistribution of ^{131}I within the animal. Pharmacokinetics of ^{131}I was assessed with 15-s time frames from the sequence of dynamic images and time–activity curves of ^{131}I-NaI.
Conclusions: High-resolution quantitative and fast dynamic ^{131}I SPECT in mice is possible by means of a high-energy collimator and optimized system modeling. This enables analysis of ^{131}I uptake even within small organs in mice, which can be highly valuable for development and optimization of targeted cancer therapies.

1. Introduction

Although the combined γ- and β-emitter ^{131}I is best known for its use in thyroid cancer therapy, it is also an important nuclide for other existing and new therapeutic approaches. As an example, ^{131}I has been used in treating non-Hodgkin's [1–4] and Hodgkin's lymphoma [5], also liver cancer [6,7]. Alkylphosphocholine analogs labeled with ^{131}I were reported to be very promising for therapy of a broad spectrum of solid tumors [8]. Furthermore, the use of sodium–iodine symporter (NIS) mediated uptake of ^{131}I, following transfection of NIS-containing vectors into non-NIS-bearing tissues, recently showed successful results in antibody-based treatment of non-Hodgkin's lymphoma [9], gene transfer [10,11], and viral and cell-based [12,13] therapeutic approaches for cancer. Nevertheless, despite the standard use of direct ^{131}I SPECT imaging in the clinic (*i.e.* for monitoring the response to therapy and patient-specific dose calculations), low resolution and poor quantification accuracy of *in vivo* ^{131}I imaging in the pre-clinical field [14] requires *ex vivo* analyses [8,13] or the use of imaging substitutes (^{99m}Tc-pertechnetate or ^{123}I/^{124}I-based compounds) [15] for the assessment of therapy progression. If it were available, quantitative and high-resolution SPECT imaging of ^{131}I in small animals would benefit the development of translational radioisotope therapies.

Imaging ^{131}I in mice is rather challenging due to the relatively high energy of its gamma photons (364 keV), that consequently penetrate the collimator wall and pinhole edges. Although extensive investigations on optimal collimator design [16,17] and system modeling [18–20] for medium- to high-energy clinical SPECT were performed, pre-clinical ^{131}I imaging with sub-mm resolution was not possible up to now. Recently, SPECT and PET imaging have been combined in a novel versatile emission computed tomography system (VECTor, MILabs, The Netherlands) [21] that showed simultaneous sub-mm imaging of ^{99m}Tc and ^{18}F by means of a dedicated clustered multi-pinhole (CMP) collimator. Compared to pinholes used in conventional SPECT collimators, the pinholes in the CMP collimator have narrower opening angles (Fig. 1,a), which significantly decreases the penetration of the photons through the pinhole edges. Due to VECTor's ability to deal with high energy annihilation photons, it is interesting to investigate its ability to image the 364 keV photons from ^{131}I.

The aim of this study is to optimize and characterize VECTor for performing *in vivo* ^{131}I mouse SPECT imaging. To this end, we first optimized image reconstruction for imaging 364 keV photons of ^{131}I

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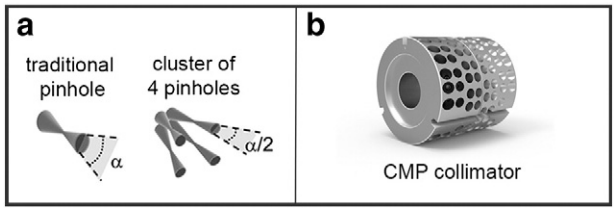

Fig. 1. (a) Traditional pinhole with opening angle α and cluster of 4 pinholes with approximately the same field of view and opening angle α/2. (b) CMP collimator optimized for imaging high energy gamma rays.

and evaluated the quantification accuracy and image quality of ^{131}I SPECT using multiple phantoms. Additionally, we show several examples of *in vivo* imaging performance with multiple static and dynamic ^{131}I-sodium iodide (NaI) SPECT/CT scans of mice.

2. Materials and methods

2.1. Imaging system

The detector geometry and scanner design of VECTor are equivalent to those of the U-SPECT system (MILabs B.V., The Netherlands) [22]. The VECTor system uses a CMP collimator (Fig. 1,b) mounted in the center of three large NaI(Tl) gamma cameras in a triangular setup. The CMP collimator used for this study consists of a tungsten cylinder with a wall thickness of 43 mm and it enables collimating gamma photons up to approximately 600 keV. The collimator contains 162 0.7-mm-diameter pinholes, organized in clusters of 4 pinholes (Fig. 1,a). The pinholes in the inner 2 rings of the collimator have opening angles of 18°, while the outer rings contain 16° opening angle pinholes. More details about the geometry of the collimator can be found in Goorden et al. [21]. All the pinhole clusters together observe a field of view that extends over the entire collimator tube diameter [23]. The part of the field of view (CFOV) that is seen by all clusters simultaneously, the so called "central field of view" (an ellipsoid of 12 × 12 × 7 mm), provides complete data sampling (sufficient angular data to reconstruct an image) without any translations of the animal bed. Note that such an area does not exist in traditional systems, since they require rotation of heavy gamma ray detectors to get sufficient angular data. Complete data (up to total body mouse imaging) are obtained by moving the animal through the scanner in a multi-planar or spiral trajectory [24]. Data are collected in list-mode.

2.2. Image reconstruction and analyzing

The activity distributions were reconstructed from the list-mode data using pixel-based OSEM [25] with resolution recovery and compensation for distance-dependent pinhole sensitivity. The system matrix was calculated in three different ways in order to be able to compare the reconstructed images based on the same acquired data. The first model was based on ^{99m}Tc point source measurements [26], resulting in a system matrix suitable for reconstructing ^{99m}Tc (140 keV) and other low-energy isotopes. The second model was the model that is normally used in VECTor for reconstructing positron emitters such as ^{18}F (511 keV). The position and orientation of the collimators and detectors were determined by means of a geometrical fit from the ^{99m}Tc point source measurements [26]. Given the energy-specific values of the linear attenuation coefficients of the collimator (modeling edge penetration) and detector (modeling depth of interaction) materials, the system matrix was calculated by an analytical ray-tracing code as described in Goorden et al. [27–28]. The third model used the same ray-tracing code as the second, where the linear attenuation coefficients for the collimator and detector were set for 364 keV, resulting in a dedicated system matrix for reconstructing ^{131}I.

For the SPECT images shown, we reconstructed images for 50 iterations and 32 subsets [25] with an isotropic 0.25 mm voxel grid. A 20% ^{131}I photo peak window centered at 364 keV was used. Two background windows were placed on both sides of the photo peak window with a width of 4% of the photo peak energy, *i.e.* 14.2 keV each. Compton scatter correction was applied *via* the triple energy-window method [29]. All SPECT images were attenuation corrected using CT data [30]. After this, absolute quantification of the images was enabled using a scaling factor obtained from scanning a small ^{131}I source with known activity [30].

Image volumes used for time–activity curve (TAC) generation were reconstructed as a dynamic frame sequence, decay-corrected, but otherwise unprocessed. TACs were generated for two ROIs that were manually drawn around the left lobe of the thyroid and salivary gland. The uptake in the ROI was calculated as the percentage injected dose per mL of tissue volume (%ID/mL).

For visual representation in the manuscript, reconstructed volumes of SPECT scans were post filtered with a 0.35 mm FWHM 3D Gaussian filter.

2.3. Phantom experiments

The peak sensitivity of the collimator was measured in counts per second per MBq of activity (cps/MBq) by scanning a small ^{131}I source of known activity placed in the center of the "central field of view".

The spatial resolution was determined with micro-hot-rod capillary resolution phantom scans. The phantom consists of 6 sectors with rods of 1.0, 0.8, 0.7, 0.6, 0.5 and 0.4 mm diameter. The minimal distance between the capillaries in each sector equals the capillary diameter in that sector. The phantom was filled with 76 MBq of ^{131}I-NaI solution. A two-hour SPECT scan with 30-min time frames was performed.

The quantification accuracy of reconstructed images was evaluated by means of scanning a 20 mL syringe (19 mm diameter) that was filled up to 6.5 mL with 12.69 MBq/mL ^{131}I-NaI and scanned for 2 h. The activity in the syringe was measured in a dose calibrator (VDC-304, Veenstra Instruments, The Netherlands) with an accuracy of ± 3% or ± 0.38 MBq/mL.

2.4. In vivo animal experiments

Animal experiments were performed with healthy C57Bl/6 mice according to protocols approved by the Animal Ethical Committee of the UMC Utrecht and in accordance with Dutch Law on Animal Experimentation.

Two mice were anesthetized with isoflurane and injected with respectively 60 (mouse 1) and 5 MBq (mouse 2) ^{131}I-NaI *via* the tail vein. Fifteen minutes after the injection, 15-min total body SPECT scans followed by 15-min focused thyroid scans were performed on each animal. After the end of the SPECT acquisition total body X-ray CT scans were acquired.

One mouse was anesthetized with isoflurane and a tail vein catheter pre-filled with saline was placed. Just after the start of a dynamic 30-min focused thyroid SPECT scan the animal was injected with 26 MBq of ^{131}I-NaI. The first 15 min of the scan was acquired using 15-s time frames, for the remainder the frame duration was increased to one minute.

3. Results

3.1. Phantom scans

In this section we evaluate the ^{131}I imaging performance of VECTor based on resolution and uniformity phantom scans reconstructed with three types of system matrixes: one containing a dedicated system model for ^{131}I (364 keV) and two standard models used in VECTor, one for ^{99m}Tc (140 keV) and one for ^{18}F (511 keV) photons. This was done to assess the level of improvement in VECTor's performance for quantitative ^{131}I imaging.

Fig. 2 shows a 4-mm-thick slice from the resolution phantom scan with ^{131}I. The reconstructed image resolution was evaluated for 120