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Technical Innovation

HUMAN PET/CT SCANNERS: FEASIBILITY FOR ONCOLOGICAL IN VIVO IMAGING IN MICE

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Abstract: PET/CT imaging is a highly valuable oncological imaging modality. The combination of positron emission tomography (PET) and computed tomography (CT) provides the ability to accurately register molecular and metabolic aspects of cancers with anatomical and morphological findings in human clinical routine examinations and for animals in vivo research. Small animal models of mice are widely used in biomedical research for mimicking and studying the human nature, because of their genetic resemblance and the feasibility of gene transfer and gene modification. The recent generation of high performance human PET/CT scanners combines a state of the art full-ring 3D PET scanner and a high-end 16-slice CT scanner (biograph Sensation 16, Siemens AG, Erlangen, Germany). Small animals can be examined with special scanning and reconstruction protocols. The examination of tumor-bearing small animals using a modern human PET/CT revealed excellent image quality. CT can be performed with a maximum spatial resolution of 0.6 x 0.6 x 0.6 mm and PET with a maximum spatial resolution of 6.3 x 6.3 x 6.0 mm. The examination of tumor-bearing small animals using human PET/CT allowed accurate correlation and evaluation of metabolic and anatomical information and is promising for in vivo research purposes. Although image quality is limited by spatial resolution, human PET/CT is widely available and expected to contribute significantly to research with small animal imaging. The investigation of cancer in small animals with PET/CT is probably one of the most challenging tasks in nuclear medicine for the evaluation of tumor growth and growth inhibition factors; development of new anti-tumor drugs and measuring of anti-tumor effects; and cancer treatment response of immunotherapy, chemotherapy and radiation therapy.

Key words: Positron emission tomography (PET) - Computed tomography (CT) - PET/CT - PET-CT - Image fusion - Small animal study - in vivo imaging

INTRODUCTION

Small animal models of rats and mice are widely used in biomedical research for mimicking and studying the human nature in healthy or diseased situations, because of their genetic resemblance with humans and the feasibility of gene transfer and gene modification [6,8]. Single photon computed emission tomography (SPECT) and positron emission tomography (PET) are the only clinically available non-invasive imaging techniques that can assess molecular aspects and metabolic alterations that are fundamental to cancer detection, therapeutical response and recurrence using small amounts of radioactive labeled molecules in vivo [8]. In general, accelerated radiotracer activity can be seen before anatomical structure changes. In most cancers, malignant cells are associated with increased metabolic activity. Therefore, increased uptake of a glucose analogue, ^{18}F-labeled 2-fluoro-2-deoxy-D-glucose (^{18}F-FDG) has become an accepted and valuable sensitive imaging technique for patients with cancer because it can be used to spot areas of malignancy, tumor growth and to detect stage and assess treatment of many processes. ^{18}F-FDG-PET has also been used for research purposes because it offers metabolic images non-invasively, quantitatively, and repeatedly, not just in humans but also in small animals, using specially designed high-resolution small animal scanning equipment [2, 7]. Due to the small dimensions of the structures to be imaged in animals, especially in mice, high-resolution instruments are required. During the past few years dedicated small animal PET scanners with enhanced spatial resolution were developed to overcome the limitation of human PET scanners for use with small species [2]. The huge variety of dedicated PET devices developed so far for imaging small animals indicates that there is a strong interest in applying non-invasive imaging techniques to animal research [8]. Designing systems with high spatial resolution and high sensitivity at the same time is still the main challenge in scanner development [8]. The main difficulty with PET is the lack of an anatomical reference frame. Therefore, the combination of PET and CT imaging devices into one single scanner offers several advantages in comparison to PET and CT imaging alone and improves the diagnostic value of both imaging modalities in identifying and characterizing of malignancies. In combined systems, the CT can be used for the precise anatomical localization of the radiotracer uptake, for the attenuation correction and therefore to reduce the PET examination time.

PET/CT is a highly valuable oncological imaging modality. In this study, the feasibility of in vivo imaging of tumor-bearing mice for potential use in oncology research using special scanning and reconstruction protocols of PET and CT of the recent generation of human PET/CT scanner (biograph Sensation 16, Siemens AG, Erlangen, Germany) was evaluated.

Materials and Methods

Animal Preparation and Radiotracer

All animal experiments were conducted in compliance with the guidelines for the care and use of research animals established by the local animal research committee. Female BALB/c tumor-bearing mice (20-25 g) were used. ^{18}F-labeled 2-fluoro-2-deoxy-D-glucose (^{18}F-FDG) was used as a radioactive tracer for imaging and detection of an increased rate of aerobic glycolysis and ^{18}F-labeled 1-α-D-(5-fluoro-5-deoxyarabinofuranosyl)-2-nitroimidazole (^{18}F-Fluoroazomycinarabinofuranoside; ^{18}F-FAZA) was used as a tracer for imaging and detection of regional tissue hypoxia. The radiotracer were injected via the tail vein. The mice were anesthetized and positioned prone inside the human PET/CT

Multi-detector Computed Tomography (MDCT)

High-resolution CT examinations were performed with a 16-slice computed tomography scanner (biograph Sensation 16; Siemens AG, Erlangen, Germany). An anterior-posterior scout-view was obtained for planning and determining the location of the scanning volume. Scans were acquired in a cranio-caudal direction using a tube voltage of 120 KV, tube current of 240 mAs, slice collimation of 16 x 0.75 mm, table feed of 12.0 mm, rotation time of 1.0 second and a 512 x 512 matrix. After data acquisition, the axial images were reconstructed in order to reduce the primary field of view (FOV) to 50 mm to decrease pixel size and provide high spatial resolution using a 0.3 mm increment, a 180° interpolation and high-resolution software algorithm (Kernel B70s very sharp).

Positron Emission Tomography (PET)

High-resolution PET examinations were performed with a full-ring 3D PET scanner with a Lutetium Oxyorthosilicate (LSO) detector (biograph Sensation 16; Siemens AG, Erlangen, Germany). The anterior-posterior scout-view from CT was used for planning and determining the location of 1 bed position. After the data acquisition of 30 min, PET images were reconstructed in order to reduce the primary field of view (FOV) with a sinogram trim factor of 3 to decrease pixel size and provide high spatial resolution using a 512 x 512 matrix, an iterative reconstruction method (attenuation weighted - ordered subset expectation maximization (AW-OSEM)), iterations of 6 and subsets of 16) and a gaussian filter. The CT examination was used for the attenuation correction of the PET images

PET/CT

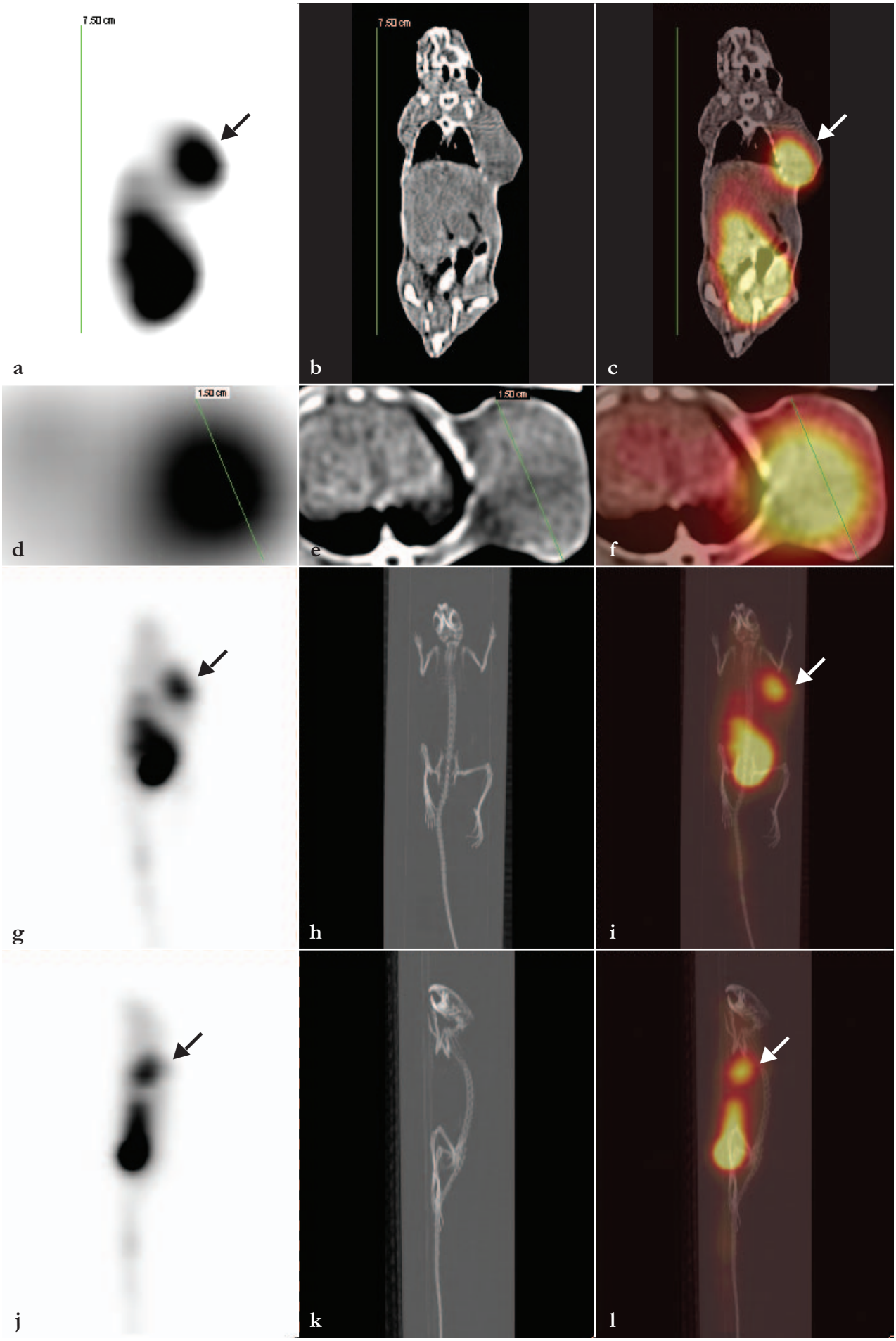
The image fusion was performed by an automatic image fusion system (MSViewer; Siemens AG, Erlangen, Germany). PET/CT allows evaluation of PET images in detail with the aid of high-quality CT images. The acquisition of PET emission data requires a relative long time (30 min) and represents an average of animal movement, free-breathing and cardiac motion. The acquisition of CT data is relatively short (up to few seconds). Therefore, the position of organs could differ between the average position obtained with PET emission and CT, especially in the region of the diaphragm. The CT images were used for the attenuation correction, the precise anatomical localization of increased radiotracer uptake of the PET imaging and for measurements of tumor lesions in distance and volume. The PET images were used for the qualitative and quantitative analysis (Bq per cm^3 x body weight (g) divided by injected dose) of tracer uptake in tumor lesions.

Results

The examination of tumor-bearing small animals using human PET/CT revealed excellent image quality (Fig. 1). Using the recent generation of high performance human PET/CT scanners with special scanning protocols, CT can be performed with a maximum spatial resolution of 0.6 x 0.6 x 0.6 mm and PET with a maximum spatial resolution of 6.3 x 6.3 x 6.0 mm.

Discussion

Human PET/CT imaging provides precise fusion of molecular and metabolic information from PET imaging with anatomical and morphological information from CT imaging [10]. PET will identify lesions with high tracer uptake, while the CT component will provide high-quality anatomical details. The precise correlation of ^{18}F-FDG uptake with anatomic images allows the differentiation of physiological variants of radiotracer uptake (urinary, bowel, fat, muscle) that can mimic tumor lesions from pathological uptake, and can help avoid potential false-positive interpretations [4]. Malignancies with low or normal metabolic activity (e.g. mucinous carcinomas, primary renal cell carcinoma and prostate cancer) in the PET image component may show clearly positive or suspicious findings in the CT image component of the PET/CT. PET/CT adds information to oncological diagnoses, allowing adequate tumor characterization and proving improved tumor staging. This yields a clear improvement of diagnostic accuracy by combining two already excellent imaging modalities. Although image quality is limited by spatial resolution, human PET/CT is expected to contribute significantly to research with small animal imaging [12]. Small animal imaging has gained increasing attention in recent years as an excellent in vivo evaluation method for molecular biology, oncology, and neuroscience research. Several groups have proposed and been developing the small animal PET/CT scanners, because they provide molecular and metabolic information non-invasively, quantitatively, and repeatedly [1, 3, 5, 11]. Multi-wire chamber animal PET scanners are currently the camera systems with the highest volumetric spatial resolution (1.1 mm^3) for in vivo imaging [8]. Schaefers et al. [9] have shown, that this imaging technology enables a clear identification of small infarcted areas of mice hearts. Nevertheless, small animal PET scanners are only available in a limited number of institutions. The main limitation of PET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imaging is the difficulty in anatomically localizing of lesions. However, it will take, at least, a few more years before the small animal PET/CT scanners are established and widely used for research purposes [12]. Human PET/CT scanner have a lower PET resolution than small animal PET scanners but are widely available. Lower PET resolution is also useful for small animal imaging, because it provides additional anatomical information by high-resolution CT images.

Tatsumi et al. [12] used for their animal studies a clinical PET/CT with a 2D PET scanner and a 4-slice CT and ^{18}F-FDG as radiotracer. Using this scanning technology with special scanning protocols, they were able to clearly visualize tumors in rabbits and rats for research purposes. With the aid of the high-quality CT mapping images, they could localize an intense FDG uptake in the solid portions of fast-growing tumors, whereas the slow-growing tumors had only a moderate or faint FDG uptake and the necrotic portions of the tumors had no FDG uptake. For the visualization of mice, the field of view (FOV) chosen for image CT reconstruction was 150 mm and the PET reconstruction resolution 5 to 6 mm. They could depict an increased FDG uptake in mice tumors with varying FDG activity levels, but detailed anatomical information was not optimally provided from the tumors. The intratumoral heterogeneity in FDG uptake could not be adequately determined in mice tumors in their study, probably because the tumors were small in size. On the basis of the results in their study, they recommend that the evaluation of tumor-bearing mice with a small animal PET/CT scanner should be performed. Although it has limitations, small animal imaging with a clinical PET/CT scanner may be quite adequate for sequential non-invasive imaging in oncology research because the CT is of high resolution, allowing for localization of PET findings and for more precise non-invasive estimation of radioactivity concentration [12]. Small animal PET/CT scanner would be better suited for evaluating tumor-bearing mice and likely could enhance imaging smaller tumors in rabbits or rats [12]. Nevertheless, the recent generation of high performance human PET/CT scanners provides better images in mice and also is accurate to examine mice, because the 3D PET provides a higher count sensitivity than the 2D PET and the 16-slice CT provides a higher spatial resolution as a 4-slice CT.

Conclusions

PET/CT definitely has a greater advantage over PET alone and is considered to be particularly well suited for research purposes. The investigation of cancer in small animals with PET/CT is probably one of the most challenging tasks in nuclear medicine, since the structures of interest are almost in the same range as the maximum spatial resolution. Very interesting topics for using PET/CT scanners are: implantation of human tumor cells in small animals and evaluation of tumor growth and growth inhibition factors; development of new anti-tumor drugs and measuring of anti-tumor effects; and cancer treatment response of immunotherapy, chemotherapy and radiation therapy using metabolical and morphological parameters. The small animal-specific protocol made it possible for tumor PET/CT images to be clear enough to resolve considerable heterogeneity of tracer uptake within the tumors with the help of thin-slice, high-quality CT images. The examination of small animals using a modern human PET/CT scanner revealed excellent image quality and allowed accurate correlation and evaluation of metabolic and anatomical information and is promising for in vivo research of tumor-bearing mice. PET techniques can assess the in vivo biodistribution of many relevant radiopharmaceuticals and thus contribute significantly and distinctively to the evaluation of tumors [12]. The results are varying from tumor cells and radiotracer. The information from PET/CT imaging would be of interest for validation of oncological research studies of evaluation of new tumor tracers labeled with different positron emitters (F-18, C-11, N-13 and O-15). Nevertheless, futher detailed and systematic studies are necessary to clearly define the value and the comparablity with other small animal imaging techniques and to define the minimum size of tumor to examine. Further diagnostic information concerning the differention of solid and necrotic tumor portions and tumor vascularity is also expected after injection of contrast material [12].

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◀ *Fig. 1.* Female BALB/c mouse (20 g) bearing a subcutaneous EMT6 tumor (murine mammary carcinoma cell line) at the left side of the thorax (arrows). ^{18}F-Fluoroazomycinarabinofuranoside (^{18}F-FAZA) was used for imaging of tumor hypoxia. Coronal slices (a-c) through the mice body and enlarged axial slices (d-f) through the tumor at the level of maximal accumulation of hypoxia tracer showing the CT-based attenuation corrected PET images (a,d), high-resolution CT images (b,e) and fused PET/CT images (c,f). PET shows a focal increased tracer uptake of the central part of the tumor lesion. CT revealed that this focal tracer uptake was corresponded to a low attenuation area (necrotic portion) of the tumor. A high radioactivity can also be seen in the small and large intestine because of tracer elimination. Anterior-posterior view (g-i) and left lateral view (j-l) of the maximum intensity projection (MIP) reconstruction of the tumor-bearing mouse showing the CT-based attenuation corrected PET images (g,j), the high-resolution CT images (h,k) and the fused PET/CT images (i,l).

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