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ABSTRACT

The feasibility of small animal imaging using a clinical positron emission tomography/computed tomography (PET/CT) scanner with [F-18]-fluoro-2-deoxy-D-glucose (FDG) was evaluated. As tumor-bearing small animal models, rabbits with VX-2 liver tumors, rats with mammary tumors on the back, and mice with LS174T human colon tumor xenografts were prepared. Two-dimensional PET, CT, and fused PET/CT images were obtained and reconstructed with a combined PET/CT system using a conventional protocol for humans and dedicated high-resolution mode protocols specialized for each species. Estimated radioactivity concentrations in tumors and normal organs determined noninvasively on FDG-PET/CT were compared with the actual tissue radioactivity levels determined from gamma-counting after vivisection in rats. In addition, recovery-corrected radioactivity concentrations were calculated and evaluated using the tumor/normal organ sizes measured on CT. Tumors in rabbits and rats were clearly visualized by FDG-PET/CT in the dedicated protocols, and images were considered suitable for research purposes. With the aid of thin-slice CT-mapping images, FDG uptake was correctly localized in the viable tumor regions. In mice, increased FDG uptake in tumors with varying activity levels was observed, but detailed anatomical information was not optimally provided from the images, even using specialized protocols. The estimated radioactivity concentrations of tumors and normal organs were close to the actual radioactivity concentrations obtained by gamma-counting (r = 0.97, P < 0.001, the estimated/actual slope: 1) when recovery correction was applied using the sample sizes measured on CT. FDG-PET/CT imaging with a modern clinical scanner was demonstrated to be feasible, of excellent quality, and quite quantitatively accurate for research in rabbits or rats with tumors of appropriate size (>2 cm without recovery correction and >1 cm with recovery correction). Evaluation of FDG uptake within a tumor was possible with the aid of CT images. Dedicated small animal PET/CT scanner would be better suited for evaluating small mice and likely enhance imaging smaller tumors in rabbits or rats. Although it has limitations, small animal imaging with a clinical PET/CT scanner may be quite adequate for sequential noninvasive imaging in oncology research because the CT is of high resolution, allowing for localization of PET findings and for more precise noninvasive estimation of radioactivity concentration through partial volume corrections.

INTRODUCTION

PET, with the glucose analogue FDG, is the first molecular imaging technique that has been widely applied for brain, cardiac, or cancer imaging in clinical settings (1). The FDG uptake detected by scans allows for estimation of the cellular activity in target tissues and can be used to detect stage and assess treatment of many processes, most notably cancers. FDG-PET has also been used for research purposes because it offers metabolic/functional images noninvasively, quantitatively, and repeatedly, not just in humans but also in small animals, using specially designed high-resolution small animal scanning equipment (2, 3). PET techniques can assess the in vivo biodistribution of many relevant radiopharmaceuticals and thus trace many processes.

Recently, combined PET and CT (PET/CT) scanners have been developed and are emerging as highly valuable imaging modalities (4, 5). PET/CT imaging provides precise fusion of molecular PET images with high-quality anatomical CT images. Computer software allows generation of anatomic/molecular images. The CT scanners used with PET/CT offer much superior spatial resolution than the PET devices.

In this study, we evaluated whether FDG-PET/CT images of tumor-bearing rabbits, rats, and mice are feasible for research purposes using a clinical PET/CT scanner designed and now applied for human use and determined the ability of PET/CT to noninvasively quantify radioactivity concentration in vivo.

MATERIALS AND METHODS

Small Animal Models. Tumor-bearing rabbits (n = 7), rats (n = 6), and mice (n = 5) were prepared and evaluated with FDG-PET/CT imaging. For a rabbit model, New Zealand white rabbits (~4.0 kg) with VX2 liver tumors were used (6). After being grown on the hind leg of a carrier rabbit for 2 weeks, the tumor was excised and minced in HBSS. The clumps of tumor cells (0.1–0.2 ml) from the minced tumors were directly implanted into the liver of the recipient rabbits under anesthesia using a midline subxyphoid incision. The clumps were then used for labeling studies 3 weeks after implantation when the tumors had grown to >3 cm in greatest diameter. Lewis female rats (200–250 g) were directly implanted with rat RMT cell lines (7). Frozen RMT cell clumps were thawed and implanted (107 cells/rat) in the interscapular fat pads of the rats under anesthesia. Imaging studies were performed with the tumor-bearing rats 4–6 weeks after implantation when the tumor reached ~2 cm in greatest diameter. In a mouse model, BALB/c (nu/nu) female nude mice (~20 g) bearing LS174T human colon cancers were used. The cancer cells were cultured in DMEM containing 10% heat-inactivated fetal bovine serum, 100 units/ml penicillin, 100 μg/ml streptomycin, and 2 mM glutamine. The mice were inoculated s.c. with 107 cancer cells in the flank, and they were used for imaging studies 2–3 weeks after inoculation when tumors had grown to ~1.0 cm in greatest diameter. We also imaged one tumor-bearing mouse, whose tumor had gradually grown to 1.5 cm in diameter over 3 months, as a model for slow-growing tumor. All animal studies were approved by the Johns Hopkins University Animal Care and Use Committee.

FDG-PET/CT Imaging. Small animal imaging studies were performed with a combined PET/CT scanner designed, approved, and optimized for clinical use (Discovery LS; GE Medical Systems, Milwaukee, WI). This scanner allows for the simultaneous acquisition of 35 transaxial images with an interslice spacing of 4.25 mm in each bed position for the PET images. Axial and transaxial PET resolution is ~4.5-mm FWHM. The FOV chosen for image reconstruction was 35, 25, and 15 cm for rabbits, rats, and mice, respectively. Fifty-cm FOV-reconstructed images were also generated for an automatic image fusion system, which is routinely used for clinical human examinations.
along with the smaller FOV images that were specific to each animal. This scanner also allowed multidetector row helical CT scanning. Technical parameters used for the CT portion of PET/CT were as follows (protocol 1 for small animals): a detector row configuration of 4 × 1.25 mm; pitch of 3:1 (high-quality mode); voltage of 120 kVp; current of 120, 120, and 80 mA; scan FOV of “large,” “small,” and “small”; and display FOV of 35, 25, and 15 cm for rabbits, rats, and mice, respectively. For attenuation correction and an automatic image fusion system, CT using the parameters for clinical examinations was also performed for all animals as follows (protocol 2): a detector row configuration of 4 × 5 mm, pitch of 6:1 (high-speed mode); voltage of 140 kVp; current of 80 mA; scan FOV of “large”; and display FOV of 50 cm.

After at least 4 h of fasting, ~37 MBq (1 mCi), 9.25–18.5 MBq (0.25–0.5 mCi), and 7.4 MBq (0.2 mCi) of FDG was administered i.v. to a rabbit (via marginal ear vein), rat (via tail vein), and mouse (via tail vein), respectively, under anesthesia. About 50 min later, whole-body CT images with protocol 1 followed by images with protocol 2 were acquired without contrast material. A whole-body emission PET scan for the same axial coverage was performed in the two-dimensional mode with 10 min of acquisition/bed position. Two and one PET bed position(s) were obtained for rabbits/rats and mice, respectively. i.v. contrast-enhanced CT images (Omnipaque 350; Nycomed, Princeton, NJ) with protocol 1 were obtained in seven rabbits (5-mL dose via marginal ear vein) and three rats (0.25-mL dose via tail vein) after PET imaging. The animals were kept in the anesthetized condition from the time of FDG injection until the end of imaging. Attenuation-corrected PET images of two types of FOV (≤50 cm) using the data from CT (protocol 2) were reconstructed with an ordered subset-expectation maximization iterative reconstruction algorithm (28 subsets and 2 iterations). The 1.25-mm thick/interval transaxial CT images of smaller FOV were reconstructed and were fused manually with smaller FOV PET images using image analysis software (Adobe Photoshop 6.0; Adobe Systems Incorporated, San Jose, CA). The PET and CT images to fuse were prepared as separate layers in the imaging software and then were manually merged using the mild FDG uptake of skin along with normal organs’ contours as landmarks. This process was easily performed because both PET and CT images were reconstructed in an equal size and were intrinsically registered by the design of the PET/CT system. The 5-mm thick/4.25-mm interval transaxial CT images of 50-cm FOV were also reconstructed for automatic fusion with 50-cm FOV PET images. FDG-PET, CT, and 50-cm FOV-fused FDG-PET/CT images were generated on a computer workstation (eNTEGRA), using vendor-supplied software. Smaller FOV-fused PET/CT images were displayed on a Windows (Microsoft Co., Redmond, WA)-based personal computer. Image evaluation was performed with smaller FOV PET, CT, and fused PET/CT images, referring to 50-cm FOV-fused FDG-PET/CT images.

In addition to the tumor-bearing animals, five normal rats also had FDG-PET/CT studies in the same manner to evaluate the quantitation ability of the scanner as described below.

**Evaluation of Quantitation Ability of the PET/CT Scanner in Small Animal Imaging.** Immediately after FDG-PET/CT imaging, eight rats, including three with tumors, were sacrificed by cervical dislocation. Major organs, i.e., brain, heart, right lung, liver, right kidney, skeletal muscle, and tumor, were excised, weighed, and assayed for radioactivity in a γ-well counter. Volumes of the samples were also measured with a water replacement method.

ROIs were placed on smaller FOV transaxial PET images to totally surround the most intense areas of FDG uptake in the target organs/tumors while avoiding nearby tissues, and the mean of each pixel’s activity value within each ROI was recorded (expressed as Bq/ml). Decay-corrected radioactivity levels obtained noninvasively from FDG-PET/CT images were compared with the actual activity levels counted directly using a gamma counter. The ratio of the radioactivity levels determined by PET to those measured by gamma counting were calculated and expressed as recovery coefficient values. As recovery coefficient values are known to have a curvilinear relationship with sample diameters in phantom studies (8–10), we analyzed the relationship of the recovery coefficient values and maximum organ/tumor diameters measured on smaller FOV CT images in normal organs and tumors. The recovery-corrected radioactivity levels were then calculated using the estimated recovery coefficient values based on the maximum normal organ/tumor diameters.

Volumes of normal organs and tumors were also measured using smaller FOV 1.25-mm thick/interval transaxial CT images and were compared with the actual volumes to demonstrate the volume quantitation ability of CT. The volume for each slice was obtained by multiplying the area of the target organ or tumor by the slice thickness and then the total volume was calculated by adding each slice volume.

**Statistics.** The relationship of the radioactivity concentration determined by FDG-PET/CT and gamma counter was evaluated by linear regression analysis and the Fisher z test. The relationships between the recovery-corrected and actual radioactivity concentrations and between the estimated organ/tumor volumes from CT and actual volumes were also analyzed in the same manner. The relationship of the recovery coefficient values and maximum organ/tumor diameters was analyzed using several linear/curve fittings over scattered plots for the two factors. \( P < 0.05 \) was considered statistically significant.

**RESULTS**

**Tumor FDG-PET/CT Images.** FDG-PET/CT images clearly delineated rabbit VX2 tumors growing in rabbits (Fig. 1A–C). Intense FDG uptake is demonstrated in the tumor in the left lobe of the liver on PET. The tumor was depicted as a low X-ray attenuation area with slightly inhomogeneous contrast enhancement on CT (Fig. 1, A and B). Macroscopic pathological specimens revealed the tumor to be quite solid as Fig. 1B. In one rabbit, FDG-PET/CT detected a small tumor (7 mm in diameter) as an intense uptake focus near a granuloma, which had grown associated with the implantation procedure and exhibited mild to moderate ring-like FDG uptake with substantially cold center (Fig. 1C).

In rats, FDG-PET/CT images clearly delineated the tumor (RMT). Intense FDG uptake was observed in the solid portion of the tumor seen on CT, which corresponded to the viable, nonnecrotic tumor areas. CT depicted the solid portion as an intermediate attenuation area and as a moderately enhanced area after use of contrast material. No FDG uptake was visualized in the necrotic portion, which was identified as a low-attenuation area without significant contrast enhancement on CT (Fig. 2, A and B).

In mice, tumors with varying FDG activities were depicted differently. The faster-growing examples of LS 174T tumors showed intense FDG uptake (Fig. 3A), whereas the slow-growing tumor had only moderate uptake, despite the faster-growing tumor being a little small in size (Fig. 3B). However, the intratumoral heterogeneity in tracer uptake could not be adequately determined in the mouse tumors in this study using the clinical PET/CT scanner, probably because the tumors were small in size.

**Normal Organ PET/CT Images.** Rabbit FDG-PET/CT images showed similar findings to our experience in imaging humans regarding the relative radiotracer accumulations in normal organs. F-18 activity was most prominent in the normal brain, kidneys, bladder, and heart. A portion of the intestines also exhibited intense FDG uptake in our study. The liver was depicted as moderate areas of FDG uptake. Similar findings were observed in rats and mice as well, except for faint FDG uptake in the liver and the intense tracer uptake visualized in the dorsal cervicothoracic midline region (Figs. 2B and 3, A and B).

**Evaluation of Quantitation Ability of the PET/CT Scanner in Small Animal Imaging.** Table 1 shows the results of this analysis. The mean radioactivity was highest in the normal brain followed by the kidney and tumor on FDG-PET/CT images. The heart exhibited intense FDG uptake, however, the estimated radioactivity was less than half that seen in the brain. The lung, liver, and muscle showed faint FDG uptake. This order was the same as that obtained from γ counting, except that the actual radioactivity was higher in the lung than liver on γ counting. The decreased volume of the lung after sacrifice because of collapse likely increased Bq/ml values on γ counting after vivisection.

The recovery coefficient values were closest to the optimal value of 1 in the normal liver and in tumors, probably because their sizes were...
large enough to avoid severe partial volume recovery problems from the quantitative analysis system of the PET/CT scanner used in this study. By contrast, the recovery coefficient values were typically well <1 in other smaller organs. Fig. 4 shows the relationship between the recovery coefficient values and maximum normal organ/tumor diameters on CT. Among several fittings applied, the logarithmic function appeared to fit most appropriately the data of recovery coefficient values and maximum normal organ/tumor diameters in this study ($r = 0.81, P < 0.0001$). Using this logarithmic function, the radioactivity concentrations estimated from FDG-PET images were corrected to the ones in which the partial volume effect in small-sized targets was considered minimal. The recovery-corrected radioactivity concentrations had an excellent linear correlation with the actual radioactivity concentrations in normal organs and tumors measured by $\gamma$ counting ($r = 0.97, P < 0.0001$) with an excellent slope of 1 (Fig. 5, closed circles), which was greatly improved from the slope without recovery correction (open circles).

The estimated volumes of normal organs and tumors from CT exhibited an excellent linear correlation with the actual volumes ($r = 0.93, P < 0.0001$), excluding heart and lung, the volumes of which are not fixed during free-breathing CT scan (Fig. 6).

**DISCUSSION**

Small animal imaging has gained increasing attention in recent years as an excellent in vivo evaluation method for molecular biology, oncology, and neuroscience research. PET imaging, in particular, has been shown to be very useful for these purposes because it provides metabolic/functional information noninvasively, quantitatively, and repeatedly. Dedicated small animal PET scanners are now available in a limited number of institutions, but the best spatial resolution among them is still ~1–2 mm FWHM (2, 3). One limitation of current small animal PET imaging is the difficulty in anatomically localizing lesions seen on PET. PET/CT techniques could potentially address this limitation but are not yet generally available for small animals. Clinical PET/CT scanners, although optimized for general human use, have less good PET resolution than dedicated high-resolution small animal PET scanners. However, PET of less good resolution may also be useful for small animal imaging with the aid of detailed morphological information provided by high-resolution CT images. The purpose of this study was to determine whether FDG-PET/CT images generated using a clinical PET/CT scanner are of potential use for oncology research in living small animals and to determine whether the limited resolution PET would allow meaningful lesion radioactivity quantitation. This is of practical importance because human PET/CT imaging devices are being deployed quite widely at present.

Our study showed that tumors were clearly demonstrated on PET/CT in rabbits and rats in this study. PET images were visually similar in quality to clinical tumor images from humans and thus were transaxial high-resolution images of the rabbit at the level of the primary tumor. Intense FDG uptake was observed in the left lobe of the liver on FDG-PET (black arrow) and fused PET/CT (white arrow) images. CT depicted a low attenuation area in the corresponding region (white arrow). Heart/vascular structure and intestine showed high FDG uptake on FDG-PET and fused PET/CT images (expressed as H, V, and I, respectively, on PET). Left: contrast-enhanced CT; middle: FDG-PET, and right: fused PET/CT image. B, C, transaxial high-resolution images of the rabbit at the level of the primary tumor. Intense FDG uptake was observed in the left lobe of the liver on FDG-PET (black arrow) and fused PET/CT (white arrow) images. CT depicted a low attenuation area in the corresponding region (white arrow). Macroscopic specimen demonstrated a solid tumor. G (low attenuation area): gall bladder. Top left: contrast-enhanced CT; top right: FDG-PET; bottom left: fused PET/CT; and bottom right: macroscopic tumor image of tumor removed from liver. C, transaxial high-resolution images of the rabbit at the level of the metastatic VX-2 tumor. A small focus of intense FDG uptake is seen in the abdominal wall on FDG-PET (black arrow) and the fused PET/CT (white arrow) images. CT revealed that this focal tracer uptake was corresponded to a 7-mm diameter metastatic lesion. A known granuloma (G) associated with the tumor implantation procedure was also seen clearly on CT. Note that only mild to moderate FDG uptake was observed in the marginal area of this granuloma in contrast to the intense FDG uptake in the small metastatic lesion. Top left: contrast-enhanced CT; top right: FDG-PET; and bottom right: fused PET/CT image.
considered to be promising for research purposes. FDG uptake was observed in the solid apparently viable portion of tumor on CT, whereas no FDG uptake was demonstrated in the apparently necrotic portion. This result was not surprising given that the maximal diameter of the tumors was ~2 cm. This is a size in which both FDG-PET and CT detect tumors with high sensitivity in several clinical human studies. However, tumor FDG-PET/CT images obtained with a standard/rapid clinical PET/CT protocol for humans (with CT protocol 2) were likely not optimal for all research purposes because the detailed heterogeneity information from within the tumors was not available with the 50-cm FOV PET and 50-cm FOV thicker-slice CT images. 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 mapping images. Because the PET portion of the scanner has ~5–6-mm reconstruction resolution, better PET image quality would not be expected for tumors of ~2 cm in size used in this study. With the aid of the high-quality CT mapping images, however, FDG uptake could be localized in the solid peripheral portions of the tumors, which was believed to be comprised of viable cancer cells. Furthermore, the CT could be used to correct the PET quantitative data for resolution-linked count recovery deficits.

In mice, FDG-PET/CT images of tumors as well as of normal organs were less clear as compared with those in rabbits and rats. This is mainly attributed to the small sizes of the organs and tumors in mice, FDG-PET/CT images of tumors as well as of normal organs were less clear as compared with those in rabbits and rats. This is mainly attributed to the small sizes of the organs and tumors in

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**Fig. 2.** A, coronal images of a tumor-bearing rat. Intense FDG uptake was observed in the marginal area of the tumor on FDG-PET (black arrow) and fused PET/CT (white arrow) images. A slightly high attenuation area on CT (black arrow) corresponded to the FDG uptake. B: brain, H: heart, and K: kidney. B, transaxial high-resolution images of the rat at the level of the tumor. Intense FDG uptake was observed in the marginal area of the tumor on FDG-PET (black arrow) and fused PET/CT (white arrow) images. A moderately contrast-enhanced area on CT (slightly high attenuation: white arrow) corresponded to the FDG uptake. No FDG uptake was observed in the necrotic portion of the tumor (N on CT).

**Fig. 3.** A, coronal (top) and transaxial (bottom) images of a mouse with rapidly growing tumor (LS 174T). Increased FDG uptake was readily observed in the flank of the mouse on FDG-PET (black arrows) and fused PET/CT (white arrows) images. A tumor was observed in the corresponding region (white arrow on CT). Intense FDG uptake was observed in the dorsal thoracic midline region on PET (black arrowhead) and fused PET/CT (white arrowhead) images. Because of the poor PET spatial resolution compared with the mouse's body size, the artifact (X on PET), which was probably caused by heart and intense FDG uptake in the dorsal midline region, was substantial in the thoracic region. This is likely because of tracer uptake in structures seen better on other image planes. B: bladder. B, coronal (top) and transaxial (bottom) images of a mouse with slower-growing tumor (LS 174T). Only faint FDG uptake (black arrow on PET, white arrow on fused PET/CT) was detected in the large tumor (white arrow on CT). H: heart.
mice. We used the two-dimensional acquisition mode in PET imaging because the fused images with CT protocol 2 was not available in three-dimensional acquisition mode (automatically) when we started this study. The three-dimensional PET acquisition available at present may provide better images even in mice because of the higher count sensitivity than in two-dimensional mode. Tumors if allowed to grow to ≥2 cm in size may have been better visualized, but such tumors were considered to lack physiological relevance for mice. It should be noted, however, that information regarding the presence or absence of FDG uptake in tumors was available with the clinical PET/CT scanner used in this study. Intense FDG uptake was observed in rapid-growing tumors in contrast to the faint FDG uptake seen in slower-growing tumors. This amount of information plus more detailed anatomical information may be quite sufficient for validation studies of new tumor evaluation tracers (2, 3).

Estimated radioactivity levels of normal organs and tumors from PET images were compared with actual radioactivity levels measured with a γ counter. The recovery coefficient values were >0.80 in livers and tumors, the sizes of which were large in contrast to the smaller recovery coefficient values observed (∼0.4 to 0.6) in smaller organs. This phenomenon is fully consistent with recovery coefficient theory. Zhang et al. (8) reported that the recovery coefficient values were most affected by target sizes (diameters) as compared with target-to-background ratios in their phantom study. In this study also, we analyzed the relationship between the recovery coefficient values and maximum diameters of normal organs/tumors. As our analysis was performed using actual organs/tumors in contrast to the homogeneous artificial spheres in phantom studies by other investigators, the relationship was less clear and did not allow excellent curve fitting seen in the phantom studies. Instead of sigmoid functions, which are often used to express the relationship between the recovery coefficient values and normal organ/tumor diameters (10), the logarithmic function was observed to be the most appropriate and used for the fitting in this study. The estimated recovery-corrected radioactivity concentrations, calculated using the fitted logarithmic function and target diameters on CT, had an excellent linear correlation with the actual radioactivity concentrations with an excellent slope of 1 as shown in Fig. 5. Moreover, the estimated organ/tumor volumes from CT were quite similar to the actual volumes excluding the heart and lung in which the volumes are not fixed during free-breathing CT scan. These

<table>
<thead>
<tr>
<th>Organ/tumor</th>
<th>Volume (ml)</th>
<th>Weight (g)</th>
<th>RA on gamma counting (Bq/ml)</th>
<th>RA on PET/CT (Bq/ml)</th>
<th>Recovery coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>1.71 ± 0.31</td>
<td>1.65 ± 0.20</td>
<td>236,091 ± 56,892</td>
<td>109,907 ± 20,779</td>
<td>0.47 ± 0.03</td>
</tr>
<tr>
<td>Heart</td>
<td>0.88 ± 0.10</td>
<td>0.81 ± 0.072</td>
<td>101,948 ± 26,742</td>
<td>42,893 ± 6,766</td>
<td>0.43 ± 0.06</td>
</tr>
<tr>
<td>Lung</td>
<td>0.90 ± 0.42</td>
<td>0.58 ± 0.31</td>
<td>42,888 ± 2,402</td>
<td>21,705 ± 3,094</td>
<td>0.51 ± 0.06</td>
</tr>
<tr>
<td>Liver</td>
<td>11.68 ± 2.72</td>
<td>9.77 ± 1.35</td>
<td>30,754 ± 12,339</td>
<td>24,192 ± 5,923</td>
<td>0.82 ± 0.11</td>
</tr>
<tr>
<td>Kidney</td>
<td>1.00 ± 0.25</td>
<td>0.94 ± 0.17</td>
<td>159,572 ± 98,966</td>
<td>88,489 ± 49,477</td>
<td>0.61 ± 0.17</td>
</tr>
<tr>
<td>Muscle</td>
<td>1.02 ± 0.18</td>
<td>0.99 ± 0.18</td>
<td>22,438 ± 5,160</td>
<td>12,750 ± 1,598</td>
<td>0.59 ± 0.18</td>
</tr>
<tr>
<td>Tumor</td>
<td>7.99 ± 0.26</td>
<td>13.4 ± 3.26</td>
<td>98,966 ± 88,489</td>
<td>56,892 ± 10,927</td>
<td>0.81 ± 0.21</td>
</tr>
</tbody>
</table>

Table 1. Comparison of radioactivity levels measured by FDG-PET/CT and ex vivo gamma counting (rats)

Fig. 4. Recovery coefficient values, the ratios of radioactivity concentrations estimated on PET to those directly measured by γ counting, showed a logarithmic relationship with maximum normal organ/tumor diameters measured on CT.

Fig. 5. The relationship between the radioactivity concentrations estimated from PET images and those directly measured by γ counting in normal organs and tumors without recovery correction (○). Although an excellent linear correlation was obtained between the two parameters, the slope was rather flat (0.46). With partial volume correction using the recovery coefficient values estimated from organ/tumor diameters (Fig. 4), the slope was improved to the optimal value of 1 (●).

Fig. 6. Sample volumes estimated from thin-slice CT images were quite similar to the volumes directly measured with a water replacement method.
results clearly demonstrated the good quantitation ability of the clinical PET/CT scanner with the help of thin-slice CT images. In this point, PET/CT definitely has a greater advantage over PET alone and is considered particularly well suited for research purposes.

Attenuation correction is an important factor in quantitative PET studies. We evaluated if attenuation correction was also required in the small animals used in this study by comparing ROI values on nonattenuation-corrected and CT attenuation-corrected PET images (data not shown). According to the analysis, in rabbits, attenuation correction appeared to be required and in rats was considered to be desirable for accurate quantitation. By contrast, in mice, attenuation correction may not necessarily have been required. PET/CT offers attenuation correction CT data quite easily and quickly, which is also a feature of the combined PET/CT system, not expected in dedicated small animal PET scanners.

Imaging separately with a dedicated small animal PET scanner and a CT scanner with subsequent software fusion may provide similar information to that provided with a PET/CT scanner. However, the great advantage of PET/CT is that PET and CT images of the same location are consistently provided without significant technical difficulty and without major concern regarding misregistration of data sets. This technical feature is expected to contribute significantly to research with small animal imaging. PET/CT allows evaluation of PET images in detail with the aid of high-quality CT mapping images. With respect to FDG, the tracer uptake is not necessarily homogeneous inside tumors. The information about corresponding tissues is therefore of interest from a functional/metabolic and morphological point of view. Changes in FDG distribution within tumors or in FDG lacking abnormal soft tissues may be observed and evaluated rather accurately after treatment intervention with PET/CT. F-18 of FDG is known to have a shorter path length (<2 mm), the distance from the point of positron emission to that of annihilation, compared with other positron emitters with higher energy such as C-11, N-13, or O-15 (>4 mm). This phenomenon also helps the detailed evaluation of FDG uptake with PET/CT images. Small animal PET/CT imaging using tracers labeled with other than F-18 would be of interest, however, the accuracy of quantitation may be degraded because of the blurred contours or enlarged target sizes of normal organs/tumors compared with CT images on reconstructed PET images.

Thin-slice CT images functioned as in vivo low-power microscopic images in this study. Solid and necrotic portions within tumors were depicted differently, and they were distinguishable more clearly after giving i.v. contrast material. We injected the contrast material manually as a bolus, but the administration of the material with an automatic injector may allow evaluation of the vascularity status inside tumors on CT. Because the relationship between FDG distribution and tumor vascularity has been an attractive topic in oncology research, additional experimental studies are desired using a more specific protocol to evaluate that relationship.

Small animal PET imaging provided metabolic functional information noninvasively, quantitatively, and repeatedly. PET/CT imaging provides additional anatomical information. If we focus on research in the oncology field, these kinds of information are considered to contribute significantly and distinctively to the evaluation of tumors before and after treatment interventions. Sequential observation of metabolic and morphological status in a tumor after treatment would be a very interesting topic with the PET/CT scanner because human tumor response assessment moves from anatomical to functional methods. Evaluation of new antitumor drugs developed from basic sciences, especially, would be a target for research with imaging techniques. Small animal PET/CT imaging potentially plays an important and great role in the translational research in the oncology field such as PET/CT plays a growing role in cancer treatment response monitoring in humans.

Several groups have proposed and been developing the dedicated small animal PET/CT scanners at present (11). Although the dedicated scanners are not yet established, one group has reported promising results recently (12). On the basis of the results in this study, mouse PET/CT imaging studies are recommended to be performed with a dedicated small animal PET/CT scanner, if possible. However, it will take, at least, a few more years before the dedicated small animal PET/CT scanners are widely used for research purposes, hence, the importance of this work with the more widely available human PET/CT systems.

In conclusion, FDG-PET/CT imaging with a modern clinical scanner was demonstrated to be feasible, of excellent quality, and quite quantitatively accurate for research in rabbits or rats with tumors of appropriate size (>2 cm without recovery correction and >1 cm with recovery correction). Evaluation of FDG uptake within a tumor was possible with the aid of CT images. A dedicated 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. Although it has limitations, small animal imaging with a clinical PET/CT scanner may be quite adequate for sequential noninvasive imaging in oncology research because the CT is of high resolution, allowing for localization of PET findings and for more precise noninvasive estimation of radioactivity concentration through partial volume corrections.

ACKNOWLEDGMENTS

We thank Masayuki Kudo (GE Yokogawa Medical Systems, Ltd, Tokyo, Japan), for his helpful information regarding the CT imaging protocol for small animals. We also thank the PET imaging technologists and the PET radiopharmacy staff in the PET Center in The Johns Hopkins Hospital for their excellent technical assistance.

REFERENCES


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