Applications of Positron Emission Tomography/Computed Tomography Image Fusion in Clinical Positron Emission Tomography—Clinical Use, Interpretation Methods, Diagnostic Improvements

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Positron emission tomography (PET)/computed tomography (CT) scanners with combined dedicated high-performance PET and CT scanners have been introduced recently in PET imaging. Oncological imaging with fluorodeoxyglucose (FDG) is currently the dominant application of PET. The addition of CT to PET offers many advantages, including obtaining a fast and relatively low-noise transmission scan, shortening the duration of the examination, adding precise anatomical information to FDG imaging, and providing additional diagnostic information. However, the use of CT for attenuation correction can lead to some artifacts that need to be considered when interpreting a PET/CT study: quantitative measurements may be altered, high density IV and oral and metallic objects may produce artifacts, and the registration of PET and CT may occasionally be suboptimal. Areas where using PET/CT offers particular potential advantages include the head and neck region, abdomen, and pelvis. Even in the thorax, PET/CT offers some advantages. Although clinical data evaluating the added value of PET/CT over PET are presently limited, preliminary results are very encouraging. More studies are warranted to clearly define the clinical impact of PET/CT over PET; however, it is clear this dedicated fusion technology will be very important for patient imaging in the coming years.

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position with a $^{68}$Ge source. For a regular “whole-body” study with a BGO PET camera, we usually acquire data from the base of the skull to proximal thigh, which requires five to seven bed positions, depending on the patient’s height. With 5 and 3 min per bed position for emission and transmission acquisition respectively, this makes the total duration of examination vary from 40 to 56 min, excluding the time needed for patient positioning.

**Use of CT for Attenuation Correction**

CT images are tomographic displays of body x-ray density expressed in Hounsfield units (HU). They are obtained from the attenuation of low-energy high-intensity x-ray sources by the body. Thus, they have high spatial resolution and low noise. It is logical to use them to generate a transmission map by converting HU into attenuation coefficients. Because attenuation coefficients are different for the 511 keV and CT x-ray photons, and because this difference varies depending on the material or tissue that is imaged, an algorithm is necessary to scale the attenuation coefficient of the much lower x-ray energy levels to 511 keV energy level.6

**Decrease of Study Duration**

With the multidetector CT of the Discovery LS scanner, the CT acquisition from the base of the skull through mid thigh typically lasts less than 1 min. The transmission scan time is thus reduced, compared with the standard PET transmission scanning approach that uses $^{68}$Ge sources rather than x-rays. This shortens the duration of the overall examination by 15 to 21 min. Total scanning time, excluding patient positioning, can be reduced to about 26 to 36 min. Throughput can be increased by nearly 50%, with a turnaround time for every patient being decreased to 35 to 45 min.

**CT Current**

The CT-based attenuation map has high statistical quality and thus a low-noise level, which decreases the introduction of noise and potential noise-related artifacts in the attenuation correction process. The current setting is a compromise between the diagnostic quality of the resulting CT scan, the smallest current necessary to get a high-quality transmission map, and a minimum radiation dose to the patient. Investigators in Zurich, Switzerland, demonstrated that an adequate transmission map for emission PET to be quantitatively correct can be obtained with very low current (10 mA).7 However, higher CT currents are required to produce diagnostic quality CT scans.7,8

The CT parameters used for PET/CT scanning in our department are given in Table 1. To reduce the radiation dose to the patient, an “intermediate-dose” CT scan is performed. Initially a fixed 80 mA scan was performed, but the quality of the resulting CT scan was clearly suboptimal in large patients. The CT current is now adjusted according to patient weight (Table 1). The resulting diagnostic quality CT scan is usually satisfactory.

**Quantitative Measurement**

The use of CT-derived transmission map is usually adequate for attenuation correction. However, there is a potential risk of over-estimating the true tracer activity with CT-based attenuation correction. Nakamoto et al demonstrated that the measured activity in bone with CT-based attenuation correction was overestimated by an average 11% compared with $^{68}$Ge based attenuation correction (AC).9 In soft tissue, there was only a 2.1% overestimation when using CT-based attenuation correction methods. It is, thus, important to take this into

| Table 1. Suggested patient preparation and parameters for a 2D PET/CT study |
|---------------------------------|-------------------------------|
| **Preparation**                 | **Acquisition Parameters**    |
| PET                             | PET reconstruction            |
| 4 hours fast, minimum           | OSEM algorithm (2 iterations, 28 subsets) |
| Glucose level ≤ 200 mg/dL       | CT-based attenuation correction|
| 60 min uptake phase             | 8 mm Gaussian filter          |
| FDG injected dose: 0.22 mCi/kg IV (min 5, max 25 mCi) for a 2D whole-body acquisition | 128 × 128 matrix |
| CT                              | 140 kV                        |
| Oral contrast:                   | 0.8 s per CT rotation         |
| 2 bottles (900 mL) of barium sulfate 1.3% w/v 15 minutes before FDG injection, 1 bottle (450 mL) 30 minutes after. | Pitch of 6 |
| No contrast if head and neck or thyroid case. | 22.5 mm/s table speed |
|                                 | 5 mm CT slice thickness       |
|                                 | 512 × 512 matrix, resized to 128 × 128 |
|                                 | MAs:                          |
|                                 | <100 lbs, 40 mA, 101-150 lbs; 60 mA |
account when interpreting quantitative or semiquantitative (standardized uptake value) changes between a study performed with CT AC and a study performed with $^{68}$Ge AC.

**Oral Contrast**

Low-density oral contrast can result in minimal overestimation of true tracer uptake in the bowel. However, in the presence of high-density oral contrast, artifacts of markedly increased apparent tracer uptake have been reported in both human and phantom studies.$^{10,11}$ There is an overestimation of the measured activity with commercially available CT correction versus $^{68}$Ge correction. Use of CT oral contrast is useful in interpreting CT scans of the abdomen. In PET/CT, it is potentially helpful to better localize pathological from physiological tracer uptake. Low-density oral contrast is easily given and does not result in major artifacts.$^{10,11}$ Conversely, high-density oral contrast should be avoided. If there is increased activity in a region of contrast, review of the uncorrected images can help discriminate overcorrection artifacts from “true” uptake.

**IV Contrast**

IV enhancement can improve the diagnostic utility of CT. However, IV contrast works by producing regions of high-density on CT, mainly during the arterial or mixed arterio-venous phases. These images, if applied as transmission images, can produce artifacts of increased tracer uptake in the area of high contrast, as shown in phantom, animal,$^{12}$ and human studies.$^{13}$ This could affect the qualitative interpretation of studies and can affect quantitative measurements by inducing an overestimation of the true tracer uptake. If a diagnostic IV-contrast enhanced CT is required and those artifacts have to be avoided, the following sequence can be performed: initially, acquire a low or intermediate dose unenhanced CT, then acquire the emission data, and subsequently perform an IV contrast enhanced CT. These enhanced CT scans could be performed for the whole body, or to limit the radiation dose to the patient, could be centered on the specific region of interest in the body. The non-contrast CT will be used to perform attenuation correction without introducing overestimation, while the CT with IV contrast and “diagnostic” quality will be used for interpretation. Patient preparation should consider CT and PET requirements. Experience in the use of IV contrast is growing.

**Metallic Artifact**

Artifacts of increased tracer activity have been reported with metallic objects in addition to contrast (IV and oral). Such artifacts have been reported with dental implants,$^{14}$ a bullet, pacemakers, injection ports, and metallic orthopedic hardware.$^{15}$ Such metallic objects result in an overestimation of attenuation correction measured at x-ray energies and incorrectly scaled to the 511 keV energy. Review of the “scout” x-ray image for the presence of metallic objects is useful. The presence of apparent increased tracer uptake in the region of a metallic object in a study with CT-based attenuation correction should raise the possibility of an artifact. In this situation, review of the uncorrected images allows the differentiation between true tracer uptake and artifact. The absence of increased activity on the uncorrected images will confirm the absence of true tracer activity in the region of the object, preventing “false” interpretations of infection, inflammation, or even malignancy around the object.

**Registration of PET and CT Data**

In line PET/CT scanners offer the advantage of mechanical fusion and coregistration of PET and CT images. PET images in the chest are the result of the averaging of emission data over 5 min and of integrating patient, respiratory, and cardiac motion. Images at the chest-abdomen interface thus represent an average diaphragmatic position, usually similar to that obtained with the high-energy transmission scan acquired over a few minutes. However, the acquisition is rapid with CT, and the resulting image is a virtual “snapshot” of the diaphragm position, which could be markedly different from the average position obtained with PET emission. The discrepancy in diaphragmatic position between emission PET and CT can result in the appearance of a “cold” artifact at the lung base,$^{16}$ when using CT attenuation correction (Fig 1). In some studies, this phenomenon will be more pronounced and will result in marked mislocalization of lesions that will appear to be located in the wrong organ. After evaluating 250 PET/CT scans, six cases of mislocalization of liver metastasis appeared to be in the “lung” on the CT-corrected images in which free tidal breathing was allowed.$^{17}$ The quality of the registration between PET and CT has been evaluated recently. On average, misregistration between center of lung nodules on PET and CT was determined to be 7.6 mm for FDG-avid lung lesions, with a tendency to be more marked in the lung bases than in the middle lung zone and apex.$^{18}$ Other investigators have reported similar findings.$^{19}$

Breathing technique to improve registration in the lung has been evaluated extensively.$^{19,20}$ Although breath holding is the standard technique for CT, it is often impractical for the longer PET emission acquisition. Goerres et al reported that a normal expiration technique during the CT acquisition, where the patients stops his respiration at the level of a normal expiration, provides the best match of PET and emission data.$^{19,20}$ In our practice, we implemented a normal tidal breathing technique for both PET and CT.
acquisition that is feasible in a sometimes heavily debilitated patient population. Although it may infrequently result in major mislocalization, liver metastasis mislocalizations are usually easily recognized because the focal uptake in the lung on PET will present without a corresponding lung nodule on CT.

Patient Motion

Reducing patient motion is also of primary importance in PET/CT imaging. If the patient moves between PET and CT acquisitions, fusion images will be irrelevant. This will be particularly deleterious in head and neck cases, where CT is performed initially, followed by a PET acquisition beginning at the level of the thighs and finishing at the level of the neck 30 to 35 min later. The risk of significant motion is thus significantly increased by a long time interval between anatomic and functional imaging. In head and neck cases, we proceed routinely to a one or two bed acquisition centered on the neck (CT first followed by PET), reducing the time interval time between the two modalities acquisitions and reducing potential motion. In all cases, instructions to the patient and careful positioning are warranted. Depending on the level of patient’s cooperation, immobilization devices (thermoplastic masks, taping) can provide better immobilization. Clearly, for incremental value to result from PET/CT fusion, a lack of patient motion between PET and CT is required. Arms are positioned above the head for most procedures, if the patient can tolerate it, whereas they are positioned along the torso when the region of interest is the neck (head and neck, thyroid cancers).

PET/CT IMAGING: CLINICAL APPLICATIONS

As stated previously, in addition to attenuation correction, CT can be used for localization and diagnostic purposes. The published data are presently limited regarding the added value and clinical impact of PET/CT over “regular” PET.

In a retrospective review comparing PET and PET/CT in 32 patients with various proven or suspected cancers, PET/CT and PET gave comparable information in 18 patients.21 In 10 patients, PET/CT allowed correct characterization of physiological FDG uptake as benign. In nine patients, PET/CT resulted in improved localization of FDG uptake.21 A mixed population of 53 patients with cancer has been evaluated with a PET/CT scanner.8 On a lesion-by-lesion analysis, PET alone showed a sensitivity of 90% and a specificity of 93%, whereas PET/CT showed a sensitivity of 98% and a specificity of 99%. On a patient-by-patient analysis, 72% of patients had correct disease identification with PET alone, whereas with PET/CT and a 120 mA current setting, 92% of the patients have their disease correctly identified. The authors of those studies used different current settings for their CT examination. The 120 mA setting did not
improve lesion classification over the 80 mA setting. In addition to the improvement of the diagnostic accuracy, PET/CT helped in clarifying some of the normal physiological variants of FDG uptake. For instance, PET/CT allowed precise characterization of FDG uptake fusing in fat that has been previously described as muscle uptake.22,23 With the precise correlation of PET uptake in fat that has been previously described as muscle physiological variants of FDG uptake. For instance, PET/CT helped in clarifying some of the normal physiological variants of FDG uptake. For instance, PET/CT allowed precise characterization of FDG uptake fusing in fat that has been previously described as muscle uptake.22,23 With the precise correlation of PET uptake in fat that has been previously described as muscle uptake.

**Brain**

Our experience with brain imaging suggests that the added value of PET/CT in the assessment of brains without significant morphologic abnormalities, which is the case for most evaluations of dementia and epilepsy evaluations referred for PET, is limited in comparison to PET alone. One theoretical exception will be using the CT data to correct the PET metabolic activity for atrophy. In contrast, for the evaluation of brain tumors, the CT component significantly adds to the interpretation by precisely localizing FDG uptake to CT abnormalities. An IV-enhanced CT would certainly be more accurate in delineating the anatomic abnormalities. It is, however, not clear whether software fusion with a separate anatomic imaging modality, a method well-established in the brain, would not be comparable to the intrinsic fusion of inline PET/CT scanner. Systematic studies of PET/CT in brain imaging are still in evolution.

**Head and Neck**

In an early report of 5 cases selected from their initial 275 patients, the Pittsburgh group showed that PET/CT was particularly useful in the head and neck. It localized pathological uptake outside of the muscle planes, thus allowing discrimination between muscle uptake and malignant uptake.24 Normal structures in the neck region can have some increased metabolic activity, and localization of abnormal tracer activity to a precise anatomical region can be difficult with PET alone. Normal variants, benign lesions, and post therapy changes in the head and neck region were reviewed recently.25 The head and neck is a region with complicated anatomy, where the use of IV contrast should significantly help in localization of PET activity by allowing clear delineation of vascular structures and allowing their differentiation from nodes and masses. Careful positioning of the head, performing a separate acquisition centered on the neck, and using appropriate immobilization devices could minimize patient motion and improve coregistration of PET and CT images. In patients with lung cancer, PET/CT allowed the correct identification of contralateral vocal cord paralysis as the etiology of increased vocal cord activity, thus allowing discrimination of this benign activity from a second primary head and neck tumor.26,27

**Thorax**

PET is a useful tool in the characterization of solitary pulmonary nodule (SPN) and staging lung cancer. The impact on PET/CT in the evaluation of SPN is probably limited because normal lung parenchyma usually has a limited metabolic activity, rendering detection of an FDG-avid lesion in an area of low background relatively easy with a “regular” PET. However, precise localization of an FDG-avid lesion in the lung versus the chest wall or mediastinum (Fig 2) and assessment of chest wall invasion can be more problematic, even when using the transmission scan as a primitive fusion tool. Correlation with a contemporary chest CT is warranted and can often help to visually localize the FDG-avid lesions. Software fusion of PET and CT was reported to be marginally superior to visual fusion of PET and CT in the evaluation of mediastinal staging of patients with lung cancer,28 but of limited value in another study.29

CT abnormalities can vary rapidly over a few weeks in the case of inflammatory or infectious conditions, rendering visual registration with CT less optimal. In these situations, PET/CT will provide a truly “contemporary” CT for an “instant” mechanical fusion. Furthermore, significant changes between the CT from PET/CT and the previous CT can guide diagnostic thinking, a regression of pulmonary infiltrates leading toward a benign infectious or inflammatory process. As stated previously, the registration of FDG and PET data sets in lung is not perfect. The average misregistration was found to be 7.6 mm.18 PET has significant limitations for the tumor (T) staging. Combining PET and CT could provide improved tumor staging. In the presence of a mediastinal mass, it can be difficult to precisely localize the mass within the mediastinal activity. PET/CT will provide precise localization of the mass and will allow its differentiation from the mediastinal blood pool activity and, thus, will allow adequate characterization. PET/CT should allow differentiation of a mass devoid of any metabolic activity from a mass with mild activity similar to that of blood pool.

One study evaluated the impact of PET/CT over PET in the localization and the diagnostic impression certainty.30 PET/CT led to a 32% reduction in the number of “probable and equivocal” lesions and to a 41% increase in the number of “definite” localizations. A systematic and thorough review of the lung in the lung windows setting should be performed to detect lung nodules cold on PET that can represent malignancies with low glucose metabolism or that are smaller than the resolution of PET alone.

**Abdomen and pelvis**

Interpretation of PET scans in the abdomen and pelvis is sometimes limited by physiological FDG activity in the urinary tract and the variable bowel activity.31 PET/CT has been reported to be useful in the evaluation
of the abdomen and pelvis, allowing differentiation of urinary and bowel uptake from pathological uptake. One preliminary study evaluated the impact of PET/CT over PET in colorectal cancer. PET/CT led to reduction in the number of equivocal and probable diagnostic impression lesions by 50%, whereas the number of definite localization was increased by 66%. A small retrospective study of eight patients with ovarian and fallopian tube cancer compared CT and PET/CT. PET/CT detected five of the eight recurrences.

FDG-PET is generally superior to anatomical imaging in the detection of liver metastasis in cancer of gastrointestinal tract origin. It is not infrequent that PET/CT demonstrates liver metastasis without corresponding abnormalities on the non-contrast CT. PET/CT fusion can help to direct the site of biopsy (Fig 3). Use of IV contrast will sometimes clearly lead to the detection of a metastasis on the CT scan. It is probable that IV contrast will be increasingly applied in the evaluation of the liver. FDG-PET also proved to be useful in the detection of recurrence from colorectal cancer and ovarian malignancies. PET/CT appears useful in the differentiation of implants on the liver surface from superficial liver metastasis. Recognition of peritoneal implants is usually
straightforward when FDG uptake is focal and intense, but because bowel and urinary activity can have a similar distribution pattern as some tumors, PET/CT can, in some instances, clarify equivocal PET findings, particularly with the use of oral contrast.

CT can add to PET in the evaluation of malignancy with known low metabolic activity with FDG. These lesions, particularly mucinous carcinomas, sometimes lack metabolic activity on PET, but have clearly positive findings on the CT. In this situation, the presence of a suspicious lesion on CT should raise the likelihood of malignancy even with a negative PET (Fig 4). Similarly, because of the frequent low metabolic activity of primary renal cell carcinomas, we suggest that the kidneys should also be evaluated carefully for masses that appear on the CT scan. Renal cell carcinoma can present as a cold lesion, and thus any suspicious renal lesion on CT, even with minimal FDG uptake, warrants further diagnostic work-up.

Tracer activity in ureters can be focal and can mimic metastatic lymph nodes. Administration of diuretics can induce washout of the urinary activity, or at least a significant reduction of its intensity, thus allowing its characterization as a physiological process. If diuretics are administered after PET acquisition, it requires an additional delayed acquisition over the abnormal region. With PET/CT, focal tracer uptake along the ureters path usually will have a much smaller corresponding CT finding (ureter) if it corresponds to urinary activity, whereas it will fuse to a larger, soft tissue abnormality if it corresponds to a pathological lymph node. In our experience, use of diuretics is generally not necessary when using PET/CT.

Bone Metastasis

FDG-PET is more accurate than a bone scan in detecting bone metastasis in some cancers. However, precise characterization of some FDG-avid lesions with PET can be difficult because of the limited anatomical resolution. Fusion of the focus of increased FDG uptake into a benign lesion (degenerative or traumatic changes in bone or extraosseous) can help avoid false-positive readings. In cases of FDG uptake fusing in bone, it is not infrequent, in our experience, that there are no or only minimal changes corresponding to the FDG uptake. In other instances, findings of congruent bone destruction or highly suspicious lesions can help confirm that the lesion is a metastasis. This warrants systematic study. In breast cancer, FDG-PET is more accurate than a bone scan in detecting bone metastasis, with the exception of osteoblastic metastases, which
can be undetectable by PET. Detection of osteoblastic lesions with low or normal metabolic activity by the CT component of the PET/CT can be useful in some cases. Experience with PET/CT is growing, but detailed evaluations, by disease type, have not yet been reported.

**Guidance of Biopsy**

Obtaining histological confirmation is of primary importance to determine the appropriate treatment. Biopsy of a suspected lesion is often required, but is subject to sampling errors. A large mass can present with areas of necrosis that may not yield the diagnosis of cancer when biopsied. A suspected lesion on PET can be normal-sized by CT criteria, but clearly abnormal by PET. Similarly, CT can be falsely negative in some situations. PET will thus identify lesions with the highest FDG uptake that can be biopsied, while the CT component will provide anatomical details to precisely guide the biopsy (Fig 5).

**Added value of CT in PET/CT**

The detection of incidental lesions on the CT that warrant further work-up is an infrequent, but significant, issue with PET/CT. An independent review of the CT component, without contrast, of the PET/CT among 250 scans revealed 7 clinically important lesions, including suspicious renal masses or indeterminate cysts, a large
abdominal aneurysm, sclerotic bone metastasis, and hepatic cirrhosis with portal hypertension. The findings were not detected on the PET component alone. Thus, a clear abnormal CT, with a normal PET, occurred in 2.8% of the total scans evaluated. These preliminary observations suggest that the CT component of PET/CT should be carefully reviewed.

CONCLUSION

The introduction of inline dedicated PET/CT scanners, combined with the rapid growth of the clinical use of PET imaging, has already led to an expanding role of PET/CT in oncologic imaging. This technology offers unique opportunities by combining two already excellent modalities, PET and CT scanning. A PET/CT study has the ability to provide a synergistic combination of PET and CT, which could potentially be more valuable than the two exams performed separately. PET/CT is still in its infancy, and the full extent of its ability to enhance diagnostic accuracy is still unknown. Because the clinical data regarding PET/CT is presently limited, the true added value of PET/CT over PET has to be evaluated carefully by clinical studies. Based on its speed and the clear improvement in diagnostic certainty in a significant number of cases, PET/CT has become our preferred and routine method of performing oncological PET imaging.

REFERENCES


Fig 5. Patient with a newly diagnosed left lung mass. IV enhanced CT (not displayed) showed, in addition to the mass, a large left hilar mass and slightly enlarged subcarinal lymph nodes. The maximum intensity projection image not only showed intense activity in the lung mass and the hilar and subcarinal lymphadenopathy, but also a small focus of intense uptake in the right paratracheal region. (B) The transverse CT showed the normal-sized right paratracheal lymph node (arrow), with corresponding intense activity on the attenuation-corrected (C) PET, (D) fused, and (E) non-attenuation-corrected image. The left lung mass demonstrated intense FDG uptake. Based on the fused PET image, the patient underwent a transbronchial biopsy of the right upper paratracheal node, which demonstrated malignant involvement, not recognized on CT.
APPLICATIONS OF PET/CT IMAGE FUSION


