

DISCUSSIONS IN

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Whole-Body FDG-PET and PET/CT Cancer Scanning

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LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Explain the advantages and limitations of FDG-PET in cancer imaging
- Discuss the limitations of CT in cancer imaging
- Review the advantages of PET/CT in oncology
- Describe PET/CT artifacts, pitfalls, and imaging protocols

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Dr. Osman has no significant financial arrangement or affiliation with any manufacturer of any pharmaceutical or medical device and is not affiliated in any manner with any provider of any commercial medical or healthcare professional service.

Modern imaging technologies visualize various aspects of cancer noninvasively by taking advantage of different anatomic, molecular, and functional alterations common to malignant cells. In the last few years, we have witnessed significant advancements in anatomic imaging modalities such as CT. Based on its fast image acquisition and high spatial resolution, CT is particularly well suited for daily use in the management of cancer patients, but it has limitations. These include difficulty diagnosing malignancy in a normal-sized lymph node, distinguishing between an enlarged lymph node caused by malignancy and one due to benign disease, and differentiating disease recurrence from post-therapeutic changes.

Whole-body (WB) PET imaging with fluorine-18 deoxyglucose (FDG) is a functional imaging modality that addresses many of the limitations of CT. FDG-PET detects metabolic/ molecular alterations common in malignancy and takes advantage of one such alteration, accelerated glucose metabolism. F-18 FDG-PET imaging diagnoses, stages, and restages many cancers with accuracies ranging from 80% to 90%.¹ The FDA has approved PET-FDG for all cancers because of its high accuracy as a molecular imaging technique for disease biology. The Centers for Medicare and Medicaid Services has approved Medicare reimbursement of FDG-PET imaging for vari-

ous types of cancer: solitary pulmonary nodule, non-small cell lung cancer, colon cancer, lymphoma, and melanoma. And it is considering approval for additional types: brain, pancreatic, cervical, ovarian, testicular, and small cell lung cancers.

FDG-PET has limitations, however. On one hand, increased FDG avidity is not limited to malignancy, resulting in false positives; on the other hand, not all malignancies are FDG-avid, resulting in false negatives. In addition, whole-body FDG-PET is a slow imaging technique that requires two hours for a WB field-of-view, as compared with less than a minute for the same FOV using a multislice CT scanner. Furthermore, the lack of anatomic landmarks in FDG-PET facilitates lesion identification while complicating localization of such lesions.

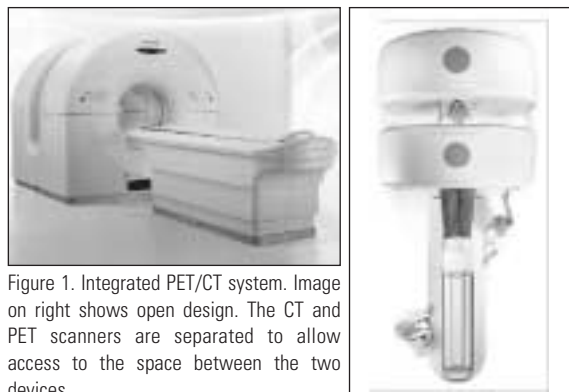


Figure 1. Integrated PET/CT system. Image on right shows open design. The CT and PET scanners are separated to allow access to the space between the two devices.

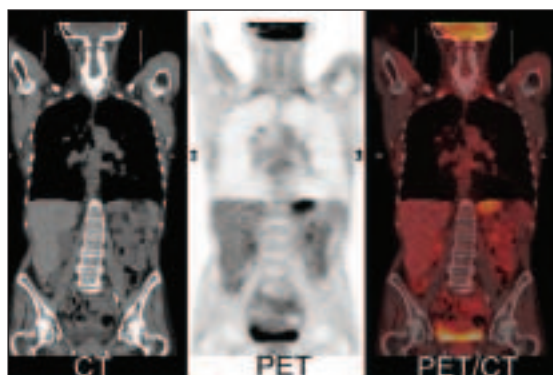


Figure 2. Limited whole-body F-18 FDG-PET/CT from the base of the skull to the upper thigh.

PET/CT IMAGE FUSION

Fusion of PET and CT images enhances the inherent clinical potential of each technique and provides synergistic knowledge that is greater than the sum of information provided by each modality alone. Fusion images can be performed at three levels: visual, software, and hardware. In traditional visual fusion, a physician compares separate PET and CT images viewed next to each other; the fusion takes place in the physician's head. Visual fusion was often considered sufficient, but clinical practice has proved it to be suboptimal and frequently unsuccessful, underscoring the need for a better fusion mechanism.

The concept of "anatometabolic" software fusion of PET and CT studies using fiducial and internal markers was introduced more than 10 years ago.² Since then, several sophisticated software fusion algorithms have been developed and validated, particularly in the brain. Software fusion is often logistically challenging, however, due to differences in the patient's positioning when imaged by two different modalities on two different occasions. The alignment process is labor-intensive and far from routine at most medical centers.

This situation changed dramatically in 1998 with the introduction of a hardware fusion technique in the form of a combined PET/CT scanner. PET/CT systems can acquire anatomic and functional information in the same examination in very close temporal proximity.³ In such systems, CT data can be used for PET attenuation correction instead of the traditionally used germanium-68.⁴ It is safe to say that the most exciting development in PET is the emergence of combined PET/CT imaging devices (Figure 1). The combination of form (CT) and function (PET) has several advantages.¹ First, biological and anatomic

WB imaging can be performed in one examination. Second, near-ideal fusion of biological and anatomic images can be achieved because of limited patient motion due to the almost simultaneous acquisition of PET and CT images. Finally, anatomic landmarks provided by CT greatly facilitate the assignment of biological abnormalities to anatomic structures.

CLINICAL DATA SUPPORTING PET/CT

Although PET/CT is still in its infancy, several studies published in the last few years demonstrate that it moves image fusion from primarily a research tool to routine use in everyday clinical practice. These studies also prove that PET/CT has a higher diagnostic accuracy than PET or CT alone or visually correlated PET and CT.

More data exist regarding the use of PET/CT in lung cancer than for any other type of malignancy. One study evaluated the advantage of PET/CT over PET in the localization and diagnostic certainty in patients with non-small cell lung cancer (NSCLC).⁵ PET/CT led to a 32% reduction in the number of "probable and equivocal" lesions and a 41% increase in the number of "definite" localizations.

Another prospective study assessed the diagnostic accuracy of PET/CT in 50 patients with NSCLC.⁶ Integrated PET/CT provided additional information in 41% of patients beyond that obtained by conventional visual correlation of the two modalities. Examples of additional information included precise localization of lymph nodes, identification of chest wall infiltration, differentiation between inflammation and malignancy, and localization of distant metastases. Integrated PET/CT had better diagnostic accuracy than PET alone, CT alone, or visual correlation of PET and CT.

A more recent prospective study assessed the value of PET/CT in the diagnosis and clinical management of suspected recurrent NSCLC in 42 patients.⁷ The sensitivity, specificity, and positive and negative predictive values of PET/CT for diagnosis of

recurrence were 96%, 82%, 89%, and 93%, respectively, compared with 96%, 53%, 75%, and 90% for PET. Furthermore, PET/CT changed the PET lesion classification in 52% of the patients by determining the precise localization of sites of increased FDG uptake. It also changed the management in 29% of patients by eliminating previously planned diagnostic procedures, initiating a previously unplanned treatment option, or inducing a change in the planned therapeutic approach.

The added value of PET/CT over PET or CT alone is not limited to NSCLC. A prospective study assessed the clinical performance of a combined PET/CT system in patients with various types of cancers.⁸ In 204 patients with 586 suspicious lesions, PET/CT provided additional information over the separate interpretation of PET and CT in 99 patients (49%) with 178 sites (30%). As expected, PET/CT precisely defined the anatomic location of malignant FDG uptake in 6%, and it led to retrospective lesion detection on PET or CT in 8%. Moreover, PET/CT improved characterization of equivocal lesions as definitely benign in 10% of sites and as definitely malignant in 5% of sites. The PET/CT results had an impact on the management of 28 patients (14%), eliminating the need for further evaluations in five patients, guiding further diagnostic procedures in seven, and assisting in planning therapy for 16 patients.

Data comparing PET/CT with other imaging modalities are not limited to PET

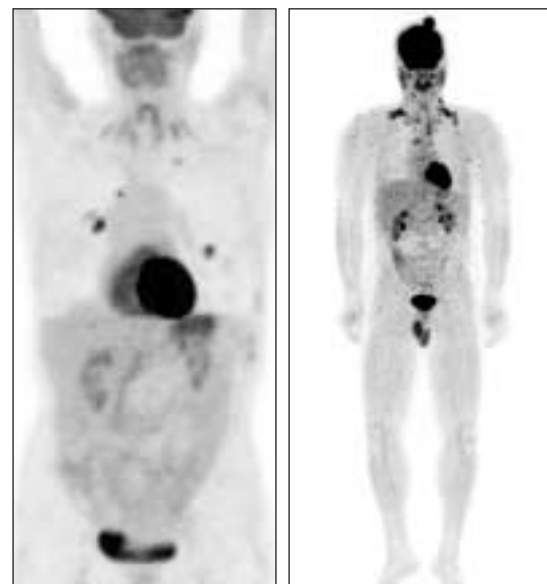


Figure 3. Whole-body F-18 FDG-PET. A: Limited whole-body image from chin to upper thigh. B: True whole-body image from top of skull to toes. Of note, patient on the right has a scalp lesion biopsy, which revealed melanoma.

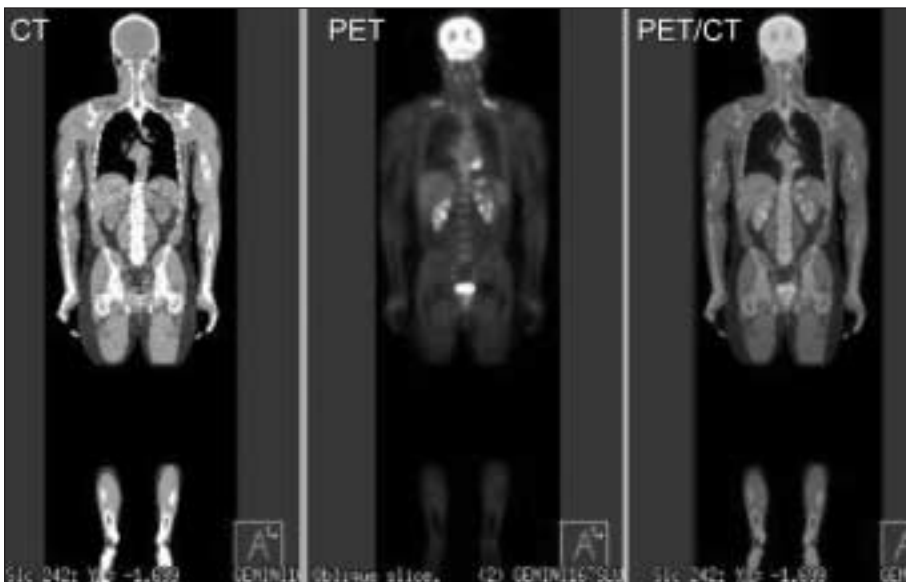


Figure 4. True whole-body F-18 FDG-PET/CT from the top of the head to the soles of the feet.

and/or CT. A prospective study published in the *Journal of the American Medical Association* compared the staging accuracies of both WB PET/CT and WB MRI for different malignant diseases.⁹ In 98 patients, the TNM (tumor, node, metastases) stage was correctly determined in 77% with PET/CT and in 54% with MRI. Moreover, impact on patient management was 12% with PET/CT, compared with 2% with MRI. The authors advocate the use of PET/CT as a first-line imaging modality for WB tumor staging, restaging, and assessing response to therapy in different types of cancer.

PITFALLS, ARTIFACTS, AND PROTOCOLS

• *Brown adipose tissue (BAT)*. PET/CT allows the reassessment of previously recognized patterns of physiologic tracer distribution. Muscle uptake of F-18 FDG is a well-known cause of findings on PET imaging¹⁰ and has been described as a potential source of false positives in cancer patients.¹¹ The presence of increased F-18 FDG metabolic activity occurring in fat tissue, previously attributed to muscular uptake, has been reported on PET/CT images.¹² In one study, supraclavicular uptake was present in 14.1% of patients referred for oncologic PET imaging.¹³ This study showed that 28.6% of abnormal foci of supraclavicular uptake was caused by uptake in BAT. The same study observed that uptake in BAT, when present, showed a high female-to-male ratio (6:1). Moreover, the incidence of uptake in BAT (or “USA-fat”) was shown to increase during the cooler periods of the

year, suggesting that a cold temperature upregulates BAT as a valid explanation for the USA-fat.

Uptake in BAT is not limited to one anatomic location. A recent study evaluated the prevalence, location, and appearance of hypermetabolic brown fat in the mediastinum.¹⁴ Of 845 oncologic patients, 15 (1.8%) had focal hypermetabolic mediastinal brown fat uptake. This uptake was more common in children (4/8) than in adults (11/837) and more common in women (9/372) than in men (2/465). Foci of BAT uptake included paratracheal, paraesophageal, prevascular, and pericardial regions, interatrial septum, and azygosoesophageal recess.

Another study used PET/CT to evaluate the BAT pattern of infradiaphragmatic fat uptake (IDFU) in cancer patients.¹⁵ Of 1241 patients, IDFU was documented in nine (0.7%). The IDFU included the perirenal uptake as well as paracolic and parahepatic uptake. The above-mentioned studies concluded that the CT portion of a PET/CT study allows for precise localization of increased FDG uptake in the fat, as well as documenting the low-Hounsfield-unit characteristic of fat.

Certainly, the need to eliminate BAT uptake as a major potential source of false positives in cancer still exists. A study that evaluated F-18 FDG uptake in the BAT of rats stimulated by cold exposure and the anesthetic ketamine, which has sympathomimetic properties,¹⁶ demonstrated that BAT can exhibit high F-18 FDG uptake under stimulated conditions, including ex-

posure to cold, and that propranolol or reserpine treatment can substantially reduce the high F-18 FDG uptake in BAT. Clearly, species differences may exist, and the optimal clinical preparations are yet to be determined.¹⁷

• *Respiration artifact*. Curvilinear cold artifacts paralleling the dome of the diaphragm at the lung bases is frequently present on PET/CT images obtained at free tidal breathing. One study showed that this respiratory motion artifact (RMA) at the lung/diaphragm interface was present in 84% of studied patients.¹⁸ Marked RMA was seen in only 10% of patients. The most likely explanation of the artifact is underattenuation correction for the upper liver imaged at PET, due to larger lung volumes on the CT scan (single breath) than on the emission PET scan (free breathing with the expiratory phase predominant).

Another study reported that normal expiration provides excellent coregistration between PET and CT.¹⁹ But as many cancer patients cannot tolerate a long breath-hold, the breath-holding approach may not be practical in day-to-day clinical practice in all patients. RMA was shown to result in infrequent (2%) but potentially serious lesion localization errors.²⁰ Physiologic motion artifacts are not limited to the lungs. Accuracy of image fusion of normal upper abdominal organs visualized with PET/CT was evaluated,²¹ and minor mismatches in location and organ size were found to exist between CT and PET images, in part due to physiologic motion. A more recent study showed that physiologic bowel motion may result in attenuation differences and subsequent differences in standard uptake values (SUVs).²²

• *Not truly whole-body*. Accurate tumor staging encompassing the entire body is of essential importance. However, the most commonly used axial co-scan range selected for the arms-up PET/CT protocols covers an FOV only from the base of skull to the upper thighs (Figure 2). The continued use of the term “whole-body” is misleading, as it does not include the brain, skull, and significant portions of both upper and lower extremities (Figure 3). It is the PET market and not science that dictates the use of the current axial FOV and has mislabeled it as whole-body. The routinely used limited FOV may underestimate the true extent of disease by missing metastases to areas outside the typical “whole-body.”

We evaluated the incremental added value of true whole-body (TWB) FDG-PET

