Use of Dual-Modality Positron Emission Tomography/Computed Tomography in Oncology

Thomas A. Ratko, PhD, Amolak Singh, MD, Joseph P. Cummings, PhD, and Karl A. Matuszewski, MS, PharmD

Abstract

Objective: To review the literature relating to imaging using positron emission tomography (PET) with 18-fluorodeoxyglucose (FDG) and computed tomography (CT) in oncology.

Methods: Search of the MEDLINE database through 30 June 2005.

Results: There were 22 peer-reviewed publications in which dual-modality FDG-PET/CT was compared with CT alone, PET alone, or other imaging techniques in a total of 1596 cancer patients. Data from these studies suggest that dual-modality FDG-PET/CT is superior to either FDG-PET alone or CT alone in detecting, localizing, and characterizing a variety of cancer types. The evidence is limited in that none of the studies used a randomized controlled design in which PET or CT images obtained with stand-alone devices were compared with images acquired using dual-modality instruments.

Conclusion: Although explicit patient selection guidelines for the use of dual-modality FDG-PET/CT have not been published, evidence suggests that dual-modality PET/CT may be considered medically necessary when PET is considered medically necessary for cancer patients. This technology represents a major advance in diagnostic imaging in oncology that will quickly become the standard of care.

PET radiopharmaceuticals are available to evaluate diverse physiologic or biochemical processes [3–6]. The most important in oncology, 18-fluorodeoxyglucose (FDG), is an analogue of D-glucose that becomes trapped within cells after being metabolized through glycolysis [7]. Because cancer cells exhibit increased glucose transport and glycolysis relative to untransformed normal cells, cancerous foci show up as “hot spots” on a FDG-PET image compared with normal surrounding tissues and organs [8].

FDG-PET has multiple accepted indications in oncology (Table 1) [3,9,10]. The clinical interpretation of an FDG-PET image, however, may be compromised by the limited spatial resolution of PET relative to other methods, in particular computed tomography (CT). It also may be difficult to differentiate foci of pathologic FDG uptake from sites of increased normal physiologic uptake, such as the brain, heart, liver, certain muscles, and soft tissues [11]. The renal collecting systems and the bladder also pose interpretive problems because FDG is excreted through the urinary tract.

High-resolution CT is indispensable in cancer diagnosis, treatment, and management but also has specific limitations [12]. In particular, by the time a tumor is sufficiently sized to be detected in a CT image, the disease may well have progressed beyond curable. CT also is not adequate for differentiating posttherapy artifacts from tumor recurrence nor in discerning nonopacified bowel loops from abdominal or pelvic metastases [11].

To address the limitations of PET and CT and enhance the clinical value of the information acquired, separate images may be combined, or fused, either retrospectively or prospectively [13]. Side-by-side visual comparison evolved with the development of computer algorithms and software that electronically coregister images [14,15]. Software-based retrospective techniques are adequate for organs such as the brain, which is fixed relative to external rigid reference markers on the skull. They are less accurate in nonrigid anatomic areas due to patient movement or differences in patient positioning.
PET/CT Imaging

Table 1. Indications for FDG-PET

<table>
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<th>Main indications</th>
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<td>Preoperative staging of NSCLC</td>
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<td>Staging of recurrent lymphoma and CRC</td>
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<tr>
<td>Assessment of stage II or greater melanoma</td>
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<td>Investigation of SPN</td>
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<td>Secondary indications</td>
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<tr>
<td>Preoperative staging of head and neck cancer</td>
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<tr>
<td>Staging of recurrent breast cancer</td>
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<tr>
<td>Distinguishing scar or recurrence or tissue necrosis or recurrence</td>
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<td>Brain tumor grading</td>
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<td>New indications</td>
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<td>Assessment of tumor response to therapy</td>
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<td>In vivo imaging of drug activity</td>
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Clinical Evidence Summary

Literature Search Strategy

Peer-reviewed publications on the clinical use of dual-modality PET/CT were identified by a search of the MEDLINE database conducted through 30 June 2005 using the following strategy: “pet-ct”[All Fields] OR (“dual-modality”[All Fields] AND “pet-ct”[All Fields]) NOT (“editorial”[All Fields] OR “case report”[All Fields] OR “meta-analysis”[All Fields] OR “letter”[All Fields] OR “comment”[All Fields]) AND English[Lang] AND “humans”[MeSH Terms]. The search was limited to studies that were published in the past 5 years. This yielded 266 citations, 75 of which were indexed as reviews. Review articles on the clinical use of dual-modality PET/CT were obtained to provide background information, and their bibliographies were scanned to find additional primary articles that may have been missed in the electronic searches. The “related articles” function of MEDLINE was used to find additional publications that may have eluded the initial electronic search, and bibliographies of relevant articles were scanned for this purpose. This function does not adhere to the limitations placed in the initial search and so may yield earlier citations as well as non-English language articles.

To be included in this analysis, original articles must have provided direct comparative clinical data on the diagnostic performance of dual-modality PET/CT versus that of PET, CT, or other modalities (eg, magnetic resonance imaging [MRI]) in human cancer patients. A modified grading system was used to categorize the levels of evidence according to study design [23–25]. Endpoints used for evaluating the clinical effectiveness of PET/CT included measures of diagnostic effectiveness (sensitivity, specificity, accuracy) and clinical findings. The evidence grading system measures the strength of the available data based on study design elements. Each primary paper was abstracted by 1 of the authors (TAR), and an evidence table was constructed to summarize salient details of original published clinical trials.

Results

Twenty-two clinical trials that involved 1596 patients are summarized in Table 2, organized by cancer site [26–47]. Thirteen were evidence grade II-1/II-2, and 9 were retrospective studies (grade III). None of the studies used a randomized controlled design. In each study, dual-modality FDG-PET/CT was used primarily to stage or restage recurrent disease and was compared with PET, CT, MRI, or other imaging modalities. The PET/CT protocol was similar among the studies, with 6 to 20 millicurie (mCi) of FDG injected intravenously, 40 to 60 minutes of FDG uptake time, and a whole-body PET emission acquisition period of 3 to 10 minutes per bed position for 2 to 10 bed positions. A CT transmission scan was used to generate PET attenuation correction (continued on page 161)
maps in 21 of 22 trials. In most cases, a multislice helical CT was used, with slice thickness ranging from 1 mm to 7 mm, most commonly 4 to 5 mm. Iodinated contrast media were administered orally or by intravenous (IV) injection prior to a CT scan in 8 investigations.

The study results summarized in Table 2 suggest that dual-modality FDG-PET/CT is superior to either FDG-PET alone or CT alone in the detection, localization, and characterization of a variety of cancer types, as reflected by parameters of diagnostic performance (sensitivity, specificity, accuracy) and other measures. Dual-modality FDG-PET/CT had a significant impact on the clinical management of patients with non–small-cell lung cancer, improving the accuracy of lesion staging and thus altering treatment plans in 3 studies [36–38]. Findings from the largest study suggest that dual-modality FDG-PET/CT can directly impact patient management, although it is difficult to generalize these results because of the heterogeneous patient sample [44]. Some data also suggest dual-modality PET/CT can alter the clinical management of patients with recurrent ovarian or fallopian tube cancer [31], thyroid cancer [47], colorectal cancer [29], and head and neck cancer [34,35].

Several caveats must be considered in the compilation and interpretation of the available literature. First, none of the available data were obtained using a randomized controlled trial design (grade I evidence) in well-matched patient populations. Second, interstudy comparisons are potentially confounded by differences in patient demographics and types of cancers, the endpoints or aims of each trial, the imaging instrumentation and protocols that were used, and image interpretation methods. Therefore, we made no attempt to compare the diagnostic parameters of FDG-PET/CT for 1 type of cancer versus another. Third, in only 1 of the studies were PET or CT images obtained on stand-alone devices compared with images acquired using dual-modality instruments. Finally, the absolute value of this technology is limited by the inherent resolution of PET and CT and the amount of radionuclide that is taken up by the tumor. These factors make it difficult to quantify the incremental value of prospective image fusion with dual-modality PET/CT versus retrospective fusion methods in terms of routine cancer diagnosis and patient management.

**Practical Considerations in Dual-Modality PET/CT**

While the hardware components of commercially available dual-modality PET/CT systems can vary significantly, the procedures used for oncology generally follow standard whole-body PET and CT acquisition protocols [12,22]. The PET portion of a dual-modality PET/CT protocol is usually comparable with a stand-alone PET protocol, except a CT transmission scan replaces the standard PET transmission scan that uses external beam sources. In contrast, the CT portion can vary depending on whether it is meant to be diagnostic or used solely for attenuation correction of the PET data.

A dual-modality PET/CT examination is preceded by the acquisition of a CT topogram or scout scan that is essentially an x-ray overview of the body from the neck through the pelvis. This scan is acquired during continuous bed motion, while the x-ray and detector assembly is held motionless. It provides markers that are used to define the axial examination range of the subsequent CT and PET studies. The subsequent diagnostic CT examination usually comprises a contrast-enhanced CT study from neck to pelvis that takes 60 to 70 seconds to complete. A PET study that encompasses the same region follows. In the 3-D acquisition mode, this usually entails 6 to 7 bed positions, with a 5- to 7-minute acquisition period at each position.

Several image sets may be needed, depending on the reviewer and the study objectives. These may include CT, attenuation corrected PET, and noncorrected PET. Multiple postacquisition reconstruction tasks may be required to create CT image sets with alternate filter and window-level settings (eg, lung-window). Special viewing and fusion tools typically are available with standard PET/CT software to allow the viewer to scroll through any of the selected individual and fused image volumes and also to permit side-by-side viewing [22].

A number of factors must be addressed to optimize dual-modality PET/CT imaging results [13]. Knowledge of the pre-examination blood glucose level and adequate control of hyperglycemia are necessary for obtaining optimal results with FDG-PET/CT because the uptake of FDG into cells other than brain and liver is competitively inhibited by glucose [19]. Patients are required to fast for 4 to 6 hours prior to receiving an injection of FDG and are instructed to avoid strenuous activity prior to examination and following FDG injection to minimize physiologic uptake of the radiotracer that can affect interpretation of the PET images. The administration of insulin for glucose control in diabetic patients prior to FDG-PET/CT may exaggerate physiologic uptake in muscles and further confound image interpretation [19]. However, there is lack of agreement on the pre-examination use of insulin for glucose control in insulin-dependent diabetic patients.

Alignment errors due to differences in patient positioning and motion can occur with dual-modality PET/CT machines. Scans can be misaligned if the relative CT and PET scanner positions in a dual-modality machine are miscalibrated. Normal breathing can produce significant motion artifacts in the CT-corrected PET images at the level of the diaphragm, liver, and lungs. This is known as respiration mismatch and can result in the erroneous projection of lesions into the wrong organ [48–50]. Protocols have been
Table 2. Comparative Clinical Performance of Dual-Modality PET/CT versus PET, CT, and Other Imaging Procedures

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Study Characteristics</th>
<th>Results</th>
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<tbody>
<tr>
<td><strong>Colorectal Cancers</strong></td>
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<tr>
<td>Cohade et al 2003 [26]</td>
<td>45</td>
<td>Retrospective study to assess the added value of dual-modality FDG-PET/CT in patients with CRC by directly comparing FDG-PET and FDG-PET/CT for staging and restaging for possible recurrent disease (type III)</td>
<td>The frequency of definite lesion characterization was increased by 30% with PET/CT, in comparison with PET alone. The frequency of equivocal and probable lesion characterization was reduced by 50% with PET/CT, compared with PET alone. The frequency of definite lesion localization was increased by 25% with PET/CT, compared with PET alone. Overall correct staging increased from 78% to 89% with PET/CT on a patient-by-patient basis, compared with PET alone.</td>
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<tr>
<td>Even-Sapir et al 2004 [27]</td>
<td>62</td>
<td>Retrospective study to assess the role of dual-modality PET/CT in the detection of pelvic recurrence in patients with CRC who underwent abdominoperineal or anterior resection (type III)</td>
<td>Patient-based detection of pelvic recurrence PET/CT: Sens = 96% Spec = 89% Acc = 92% PET: Sens = 88% Spec = 74% Acc = 79% No significant differences Patient-based discrimination of malignant and benign presacral abnormalities PET/CT: Sens = 100% Spec = 96% PET/CT findings were deemed clinically relevant in 29 (47%) of 62 cases. The most common cause of false-positive interpretation of PET findings was physiologic FDG uptake in displaced pelvic organs.</td>
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<td>Kamel et al 2004 [28]</td>
<td>90</td>
<td>Retrospective study to assess the incremental value of dedicated CT interpretation to the accuracy of dual-modality FDG-PET/CT in evaluating patients with CRC (type III)</td>
<td>Overall study group PET/CT: Sens = 91% Spec = 63% Acc = 83% PET/CT + Dedicated CT: Sens = 99% Spec = 100% Acc = 98% P = 0.05 versus PET/CT.</td>
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<tr>
<td>Selzner et al 2004 [29]</td>
<td>76</td>
<td>Prospective nonrandomized study to compare the diagnostic value of dual-modality FDG-PET/CT and contrast enhanced CT in patients with metastatic CRC to the liver (type II-1/II-2)</td>
<td>Patient-based detection of liver metastases PET/CT: Sens = 91% Spec = 90% CT: Sens = 95% Spec = 70% No significant differences Patient-based detection of posthepatectomy recurrence PET/CT: Sens = 100% Spec = 89% CT: Sens = 53% Spec = 50% No significant differences In 60 patients (79%), PET/CT did not change the therapeutic strategy based on CT alone. In 16 cases (21%), PET/CT resulted in a treatment change.</td>
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investigated to reduce the influence of breathing motion on image registration [51]. The use of lower-energy CT x-rays for attenuation correction of 511 keV PET data in a dual-modality device can result in artifacts in the area surrounding artificial metal implants, such as chemotherapy ports, metal braces in the spine, artificial joints, or dental fillings [52]. In standard PET transmission scans using external sources, metal implants cause little or no artifacts.

The minimal error in dual-modality PET/CT that can be detected and corrected either manually or by automatic registration is limited by the resolution of both modalities. For PET and CT, this means 5 mm in the transverse plane and at least 5 mm along the longitudinal axis, depending on the thickness of the CT slices [13]. The minimal error is considered unavoidable in image fusion, with larger positioning errors far less likely with the integrated scanners than with stand-alone PET and CT retrospective fusion.

The integration of PET with other imaging modalities is under investigation. In particular, the combination of PET with MRI may be superior to PET/CT in some cases because MRI is superior to CT in visualizing and delineating some types of tumors [53,54]. Also, MRI does not deliver ionizing radiation to the patient. This is a key issue for cancer patients, who often undergo multiple anatomic imaging examinations as well as radiation therapy.

Implementation Issues

Prospective image fusion using dual-modality whole-body PET/CT has significant promise to improve cancer care by increasing the diagnostic accuracy of both PET and CT. The technology is diffusing rapidly from tertiary cancer centers into community oncology practice and will likely become the standard of care in diagnostic imaging for oncology [55]. The principles and practices relevant to the implementation of CT imaging are well established in community oncology practice. Those of PET are less well known, however, and dual-modality PET/CT is even less understood.

In general, 2 clinical scenarios have been proposed to help determine the performance requirements for a PET/CT device and institutional implementation of this service [22]. In the first scenario, a patient who has already undergone a complete diagnostic CT examination using a stand-alone machine also requires a PET study. The CT component of a dual-modality PET/CT device is needed in this situation only for attenuation correction of the PET transmission dataset and concurrent anatomic localization of PET findings. The PET/CT does not replace a stand-alone CT but can replace a stand-alone PET device under these circumstances. In the second scenario, a state-of-the-art diagnostic CT is clinically indicated along with a PET examination. In this situation, the CT component of the PET/CT device is used in diagnostic mode, with oral or IV contrast media, to maximize the

Comments

The major impacts of dual-modality PET/CT compared with PET alone were improvement in the certainty of lesion localization and characterization and overall staging; the evaluation of extrahepatic disease, both intra-abdominal and extra-abdominal, but not for liver evaluation. The non-contrast-enhanced CT from the PET/CT examination was not optimal for diagnostic interpretation.

Dual-modality FDG-PET/CT was valuable in the assessment of pelvic recurrence in patients who underwent surgical resection of rectal cancer. It could differentiate viable tumor tissue and treatment-associated fibrosis observed on CT images and identify peritoneal metastases and normal-sized lymph node involvement. The study was limited by the patient demographics; a lack of diagnostic quality CT images to compare visually with PET and PET/CT; and the use of PET and CT datasets obtained from the same instrument rather than stand-alone PET versus PET/CT.

The CT portion of a combined FDG/PET study provided valuable incremental information to PET. The 15% improved overall accuracy of the combined PET/CT was due mainly to improved specificity that resulted from the decreased number of false-positive PET cases. Limitations of this study included its retrospective design and lack of contrast media use.

Dual-modality FDG-PET/CT and contrast-enhanced CT alone provided comparable findings for the detection of liver metastases, but PET/CT was more sensitive and specific in detecting extrahepatic metastases including local recurrence at the site of CRC as well as local recurrence within the liver after hepatectomy. The results are limited by the small size and heterogeneity of the study population and the use of non-contrast-enhanced CT in the PET/CT examinations.
<table>
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<th>Study</th>
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<th>Study Characteristics (Evidence Grade)*</th>
<th>Results</th>
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<td><strong>Colorectal Cancers (continued)</strong></td>
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<td>Kim et al 2005 [30]</td>
<td>51</td>
<td>Retrospective study to compare FDG-PET, dual-modality FDG-PET/CT and software fusion of FDG-PET and CT for restaging of biopsy-proven recurrent CRC and to compare the accuracy of coregistration of PET and CT achieved by FDG-PET/CT and software fusion (type III) 21 women, 30 men, mean age 65 years, were referred for imaging for detection of recurrence (n = 39) or staging of known recurrence (n = 12)</td>
<td><strong>Accuracy of staging by ROC analysis by patient</strong>  PET/CT: 88%  PET: 71%  ( P = 0.01 ) versus PET/CT  <strong>Lesion-based detection of tumors</strong>  PET/CT:  Sens = 89%  Spec = 98%  Acc = 96%  PPV = 94%  NPV = 96%  PET:  Sens = 74%  Spec = 93%  Acc = 88%  PPV = 76%  NPV = 92%  ( P = 0.01 ) versus PET/CT  Software fusion:  Sens = 93%  Spec = 96%  Acc = 95%  PPV = 87%  NPV = 98%  Recurrent CRC was confirmed by histopathology or follow-up examinations in 24 of 51 (47%) patients</td>
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<td><strong>Gynecologic Cancers</strong></td>
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<td>Makhija et al 2002 [31]</td>
<td>8</td>
<td>Retrospective chart review compared dual-modality FDG-PET/CT with routine clinical evaluation including CT in patients undergoing a surgical assessment for recurrent disease (type III) Patients with median age of 55 years (range, 50–73 years) had recurrent ovarian cancer (n = 6) or fallopian tube cancer (n = 2)</td>
<td>All 8 patients had positive histology for cancer  CT study was negative in 7 of 8 (87.5%) cases with histologically proven recurrence  PET/CT was positive in 5 of 8 (62.5%) cases with histologically proven recurrence</td>
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<td>Bristow et al 2003 [32]</td>
<td>22</td>
<td>Prospective nonrandomized study to evaluate the utility of dual-modality FDG-PET/CT imaging for detecting recurrent ovarian cancer of 1 cm or greater in maximal diameter among patients with a rising serum CA125 and negative or equivocal (nondiagnostic) conventional CT imaging studies (type II-1/II-2) 22 women, mean age 55 years (range, 40–77 years) all had epithelial ovarian cancer that was surgically documented in 21 (95%)</td>
<td>PET/CT demonstrated areas of abnormally increased metabolic activity considered highly suspicious for recurrent tumor in 16 of 18 cases (89%) with lesions &gt; 1 cm or more in diameter  CT alone was reported as negative in 15 of 22 (68%) cases overall and equivocal in the other 7 (32%)  Overall patient-based accuracy of dual-modality PET/CT in predicting the presence of recurrent cancer 1 cm or greater in diameter was 82%</td>
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<td>Grisaru et al 2004 [33]</td>
<td>53</td>
<td>Prospective nonrandomized study to assess the diagnostic accuracy of dual-modality FDG-PET/CT compared with the conventional methods of CT, MRI, and US in patients with gynecological cancer (type II-1/II-2) 53 women, mean age 56 years (range, 20–85 years), 18 of whom underwent examination for staging, 35 for suspected recurrence of cervical cancer (n = 21), uterine cancer (n = 8), ovarian cancer (n = 19), and others (n = 5)</td>
<td><strong>Overall study group PET/CT:</strong>  Sens = 97%  Spec = 94%  PPV = 97%  NPV = 94%  <strong>Standard imaging modalities:</strong>  Sens = 40%  Spec = 65%  PPV = 70%  NPV = 34%  Significance not specified  PET/CT accurately detected all sites of metastases with no false-positive sites at staging  PET/CT disclosed recurrent or metastatic disease in all tumor sites that were overlooked by standard imaging for recurrence  PET/CT was false-negative in 1 case and false-positive in 1 case for recurrence</td>
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diagnostic information, for attenuation correction, and for anatomic localization of the PET findings. The hybrid dual-modality PET/CT device thus replaces stand-alone CT and PET instruments. Respiratory motion in the lungs must be accounted for in using this type of scan for attenuation correction. Similarly, IV contrast may introduce attenuation correction artifacts into the PET scan, which must be determined and accounted for during interpretation of the PET images [19].

Commercially available PET/CT technology is capable of addressing the requirements of the scenarios outlined here, which are technically identical for the PET component. They do differ, however, in the requirements for the quality of the CT portion of the device. Other factors that can be expected to affect PET/CT specifications include clinical needs, site preferences, physician training and education, and legal concerns [55].

Radiation exposure with PET/CT is a key issue in the decision to implement a dual-modality device. A standard PET emission scan delivers a radiation dose of 5 to 10 millisieverts (mSv), whereas the dose absorbed from a Ge68 transmission scan for attenuation correction is negligible [56]. Absorbed doses from CT-based transmission scans are significantly higher, particularly with a whole-body scanning protocol. Furthermore, because dual-modality PET/CT involves the acquisition of a CT scan, patients who likely have already had a diagnostic CT examination receive a second CT radiation dose [13]. Effective total doses of around 10 mSv in the high-speed mode and 20 to 25 mSv in the high-quality mode for whole-body transmission scans have been reported [56,57]. This extra radiation dose can be decreased to less than 5 mSv by using lower-energy x-rays and thicker CT slices sufficient for attenuation correction and lesion localization [56]. Nevertheless, this represents a significant increase in total radiation administered to the patient during PET scanning. One approach to reduce the radiation burden on the patient is to adopt a policy of using the whole-body CT capability in dual-modality scanners in a diagnostic mode, thereby eliminating a prior CT examination.

Several other practical issues also must be considered for institutions contemplating the addition of dual-modality PET/CT capability [58]. In this discussion, it should be understood that PET or PET/CT really refer to the same thing because of the PET component. Institutions that currently do not have a PET/CT facility should understand their market, their competition, and their payers [59]. Oncology will be the backbone of PET/CT imaging, and therefore it is necessary to know the oncology practices in their service area to estimate potential and image volume [60]. Where PET is available, an oncologist typically refers between 3 and 4 cases a week for imaging [61]. If a major payer in a geographic area has a closed network of PET
### PET/CT Imaging

#### Table 2. (continued)

<table>
<thead>
<tr>
<th>Study Characteristics (Evidence Grade)*</th>
<th>Results</th>
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<tr>
<td><strong>Head and Neck Cancers</strong></td>
<td><strong>ROC analysis by patient</strong></td>
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<tr>
<td>Branstetter et al 2005 [34]</td>
<td>PET/CT versus PET: $P = 0.14$</td>
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<td>PET/CT versus CT: $P &lt; 0.05$</td>
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<td></td>
<td>PET/CT versus CT: $P &lt; 0.05$</td>
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<td></td>
<td>Lesion-based detection of tumors</td>
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<td></td>
<td>PET/CT:</td>
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<td>Sens = 98% Spec = 92% Acc = 94%</td>
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<td></td>
<td>PET:</td>
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<td>CT:</td>
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<td>Sens = 74% Spec = 75% Acc = 74%</td>
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<td>No significant differences reported</td>
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**Prospective nonrandomized study to compare the accuracy of dual-modality FDG-PET/CT with that of either CT or FDG-PET alone in depicting malignant head and neck lesions (type II-1/II-2)**

23 women, 42 men, mean age 63 years (range, 43–83 years) were referred for imaging to stage known malignancies ($n = 11$), detect recurrence of treated tumors ($n = 46$), or to identify unknown primary lesions in the setting of nodal metastases ($n = 8$)

**Prospective pilot study to assess the degree of interobserver agreement and confidence in anatomical localization of primary head and neck tumors and their metastases with FDG-PET alone versus dual-modality FDG-PET/CT (type II-1/II-2)**

8 women, 16 men, median age 59 years (range, 36–86 years) were referred for imaging for staging of histologically proven head and neck tumors

**Prospective nonrandomized study to determine the accuracy of dual-modality FDG-PET/CT compared with stand-alone FDG-PET and CT, in the staging of NSCLC (Type II-1/II-2)**

23 men with mean age 57 years (range, 39–70 years), 4 women with mean age 48 years (range, 40–57 years) referred for either primary tumor staging ($n = 19$) or preoperative restaging following treatment with neoadjuvant therapy ($n = 8$)

**Lung Cancers**

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providers, operators of a start-up PET/CT facility will need to determine whether business from the remaining private payers and Medicare can accommodate another entry into the market. Issues of throughput must be considered to evaluate the equipment performance specifications, which require knowledge of the market [60].

Two major factors that influence the volume and profitability of a PET/CT facility are education of referring physicians and appropriate documentation and coding of studies [59]. PET is the newest imaging modality and the least understood by physicians. Operators of PET/CT facilities must endeavor to inform potential referring physicians about the appropriate indications and use of this imaging modality. This is a key factor that drives generation of volume and profits. They also need to educate referring physicians about reimbursable indications for PET and PET/CT imaging. While Medicare reimbursement is straightforward in terms of indications and billing, non-Medicare payers often set their own guidelines and rules. Therefore, it is vital for facilities to understand and communicate the billing procedures and nuances clearly to their area market.

Customer service is the final element of a successful PET/CT facility. Follow-up with referring physicians after a study to inquire about their impressions of the facility and whether the study helped guide patient management is key to generating repeat business. The content of the PET/CT report should clearly indicate what was found, what the study might indicate, and suggest possible follow-up action, such as a colonoscopy, if warranted. Communication between the physician who reads and interprets the scan and the referring doctor is the single most important marketing tool for a successful PET/CT endeavor, and its value cannot be overestimated [60].

Patient Selection Criteria

To our knowledge, specific patient selection criteria or guidelines for the use of dual-modality PET/CT have not been published. However, several lines of evidence combined can help guide the appropriate use of this technique. First, FDG-PET imaging alone is a well-supported tool to diagnose and stage cancer at a number of body sites, with a host of accepted primary and secondary indications as summarized in Table 1 [9]. Second, PET/CT was more accurate for staging of bronchogenic NSCLC than either PET alone or CT alone. Compared with PET findings alone, PET/CT findings led to a change in tumor stage in 7 patients (26%). Compared with CT alone, PET/CT enabled more accurate assessment of tumor stage in 8 patients (30%). While CT alone was more accurate than PET alone, both modalities were outperformed by dual-modality PET/CT. Limitations of this study include differentiating malignancy and local inflammatory reaction with focal increase in glucose metabolism; and detection of micrometastases with improved spatial resolution.

ROC analysis suggested that dual-modality FDG-PET/CT was more accurate than PET or CT alone for the detection of head and neck cancers. PET appeared to have a particular utility in the immediate posttreatment interval, when CT often cannot reliably discriminate residual tumor from scar or radiation-induced changes. CT was most valuable in helping to correctly characterize physiologic FDG uptake that otherwise would have been mistaken for tumor with PET alone. Limitations of this study were lack of comparison of PET/CT images with those obtained using standalone PET or CT devices; and the small size of the study population.

Combined PET/CT was superior to FDG-PET alone in localization of tumor sites in patients with head and neck cancers. There was strong interobserver agreement in lesion localization between 3 readers on PET/CT but not on PET alone. The results are limited by the small size of the patient cohort. Because patients were treatment-naïve at the time of imaging, PET and PET/CT may yield different rates of residual or recurrent disease posttreatment.

Dual-modality FDG-PET/CT was superior to PET-GPET alone in localization of tumor sites in patients with head and neck cancers. There was strong interobserver agreement in lesion localization between 3 readers on PET/CT but not on PET alone. The results are limited by the small size of the patient cohort. Because patients were treatment-naïve at the time of imaging, PET and PET/CT may yield different rates of residual or recurrent disease posttreatment.

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<td><strong>Lung Cancers (continued)</strong></td>
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| Lardinois et al 2003 [37] | 50 | Prospective nonrandomized study to compare the accuracy of dual-modality FDG-PET/CT with that of CT alone, that of PET alone, and that of conventional visual correlation of PET and CT in staging NSCLC (type II-1/II-2) 28 men, 21 women, mean age 62 years (range, 46–81 years), with adenocarcinoma (n = 28), squamous cell carcinoma (n = 13), and large-cell carcinoma (n = 8), 40 of whom had histological confirmation of their disease and nodal status | Separate TNM Stage  
T Stage:  
PET/CT correct in 35 of 40 (88%)  
PET correct in 16 of 40 (40%)  
P < 0.001 versus PET/CT  
CT correct in 23 of 40 (58%)  
P = 0.001 versus PET/CT  
Visual correlation correct in 26 of 40 (65%)  
P = 0.013  
N Stage:  
PET/CT correct in 30 of 37 (81%)  
PET correct in 18 of 37 (49%)  
P = 0.013 versus PET/CT  
CT correct in 22 of 37 (59%)  
P = 0.12 versus PET/CT  
Visual correlation correct in 22 of 37 (59%)  
P = 0.021 |
| Keidar et al 2004 [38] | 42 | Prospective nonrandomized study to assess the role of dual-modality FDG-PET/CT and to compare it to PET for the diagnosis and subsequent clinical management of patients with suspected recurrent NSCLC (type II-1/II-2) 14 women, 28 men, mean age 66 years (range, 35–82 years), had histologically confirmed NSCLC with no evidence of active malignancy for at least 6 months after initial therapy and uncertain diagnosis of recurrent disease or its extent after routine clinical and CT workup | Patient-based diagnosis of recurrence  
PET/CT:  
Sens = 96% Spec = 82%  
PPV = 89% NPV = 93%  
PET:  
Sens = 96% Spec = 53%  
PPV = 75% NPV = 90%  
No significant differences  
PET/CT changed the PET lesion classification in 22 cases (52%) by determining the precise localization of sites of increased FDG uptake  
PET/CT changed the management of 12 patients (29%) by eliminating previously planned diagnostic procedures (n = 5), by initiating a previously unplanned treatment option (n = 4), or by inducing a change in the planned therapeutic approach (n = 3 cases) |
| Allen-Auerbach et al 2004 [39] | 73 | Prospective nonrandomized study to assess the additional value of dual-modality FDG-PET/CT compared with FDG-PET alone and FDG-PET fused by software with CT, in staging of patients with lymphoma (type II-1/II-2) 37 men and 36 women, mean age 51 years, had HD (n = 20) or NHL (n = 53); 14 underwent initial staging, 59 were restaged | PET/CT:  
Sens = 91% Spec = 92% Acc = 93%  
PET:  
Sens = 88% Spec = 82% Acc = 84%  
P = 0.03 versus PET/CT  
PET and PET/CT interpretations were concordantly correct in 61 cases and concordantly incorrect in 5 cases  
A discordant interpretation between PET/CT and PET occurred in 7 cases (10%)  
PET/CT correctly upstaged 2 and downstaged 5 cases |
patient treatment decisions compared with either PET or CT alone, an important determinant of the value of the technique [37,43,62].

Taken together, it follows that dual-modality PET/CT may reasonably be considered medically necessary for any indication in which PET scanning is considered medically necessary in the management of cancer patients. While the CT component in a dual-modality device may be used simply to generate an attenuation correction map for PET, the newest multidetector CT scanner components can produce diagnostic-quality CT images [60]. Similarly, the PET component of commercially available PET/CT devices usually offers the highest level of PET performance available. Given this, some investigators believe dual-modality PET/CT will soon become the standard of care for patients with abdominal and pelvic cancers [63] and lung and head and neck disease [64].

Dual-modality PET/CT also appears to have a role in radiation therapy treatment planning [65,66]. The FDG-PET component provides information on tumor extent and stage, while the CT image is used to accurately localize the lesion. The combined image can be used to determine so-called “biological target volumes” that can be more aggressively treated compared with functionally silent portions of the clinical target volume [66]. Most of the current information on the role of fusion imaging in radiation therapy treatment planning has been on the management of lung cancers, brain tumors, and head and neck disease, although it may be useful in other malignancies, such as cervical cancer, lymphoma, and melanoma. However, additional studies are needed to ascertain whether superior local control and reduced toxicity are achievable with the use of functional imaging-based techniques in radiation therapy planning.

Future Developments

Future developments in dual-modality PET/CT imaging will occur in 3 general, interconnected areas: refinement of current technology, new radiopharmaceuticals, and new applications [12,21,61]. With regard to refining the technology, several lines of inquiry can be expected to be fruitful for both components. For both PET and CT, there is a need to extend the axial field of view to cover a larger part of the body in a shorter time. This is achieved for CT by increasing the number of detector rows and acquired slices. Commercial scanners are available that allow 16 to 64 slices to be simultaneously acquired in less than 0.5 seconds, and these are being installed in the dual-modality devices.

Improvement in crystal technology in PET/CT scanners has significant potential to reduce acquisition time, increase signal to noise ratio, and improve spatial resolution. Hybrid crystals that combine different scintillator materials in stacks, for example LSO/GSO/BGO or LSO/BGO, are under
### PET/CT Imaging

**Table 2. (continued)**

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<th>Study</th>
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<td><strong>Lymphomas (continued)</strong></td>
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| Schaefer et al 2004 [40] | 60  | Retrospective study to compare the diagnostic value of dual-modality FDG-PET/CT obtained with low-dose nonenhanced CT with contrast-enhanced CT for staging and restaging of disease in patients with HD or high-grade NHL (type III) | Patient-based nodal involvement PET/CT: Sens = 94% Spec = 100%
Contrast enhanced CT: Sens = 88% Spec = 86%
No significant difference versus PET/CT

Patient-based extranodal involvement PET/CT: Sens = 88% Spec = 100%
Contrast enhanced CT: Sens = 50% Spec = 90%
No significant difference versus PET/CT

FDG-PET/CT and contrast enhanced CT showed evidence of HD or NHL in 19/19 (100%) patients at initial staging
Agreement of both methods was excellent (κ = 0.84) for assignment of nodal involvement but only fair (κ = 0.50) for extranodal disease
At staging, PET/CT resulted in treatment changes in 3 (16%) of cases while CT results changed treatment in 1 (5%) patient
At restaging, PET/CT resulted in treatment changes in 6 (15%) of cases while CT results changed treatment in 1 (2%) patient |
|     |     | 15 women (mean age 33 years) and 27 men (mean age 37 years) had histologically proved HD; 8 women (mean age 51 years) and 10 men (mean age 46 years) had NHL; 19 (11 with HD, 8 with NHL) underwent examination for staging, 41 (31 with HD,10 with NHL) were evaluated for restaging after at least 2 cycles of chemotherapy or after 3, 6, or 12 months after the completion of therapy |
| **Mixed Cancers** |     |                                        |         |
| Charron et al 2000 [41] | 32  | Retrospective study compared dual-modality whole-body FDG-PET/CT with PET images alone to localize and distinguish neoplastic lesions and normal structures (type III) | Coregistered PET/CT images identified and localized 55 lesions in 10 patients (31%)
Improved localization was achieved in 9 patients with PET/CT compared with PET alone
No difference between PET/CT findings and PET-only findings in 18 patients, including 11 with normal results of their studies |
|     |     | All > age 18 years, with known or possible cancers, including lung (n = 6); pancreatic (n = 6); head and neck (n = 4); lymphoma (n = 4); cholangiocarcinoma (n = 3); esophageal (n = 3); melanoma (n = 2); colon, prostate, renal, sarcoma (n = 1 each) |
| Antoch et al 2003 [42] | 98  | Prospective nonrandomized study compared the cancer staging accuracy of whole-body dual-modality FDG-PET/CT and whole-body MRI (type II-1/II-2) | Separate TNM Stage |
|     |     | Patients, mean age 58 years (range, 27–94 years), of whom 63 (64%) were male, referred for primary tumor staging (n = 82) or staging of suspected recurrence (n = 16); had bronchial carcinoma (n = 29), head and neck tumors (n = 13), uveal melanoma (n = 13), cancers of unknown primary site (n = 12), genitourinary tumors (n = 8), tumors of the GI tract (n = 6), thyroid tumors (n = 6), pleural mesotheliomas (n = 6), liver tumors (n = 3), and bone tumors (n = 2) |
|     |     | Coregistered PET/CT images identified and localized 55 lesions in 10 patients (31%)
Improved localization was achieved in 9 patients with PET/CT compared with PET alone
No difference between PET/CT findings and PET-only findings in 18 patients, including 11 with normal results of their studies | T Stage:
PET/CT correct in 37 of 46 (80%) MRI correct in 24 of 46 (52%)  \( P < 0.001 \)

N Stage:
PET/CT correct in 91 of 98 (93%) MRI correct in 77 of 98 (79%)  \( P = 0.001 \)

M Stage:
PET/CT correct in 92 of 98 (94%) MRI correct in 91 of 98 (93%)

Overall TNM Stage
PET/CT correct in 75 of 98 (77%) MRI correct in 53 of 98 (54%)  \( P < 0.001 \)

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[40] Schaefer et al 2004
[41] Charron et al 2000
CLINICAL REVIEW

Investigation as a means to fine-tune temporal response rates and to measure the depth of interaction of the gamma ray in the detector. This would improve the spatial resolution of the PET system and reduce the relatively lengthy image acquisition time. While it is unlikely that the PET imaging time will be reduced to the 30 to 60 seconds required for CT scanning, an order of magnitude reduction may be attainable with the newer crystal materials.

Event scatter is a major source of error or uncertainty in PET measurements. In a whole-body 3-D PET scan, about 25% of events are true, 25% are scatter, and the remaining 50% are random, or noise. Improvements in detector efficiency are needed to reduce the noise level. From the clinical perspective, a potentially significant advance could come from investigations into photon time-of-flight (TOF). TOF refers to the transit of photons from their source in the body to the scanner’s detector scintillators. A true event requires that 2 opposing photons reach 2 scintillators nearly simultaneously, indicating the presence of a positron somewhere along a line between the 2 detectors. The ability to accurately measure TOF and incorporate that information into PET imaging could reduce the amount of noise to twofold, thereby improving the resolution. Finally, ceramic detectors are under investigation that would permit the production of a fully integrated system, using the same detectors for the gamma rays in PET and the x-rays in CT. This would be the ultimate development, resulting in a true dual-modality device rather than the current hybrid, tandem machines now available.

New radiopharmaceuticals are under investigation that could have significant impact on PET/CT imaging. Disease-specific tracers will increase the sensitivity and specificity of PET. An example of this is F-18 fluorocholine, which has been shown in preliminary studies to be superior to FDG for imaging prostate cancer [67]. F-18 fluorodeoxythymidine is another radiotracer that has demonstrated potential for assessing cellular proliferation and assessing tumor response in non–small-cell lung cancer and other lung cancer [68,69], breast cancer [70], soft tissue sarcomas [71], and laryngeal cancer [72]. Finally, copper-labeled radiotracers are being investigated along with PET to assess tumor perfusion and hypoxia [73]. This information can potentially be used in combination with CT localization to identify clusters of cells that are hypoxic and more resistant to radiotherapy than are cells that are adequately oxygenated and thus permit the delivery of a greater dose of radiation to that area to compensate for resistance. New developments in radiopharmaceuticals, however, will be limited to those that utilize F-18 as a radiotracor in the absence of on-site production capabilities and infrastructure because of the short half-life of most radionuclides except F-18.

Comments

Dual-modality FDG-PET/CT with low-dose non-enhanced CT had a superior diagnostic value compared with contrast-enhanced CT alone for staging and restaging of disease in patients with high-grade NHL or HD. PET/CT seemed to perform better in the exclusion of disease than CT alone, and had a greater effect on therapeutic decision making. The results were limited by the retrospective design; the small, heterogeneous study population; and nonstandardization of CT protocols. Only a few patients had histological verification of lesions.

Combined PET/CT imaging improved anatomically limited interpretation of PET scans. CT permitted localization of areas of increased FDG uptake to areas known to have variable physiologic uptake. However, images from the dual-modality PET/CT scanner were not compared with images obtained with different scanners and biopsy data were not available to confirm the status of metastatic lesions.

Compared with MRI, PET/CT had a direct impact on patient management in 12 patients. Limitations of this study included differences in respiration state between the CT and PET components as well as effects of contrast agents on the CT-based attenuation correction. Hospital charges were reported to be $1900 for a whole-body PET/CT and $1850 for a whole-body MRI.

(table continues on page 172)
### Table 2. (continued)

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<th>Study</th>
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<th>Study Characteristics (Evidence Grade)*</th>
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<tr>
<td><strong>Mixed Cancers (continued)</strong></td>
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<tr>
<td>Bar-Shalom et al 2003 [43]</td>
<td>204</td>
<td>Prospective nonrandomized study to assess the additional value of dual-modality FDG-PET/CT compared with FDG-PET and CT, for improving diagnostic imaging and cancer patient management (type II-1/II-2)</td>
<td>PET/CT provided additional information beyond that provided by separate interpretations of PET or CT in 99 of the patients (49%) PET/CT improved characterization of equivocal lesions as definitely benign in 10% of sites and as definitely malignant in 5% of sites PET/CT had an impact on the management of 28 cases (14%), by obviating the need for further evaluation in 5, guiding further diagnostic procedures in 7, and assisting in planning therapy for 16</td>
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<td>111 men, 93 women, mean age 59 years (range, 5–89 years) had lung cancer (n = 64), GI tumors (n = 34), lymphoma (n = 33), genitourinary tract tumors (n = 16), breast cancer (n = 13), skin tumors (n = 10), sarcoma (n = 5), and head and neck cancer (n = 4)</td>
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<td>Antoch et al 2004 [44]</td>
<td>260</td>
<td>Retrospective, investigator-blinded study to assess the accuracy of dual-modality FDG-PET/CT for TNM staging or evaluation of suspected recurrence in patients with different solid tumor malignant diseases (type III)</td>
<td>Separate TNM Stage</td>
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<td>93 men, 167 women, mean age 56 years (range, 16–94 years) had cancers including lung, head and neck, GI tract, liver, thyroid, cancer of unknown primary, genitourinary system, soft tissue or bone, breast, adrenal gland, and pleura</td>
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<td>T Stage:</td>
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<td>PET/CT correct in 63 of 77 (82%) PET + CT correct in 55 of 77 (71%)</td>
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<td>P = 0.0215 versus PET/CT PET correct in 49 of 77 (64%) P = 0.0013 versus PET/CT CT correct in 51 of 77 (66%) P = 0.0018 versus PET/CT</td>
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<td>M Stage:</td>
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<td>PET/CT correct in 248 of 260 (95%) PET + CT correct in 245 of 260 (94%) P &gt; 0.05 versus PET/CT PET correct in 231 of 260 (89%) P = 0.0005 versus PET/CT CT correct in 230 of 260 (88%) P &lt; 0.001 versus PET/CT</td>
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<td>Overall TNM Stage</td>
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<td>PET/CT correct in 218 of 260 (84%) PET + CT correct in 197 of 260 (76%) P &lt; 0.001 versus PET/CT PET correct in 166 of 260 (64%) P &lt; 0.001 versus PET/CT CT correct in 163 of 260 (63%) P &lt; 0.001 versus PET/CT</td>
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Conclusion

Dual-modality PET/CT is a relatively new development that has potential to change the approach to diagnostic imaging in cancer patients. Individually, PET and CT are well accepted and of proven value in the diagnosis, staging, and follow-up of most types of cancers. On the other hand, each technology has limitations that reduce the clinical value of the image it produces. CT is limited in particular in that by the time a tumor is clearly discernible, it often has already metastasized and progressed beyond the point where cure is possible. CT also cannot reliably discern treatment-related changes from disease recurrence in the bowels or the lungs. FDG-PET has inferior resolution capability compared with CT, which can make it difficult to reliably determine the location of a tumor where the anatomy is complex. This may be especially problematic in organs that surround the diaphragm, in the head and neck, and in the pelvis. Significant breathing-related motion causes artifacts in PET images because of the amount of time that is necessary to acquire PET data at each bed position. Finally, it often is difficult to discriminate physiologic and pathologic FDG accumulation on PET images, and there can be significant differences in FDG uptake among various tumor types.

Dual-modality FDG-PET/CT overcomes most of the limitations of the individual technologies by combining the morphologic CT findings with the functional data provided by PET. The information obtained can be considered complementary at the least but really is synergistic, and permits the physician to confidently assess the location and extent of a tumor as well as to estimate its grade based on FDG uptake. It clearly and reliably discriminates physiologic and pathologic FDG uptake, and as such increases the diagnostic specificity of a dual-modality examination relative to either technology alone. Because FDG-PET/CT can reveal the extent of viable tumor relative to the margins, it can be used to plan radiation therapy that reduces the exposure of uninvolved tissues and organs while precisely and accurately delivering therapeutic doses to the necessary location. Although published clinical data are somewhat limited in proving the superiority of dual-modality FDG-PET/CT versus the individual techniques, current clinical data support the conclusion that this technology represents a major step forward in diagnostic imaging in oncology.

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Author contributions: conception and design, TAR, JPC; analysis and interpretation of data, TAR, AS, JPC; drafting of the article, TAR, JPC; critical revision of the article, AS, JPC, KAM.

Comments

Dual-modality FDG-PET/CT improved the diagnostic interpretation of separate FDG-PET and CT in about one half of the cancer patients in this study. Patient heterogeneity and tumor types limit extrapolation of findings to routine practice, as do lack of comparison of dual-modality PET/CT with stand-alone images using those modalities.

Fused FDG-PET/CT images provided significantly more accurate interpretations regarding the overall TNM system stage than either side-by-side PET + CT or separate PET or CT datasets. Dual-modality PET/CT had an impact on the treatment plan in 16, 39, and 43 patients when compared with PET + CT, CT alone, and PET alone, respectively. In addition to being a retrospective study, these results are limited because comparison of fused PET/CT with PET + CT, PET alone and CT alone was based on datasets from a single PET/CT examination.
### Table 2. (continued)

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<tr>
<td><strong>Mixed Cancers (continued)</strong></td>
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<td>Patient-based diagnosis of recurrence</td>
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| Israel et al 2004 [45] | 36 | Prospective nonrandomized study to assess whether the information provided by dual-modality FDG-PET/CT has an incremental value in the diagnosis and localization of recurrence and in the subsequent clinical management of cancer patients with increasing serum concentrations of tumor markers and prior negative conventional imaging (type II-1/II-2) | PET/CT: Sens = 93% Spec = 67% Acc = 89%  
PET: Sens = 95% Spec = 50% Acc = 86%  
No significant differences  
Of the 36 patients with an increased serum concentration of tumor markers and negative prior CT who were evaluated with PET/CT, 30 (83%) had evidence of malignancy at surgery or biopsy (n = 14) or subsequent imaging (n = 16)  
PET/CT was the single modality that directed further management and treatment planning in 12 cases (33%) |
| Pelosi et al 2004 [46] | 210 | Retrospective study to compare the value of dual-modality FDG- or 11C-choline-PET/CT and separate PET plus morphologic imaging (MI) studies (CT or MRI) for lesion localization in patients with a variety of solid tumors (type III)  
83 women, 127 men, mean age 64 years, who had previously been treated for cancer of the prostate (n = 70), colon (n = 44), breast (n = 40), upper GI tract (n = 19), lung (n = 14), ovaries (n = 13), pancreas/liver (n = 7), and thyroid (n = 3) whole-body imaging for clinical restaging after an increase was noted in a specific serum tumor marker | A total of 207 and 196 lesions were found in the PET/CT and PET/MI groups, respectively  
PET/CT: 200/207 (97%) lesions were localized unambiguously  
PET/MI: 160/196 (85%) lesion were localized unambiguously  
P < 0.001 versus PET/CT  
Results were comparable when FDG and 11C-choline results were compared with PET/MI findings |
| **Thyroid Cancers** |    |                                                                                        | PET/CT identified recurrent tumors in 4 of 8 (50%) patients who had otherwise undetectable disease |
| Zimmer et al 2003 [47] | 8  | Prospective nonrandomized study to evaluate the use of dual-modality FDG-PET/CT for localization of recurrent disease in thyroid cancer patients in whom traditional imaging modalities have failed to localize recurrence (type II-2)  
7 women, 1 man, mean age 54 years (range, 30–78 years) had recurrent thyroid carcinoma, including papillary (n = 6), medullary (n = 1), and follicular (n = 1) based on elevated serum thyroglobulin and calcitonin levels |}

Acc = accuracy; CRC = colorectal cancer; FDG = 18-fluorodeoxyglucose; Ge$^{68}$ = germanium 68; GI = gastrointestinal; HD = Hodgkin’s disease; MBq = megabecquerel; mCi = millicurie; MRI = magnetic resonance imaging; NHL = non-Hodgkin’s lymphoma; NPV = negative predictive value; NSCLC = non–small-cell lung cancer; PET/CT = positron emission tomography/computed tomography; PPV = positive predictive value; ROC = receiver operating characteristic; Sens = sensitivity; Spec = specificity; US = ultrasonography.

*Evidence grades: Type I: Obtained from at least 1 properly designed, randomized controlled trial. Type II-1: Obtained from well-designed controlled trials without randomization. Type II-2: Obtained from well-designed cohort or case-control analytic studies, preferably from more than 1 center or research group. Type II-3: Obtained from multiple time-series with or without the intervention; dramatic results in uncontrolled experiments could also be regarded as this type of evidence. Type III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.
Comments

Although FDG-PET alone allowed for the correct diagnosis of recurrence in the majority (83%) of patients, the statistically significant improved performance of FDG-PET/CT had an impact on the subsequent management of cancer patients, beyond the diagnosis of recurrence. Changes in treatment plans were reported in patients with CRC (9 of 21), lung cancer (2 of 4), and breast cancer (1 of 7). While promising, the results were limited by the small number of cases, heterogeneous cancer types, and short follow-up.

A conclusive report could be obtained in a higher number of cases with dual-modality PET/CT (FDG or 11C-choline) imaging than with separate PET plus MI (CT or MRI). The major advantage of PET/CT was in localizing lesions in the abdominopelvic region compared with those in regions above the diaphragm. Limitations of the study include population heterogeneity and that iodinated contrast media were used in the MI (CT) studies but not in the CT portion of the PET/CT studies.

Dual-modality FDG-PET/CT identified recurrence in 4 patients who otherwise had undetectable disease. These findings helped to guide further medical and surgical management in all 4 cases. The study is limited by the small number of patients, and the lack of stand-alone PET or CT comparisons.

References

PET/CT Imaging (Continued from page 175)


55. Blodgett TM, Casagranda B, Townsend DW, Meltzer CC.


63. Wahl RL. Why nearly all PET of abdominal and pelvic cancers will be performed as PET/CT. J Nucl Med 2004;45 Suppl 1:S82S–95S.


