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Positron Emission Tomography (PET) for benign and malignant disease

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Synopsis

Functional imaging using radiolabeled probes which specifically bind and accumulate in target tissues has improved the sensitivity and specificity of conventional imaging. Positron Emission Tomography using modified glucose probes (FDG-PET) has demonstrated improved diagnostic accuracy in differentiating benign from malignant lesions in the setting of solitary pulmonary nodules. In addition, FDG-PET has become a useful modality in pre-operative staging of patients with lung cancer and is being tested with many other malignancies for its ability to change patient management. This article provides an overview of the current status of FDG-PET and presents the challenges of moving towards routine use.

Keywords

Positron Emission Tomography; imaging; fludeoxyglucose

Introduction

Imaging modalities play an important complimentary role to traditional history, physical examination and laboratory tests in the diagnosis and management of patient disease. Improved sensitivity and specificity of imaging studies with respect to diagnosis and staging represents an opportunity for advancement of quality of medical care, quality of life and even cost of medical care. For example, an imaging test that can accurately identify mediastinal lymph node metastases in a patient with primary lung cancer can result in avoidance of mediastinoscopy. In addition, a patient with a solitary pulmonary nodule could be spared a pulmonary wedge resection if accurate diagnostic imaging could confirm benign disease. In both instances, it could be argued that the quality of medical care is improved, the quality of life of the patient is improved and the cost of medical care of the individual

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patient is reduced by the introduction of accurate diagnostic imaging. Improved sensitivity, specificity and predictive value of newer imaging techniques are critical to optimizing patient care.

Functional Imaging

Functional imaging refers to modalities which combine information about anatomic location and intrinsic tissue characteristics such as metabolic rate. Functional imaging can be applied in conjunction with CT, MRI and ultrasound, and typically utilize a radiolabeled substrate which either accumulates or is converted within a tissue differentially based upon a unique tissue characteristic. For example, a radiolabeled tracer that binds dopamine receptor can be used in combination with MRI to characterize the changes in the human brain associated with Parkinson's disease¹⁻³. The ability to add information about tissue function and merge this with anatomic detail has the potential to improve the sensitivity and specificity of the imaging studies over traditional contrast-enhanced imaging.

Positron Emission Tomography (PET) is a method of functional imaging which can be merged or co-registered with traditional studies such as CT or MRI to improve diagnosis of benign versus malignant disease or extent of malignant disease. Current PET utilizes radiolabeled fludeoxyglucose (FDG), which is a glucose analogue that accumulates in tissues which are metabolically active. FDG is labeled with ¹⁸F at the 2 prime hydroxyl position which prevents the normal degradation during glycolysis and allows the radiolabeled FDG to accumulate within the tissue. Malignant tissues tend to have increased metabolism as compared to normal surrounding tissues, which provides an opportunity for differential accumulation of radiolabeled FDG in malignant tissues as compared to benign. Thus, ¹⁸F-FDG PET functional information which is co-registered with anatomic imaging such as CT provides the opportunity to identify tissues with increased metabolism which can help distinguish benign from malignant disease as well as extent or spread of malignancy. These images can alter patient management as illustrated in Figure 1(A-D) in which a patient with regional lymph node metastases of melanoma was found to have an incidental bone metastasis on the pre-operative staging PET-CT which led to the use of primary systemic therapy as opposed to radical surgery.

The purpose of this article is to provide a review of the use of PET primarily in the management of patients with malignant disease. Each disease-based section contains a short background about standard treatment and how it can be impacted by pre-operative imaging. The performance characteristics of PET-CT are reviewed for each disease type with respect to primary diagnosis of malignancy (i.e. benign versus malignant tissue), assessing extent of malignant disease in patients with a known diagnosis (i.e. staging) and follow-up of patients to determine locoregional or distant recurrence of malignant disease. Data on how PET-CT altered patient management is presented when available, although many studies report only on sensitivity and specificity of imaging findings. Finally, the use of PET-CT for radiation treatment planning, in pediatric patients and for benign disease is discussed. The goal is that the data presented in this article will provide the reader with an update on the current status of the use of PET-CT as well as future directions as to how the technology may ultimately be used to improve medical care.

Use of PET-CT in Patients with Common Malignancies

Lung

In 2008 there were over 200,000 cases of lung cancer diagnosed in the US with over 150,000 deaths. This makes lung cancer the second most commonly diagnosed cancer and the leading cause of cancer related deaths in both men and women⁴. The use of functional

imaging using PET has yielded significant results in the diagnosis and treatment of patients with lung cancer.

Primary Diagnosis- Solitary Pulmonary Nodule—Solitary pulmonary nodule (SPN) on routine chest radiograph presents a diagnostic challenge. A SPN is defined as a single well-defined opacity with normal surrounding lung and no adenopathy. Importantly, up to 50% of these SPN are eventually found to be malignant⁵. Early studies suggested that FDG-PET (without CT) was equal to dynamic contrast-enhanced CT for differentiating between benign and malignant SPN⁶. A recent study evaluated PET-CT in 56 patients who had SPN diagnosed by CT scan⁷. These patients had diagnosis confirmed either by histology or long term clinical follow-up with repeat CT. After confirmatory testing, 27 of 56 SPN were diagnosed with malignancies (either primary lung or metastatic) and PET-CT identified 26 true positives, 5 false positives, 24 true negatives, and 1 false negative. This corresponds to sensitivity and specificity of 96% and 83%, respectively. The prevalence of malignant SPNs within this study was 48%, which is consistent with previous studies⁵. The positive predictive value (PPV) and negative predictive value (NPV) for PET-CT was 84% and 96%, respectively.

One of the weaknesses of this study was the enrollment of patients with known history of cancer. In another study, 42 patients with no known history of cancer and a SPN were enrolled⁸. These patients had CT, PET, and PET-CT performed, and all patients went on to biopsy for histologic confirmation. Sensitivity and specificity were 97% and 85% respectively. This study had a higher prevalence of malignant SPN (69%), which corresponds to a PPV and NPV of 94% and 93%, respectively. Table 1, includes two more studies and shows the operating characteristic for PET-CT to be relatively consistent^{9, 10}. These studies demonstrate the benefit of using PET-CT in the noninvasive diagnosis of SPN. Importantly, the negative predictive value for all these studies is consistently greater than 90%, which can significantly reduce the need for invasive diagnostic procedures in a proportion of patients.

PET for Staging of Primary Lung Cancer—Traditionally, staging for non-small cell lung cancer (NSCLC) requires mediastinoscopy with lymph node biopsy to determine staging and treatment. In an attempt to reduce the need for mediastinoscopy, PET-CT has been extensively studied for noninvasive staging of mediastinal lymph nodes. In a prospective study by Shim et al, 106 patients with biopsy proven NSCLC underwent pre-operative CT and PET-CT prior to curative pulmonary resection¹¹. Pre-operative CT scan accurately identified 69% of mediastinal lymph node metastases while PET-CT accurately identified 84%. In addition, two other studies confirm a high specificity and accuracy of pre-operative PET-CT in identifying mediastinal lymph node metastases (Table 2)^{12, 13}. Taken together, these studies reveal a high negative predictive value (NPV) of PET-CT for mediastinal lymph node staging in NSCLC, which suggests that patients with a negative PET-CT may be able to proceed directly to curative resection without mediastinoscopy, while those with a positive PET-CT may benefit from mediastinoscopy for lymph node biopsy prior to thoracotomy. By contrast, Carnochan et al. concluded that PET-CT had a low NPV and was inaccurate in staging patient, therefore mediastinoscopy should continue to be used in all patients for staging¹⁴.

The ultimate goal of this approach would be to shorten the time to definitive intervention (either surgery or chemotherapy/radiation) and to reduce the number of futile operations. Indeed, a study by Fischer and colleagues found that PET-CT reduced the number of futile thoracotomies and the number of total thoracotomies while not significantly impacting mortality¹⁵. The authors concluded that PET-CT was able to correctly stage a patient and avoid unnecessary thoracotomy.

PET-CT for Locoregional or Distant Recurrence in Patients with Lung Cancer

—For patients with lung cancer, CT scan is currently the study of choice for the diagnosis of local or distant recurrence. The addition of functional information from PET-CT would be valuable to differentiate post-therapy fibrosis from malignancy. A study by Keidar et al highlights the benefits of PET-CT for the diagnosis of recurrent lung cancer¹⁶. This study enrolled 42 patients with suspected recurrence of NSCLC on the basis of clinical findings, biochemical markers or standard imaging and subsequently evaluated them with PET-CT. The study demonstrated promising results with sensitivity, specificity, positive predictive value and negative predictive value for recurrence of malignancy of 96%, 82%, 89%, and 93%, respectively. Other studies suggest that, despite the high sensitivity for the detection of recurrent lung cancer, the lower specificity from false positive results mean that PET-CT should not be performed for at least 3–5 months after a patient's last treatment^{17, 18}.

Breast

Breast cancer is the most common cancer in women in the United States and the second most common cause of cancer death⁴. Imaging plays an important role in the diagnosis of primary breast cancer, regional lymph node metastases and distant metastases.

PET for Primary Diagnosis of Breast Cancer—Mammography, ultrasound and MRI have been shown to be sensitive but lack sufficient specificity in differentiating benign from malignant breast disease¹⁹. Therefore, many women still undergo invasive diagnostic procedures. Functional imaging has been studied for primary breast cancer diagnosis using whole body PET-CT, dedicated breast PET-CT and Positron Emission Mammography (PEM).

A study of 40 women with suspected malignancy on conventional mammography underwent whole-body PET-CT in comparison with MRI mammography²⁰. The study reports a sensitivity of 95%, which was not different from MRI, and MRI was better able to characterize the tumor size. Avril et al reports sensitivity and specificity ranging from 64–80% and 76–94%, respectively, depending on the level of expertise of the interpreting radiologist¹⁹. In a 2009 study, Bowen reports on the feasibility and viability of a dedicated breast PET-CT scanner, but currently no studies provide data which suggest that PET-CT should be routinely used as a screening modality²¹.

PEM is a technique which uses radiolabeled FDG in combination with high-resolution detectors which can be fashioned similar to standard mammography units. The result is that PEM can detect cancers as small as 5 mm, even in the presence of breasts with significant density on mammography. Several studies indicate that the specificity of PEM is better than mammography. Two preliminary studies indicate PEM to have a sensitivity of 80–86% and a specificity of 91–100%, a significant improvement over conventional mammography^{22, 23}. One of the major limitations of PET-CT in evaluating breast cancer is decreased sensitivity for small tumors²⁴. While PEM requires a specialized piece of equipment, one advantage is that it may be able to detect smaller tumors than PET-CT, leading to earlier diagnosis²⁵. Current studies comparing the performance characteristics of PEM versus MRI are in progress, but preliminary results suggest that PEM may provide an alternative to breast MRI with similar diagnostic performance.

PET-CT for Axillary Staging Patients with Breast Cancer—One of the most important advances in the treatment of breast cancer has been the surgical management of the axilla. Routine axillary lymph node dissection (AND) is no longer the standard of care for staging of the axilla and has been replaced by sentinel lymph node biopsy (SLNB). Pre-operative ultrasound and MRI have been studied to determine whether they can accurately

predict sentinel node status with mixed results. Similarly, studies utilizing PET-CT have not shown this modality to have high enough operating characteristics to warrant replacing SLNB^{26, 27}. The shortcoming of PET-CT and other imaging studies is the failure to demonstrate micrometastases which are detected by SLNB^{28, 29}. (Table 3)

Kim et al have demonstrated that PET-CT may identify lymph node macrometastases in some instances, which would allow certain patients to proceed directly to AND rather than have SLNB³⁰. Pre-operative PET-CT had a PPV of 100% in determining axillary lymph node staging, which the authors concluded accurately upstages patients and would reduce the number of unnecessary SLNB. Several other studies have concluded that preoperative whole-body PET-CT could be used to evaluate patients for regional lymph node metastasis as well as distant metastasis^{20, 24}. They conclude that PET-CT is useful in correctly upstaging patients and, hence, avoiding unnecessary procedures such as SLNB in the presence of axillary lymph node metastases.

PET-CT to Determine Locoregional or Distant Recurrence in Patients with Breast Cancer—In a retrospective study, 46 women with elevated serum tumor markers were evaluated with PET-CT³¹. Final diagnosis was determined by pathologic evaluation of tissue samples, continued clinical follow-up or further imaging studies. The authors report a sensitivity and specificity of 90% and 71%, respectively. Diagnostic accuracy was 83% and the authors report that the results of PET-CT changed the management of 51% of patients. These findings were similar to another retrospective study that enrolled women with suspected recurrence (Table 4) 32. Pan and colleague performed a meta-analysis comparing MRI, CT, PET (with or without CT) and US for the evaluation of breast cancer recurrence³³. The study found that MRI and PET had the highest sensitivities (95% and 95.3%, respectively) while MRI and US had the highest specificities (93% and 96%, respectively). They concluded that MRI was likely the most useful imaging modality to add to current surveillance techniques. In the event the MRI was contraindicated or inconclusive, the authors, then state that PET might be of some utility.

Prostate

Prostate cancer is the most commonly diagnosed cancer in men and is the second leading cause of cancer-related death. The disease poses significant diagnostic challenges due to the high prevalence of positive screening tests which necessitate an invasive biopsy. Prostate cancer can range from highly aggressive to clinically irrelevant and the treatment (i.e. prostatectomy) has significant morbidity.

PET-CT for Primary Diagnosis of Prostate Cancer—Current standard of care following abnormal prostate-specific antigen blood testing involves multiple prostate biopsies which are known to have sampling errors³⁴. A reliable imaging technique that could accurately identify aggressive tumors would substantially improve medical care of these patients. Unfortunately, FDG-PET has significant baseline urinary excretion, which can affect the sensitivity of identifying small malignant lesions within the pelvis. In order to bypass the urinary excretion issues, studies have shown that ¹¹C-choline can be used as a radioactive substitute for FDG in the detection of prostate cancer^{35, 36}. In a study by Farsad and colleagues, 36 patients with prostate cancer and 5 controls with bladder cancer all received ¹¹C-choline PET-CT followed by resection of the prostate with subsequent histopathologic confirmation³⁷. This study demonstrated that detection of cancer using ¹¹C-choline was feasible, but the high rate of false-negatives precluded the use of PET-CT as a first line test to replace biopsy. They report a sensitivity, specificity, accuracy, positive predictive value and negative predictive value of 66%, 81%, 71%, 87%, and 55% respectively.

Another area of study involves determining the biologic aggressiveness of known prostate cancer to tailor therapy. Piert et al studied ^{11}C -choline PET-CT in 14 patients with known prostate cancer to determine whether PET-CT could help with treatment planning³⁸. The study found that using a ratio of tumor volume to benign background could predict tumors that had aggressive characteristics on final pathology. While this study was hardly conclusive it did provide a framework for future investigations.

PET-CT for Staging in Patients with Prostate Cancer—Lymph node metastases in patients with prostate cancer are associated with progressive disease and a decrease in 5-year survival from 85% to 50%³⁹. Pelvic lymphadenectomy is currently the gold standard for lymph node staging in prostate cancer, as routine imaging studies (e.g. CT, MRI) have not demonstrated sufficient sensitivity. De Jong et al studied 67 patients with biopsy-proven prostate cancer with ^{11}C -choline PET-CT prior to lymphadenectomy⁴⁰. The authors found PET-CT to have a sensitivity, specificity and accuracy in staging pelvic lymph nodes of 80%, 96%, and 93%, respectively. The authors conclude that PET-CT staging of pelvic lymph nodes could replace pelvic lymphadenectomy in select patients in the future. However, due to the lack of larger confirmatory studies, currently there is little justification for the use of PET-CT for primary diagnosis in patients with prostate cancer.

Colorectal

Colorectal cancer is a leading cause of cancer in the United States. Although there has been a slight but steady decline in incidence, it remains the third most commonly diagnosed cancer with the third highest mortality⁴. Imaging studies which could improve the detection of primary colon cancer and malignant polyps using noninvasive approaches would be desirable.

PET-CT for Primary Diagnosis in Patients with Colorectal Cancer—Colon and rectal cancers are potentially surgically curable if detected at an early stage. Currently, there are several methods being used to screen for colorectal cancer which include fecal occult blood testing, flexible sigmoidoscopy, air-contrast barium enema and CT-colonography (CTC)⁴¹. CTC has the potential to accurately detect cancer and well as improve patient compliance because it is relatively non-invasive⁴². However, CTC continues to have issues that prevent it from widespread screening, including detecting small (<10 mm) and flat/sessile polyps. In an attempt to improve the sensitivity of CTC, PET-CT is currently being developed for the screening of colorectal cancer. In several small feasibility studies, PET-CT colonography was well tolerated by patients and technically feasible but did not increase the sensitivity or accuracy of CTC^{43–45}. While it does not appear that PET-CT will improve on current screening tools for colorectal cancer, several studies have shown that PET-CT colonography is a feasible single modality study for visualization of primary tumor and the staging of colorectal cancer. Authors have suggested that this imaging modality might be particularly beneficial to patient with incomplete colonoscopies and those with synchronous lesions^{46, 47}.

PET-CT for Staging of Colorectal Cancer—Identification of liver metastases in patients with newly diagnosed colon cancer significantly alters patient management and outcome⁴⁸. In patients who have liver metastases, the presence of extrahepatic disease may affect resectability for curative intent. In a study by Sorensen et al, 54 patients with colorectal cancer were evaluated for resection of liver metastasis by their standard protocol⁴⁹. In 19% of cases, treatment plans were altered by imaging information either leading to correctly up staging or down staging patients. Studies using pre-operative FDG-PET and PET-CT have demonstrated alterations in treatment planning in a similar proportion of patients^{50, 51}. In a review by Vriens, pooled analysis of several studies showed

a change in management of colorectal liver metastasis for approximately 10% of patients after PET-CT⁵². This has led some institutions to use PET-CT as a routine part of pre-operative work-up of colorectal cancer patients. However, there is little data that demonstrates that PET-CT improves staging information when compared to conventional CT or MRI.

PET-CT for Locoregional or Distant Recurrence in Patients with Colorectal Cancer—The current modalities for evaluation of recurrent colorectal cancer include routine clinical exams, colonoscopy, CT scans, and serum tumor markers. Each is associated with certain limitations; colonoscopy only evaluates for local recurrence, CT does not detect local recurrence well, and serum tumor markers are only 60–70% sensitive⁵³. PET-CT has been investigated as a single modality method of detecting recurrence.

Two retrospective studies using PET-CT to evaluate recurrence in patients with colorectal cancer have demonstrated promising results^{54, 55}. The sensitivity and specificity of PET-CT in detecting colorectal cancer recurrence is between 89–95% and 83–92%, respectively (Table 5). The limitations addition of contrast enhancement to PET-CT may improve the diagnostic accuracy even more⁵⁶. In a review by Vogel, the author states that PET-CT appears to be the diagnostic test of choice for evaluation of recurrent colorectal cancer, especially in staging prior to surgical re-intervention⁵⁷.

Melanoma

Use of PET-CT for Staging of Patients with Melanoma—Yancovitz et al attempted to define the role of imaging for patients with early melanoma. 158 patients with T1b–T3b primary tumors and no clinical evidence of metastases were examined in a retrospective study⁵⁸. A total of 344 preoperative imaging studies (chest x-ray, CT scan, and/or PET-CT) were evaluated. Only 1 of 344 imaging studies (a PET-CT) corresponded to a confirmed metastatic melanoma. The authors concluded that for T1b–T3b tumors with history and physical negative for metastatic disease the number of false-positives and increased costs outweigh the benefits of routine imaging.

The use of FDG-PET to identify regional lymph node metastases to avoid SLNB has also been studied in patients with melanoma. In a study of 55 patients with primary cutaneous melanoma >1.0 mm in thickness, PET scan was performed prior to SLNB⁵⁹. The study demonstrated that sentinel lymph nodes were positive in 13 patients, only 2 of which were detected by PET. PET scan also showed accumulation in lymph node basin of 5 patients with no tumor positive lymph node (false positive result). These results have been repeated and lead to the conclusion that FDG-PET cannot replace SLNB for detection of regional lymph node metastases^{60, 61}.

PET-CT has been shown to be useful in high-risk melanoma patients for the detection of distant metastases. In a study of patients with T4 tumors or evidence of metastatic disease, Strobel et al, showed that PET-CT had a sensitivity and specificity of 98% and 94%, respectively⁶². The accuracy, positive predictive value and negative predictive value were 96%, 93% and 99%, respectively. Tyler et al demonstrated a change in management for 15% of patients with stage III melanoma who received a PET scan⁶³. Based upon these results, PET-CT may be a valuable study for the identification of distant metastasis in high-risk melanoma patients.

Head and Neck

Primary Diagnosis—PET-CT is being increasingly studied for the functional as well as anatomical information it provides for head and neck cancers (HNC). Branstetter and

colleagues examined 64 consecutive patients with known or suspected HNC with PET-CT⁶⁴. The authors showed the PET-CT had a sensitivity and specificity of 98% and 92%, respectively, and was superior to PET or CT alone in detection of primary tumors. Hannah et al found similar results in a previously performed prospective study⁶⁵.

Staging—Early studies using PET without CT showed that PET could be more sensitive and specific for regional lymph node metastases than CT or MRI^{66, 67}. Schoder et al showed that the sensitivity and specificity of PET-CT was between 87–90% and 80–93%, respectively, with a diagnostic accuracy between 90–96%⁶⁸. These are significantly better than MRI or CT alone. Importantly, there was a change in treatment plan in 18% of patients based on PET-CT findings. Although these results were impressive, several studies have found that in patients with clinically negative nodal status, PET-CT was not reliable enough as an initial study on which to base management decisions^{69, 70}. Thus, although PET-CT can identify clinically occult lymph node metastases, larger studies are necessary to determine whether PET-CT provides enough negative predictive value to avoid cervical lymph node dissection.

Another potential use for PET-CT at the initial work-up for patients with HNC is to evaluate for second primary tumors and distant metastatic disease. Kim et al enrolled 349 patients with primary HNC and performed whole body PET-CT for work-up of second primary tumors and distant metastatic disease⁷¹. 7.4% of these patients had distant metastases and 4% had second primary tumors. PET-CT was able to accurately detect these lesions but also had issues with false positive results.

In summary, the use of PET-CT in patients with known or suspected HNC continues to evolve. Some authors recommend only selective usage for evaluation of distant metastases⁷², while other use it as a single modality study to gain information about primary tumors, lymph node status and distant metastases⁶⁸. Table 6 shows operating characteristics for various usages of PET-CT in HNC.

Use of PET for Locoregional Recurrence in Patients with HNC—The diagnosis and staging of recurrent head and neck cancer can be very difficult due to frequent alterations in anatomy associated with extensive surgery⁵³. Therefore, PET-CT has been studied to determine if it can overcome the limitations of conventional imaging. A recent prospective study enrolled 91 patients cured of HNC with no clinical evidence of recurrence⁷³. These patients were evaluated with whole body PET-CT to determine its usefulness as an initial modality for the detection of subclinical locoregional disease. 39 patients had a positive PET-CT and in 30 patients recurrence was confirmed. 52 patients had a negative PET-CT; and all of these patients remained disease free on clinical exam for 3 months. These results correspond to a sensitivity and specificity of 100% and 85% respectively. These findings are relatively consistent with other studies demonstrating that the sensitivity and specificity for PET (with or without CT) was 83–100% and 78–98% respectively. Taken together, these studies suggest that PET-CT may be useful in the follow-up of patients with treated HNC for the detection of subclinical recurrence.

Use of PET for Radiation Treatment Planning

Radiation treatment planning has become more refined with the use of technology which allows for more precise delivery of radiation to target tissues while minimizing exposures to surrounding tissues. Intensity-modulated radiation therapy utilizes multiple beams of radiation at various angulations with varying intensity to maximize radiation delivery to tumor and minimize exposure to normal/critical surrounding tissues.⁷⁴

The ability to precisely target lesions and relatively spare surrounding structures has now made precise imaging of the target tumors the “rate-limiting step” in accurate radiation delivery. CT is the most commonly employed modality in radiation therapy (RT) planning. There is, however, well-known inter- and intra-observer variability in determining gross tumor volume (GTV) for targeting using conventional CT⁷⁵.

PET-CT is an imaging modality that is being increasingly studied for treatment planning of RT. The goal is to have a reliable imaging study that will accurately depict GTV while reducing the amount of inter- and intra-observer variation⁷⁶. PET-CT has been studied as is gaining widespread use in cancers of lung, head and neck, rectum and anus, uterine cervix, pancreas, brain as well as partial breast^{77–82}.

Kruser et al provides one of the more robust studies demonstrating the benefits of PET-CT for RT planning⁸³. This was a blinded prospective study enrolling 111 patients with various cancers (lung, head and neck, breast, cervix, esophageal, and lymphoma). Patients underwent PET-CT in preparation for RT, and one physician who was blinded to PET data designed a treatment plan based on clinical data and CT imaging. The treating physician then designed a second treatment plan based on hybrid PET-CT data. The author found that in 76/111 patients (68%), treatment plans changed with the inclusion of PET-CT data.

While there remain several technical limitations, PET-CT is becoming increasingly common in RT planning for various cancers. Ongoing research is demonstrating the feasibility of single session PET-CT in RT planning, determining the best protocols to reduce variations between institutions, and showing that treatment programs are being changed as a result of this new information. However, more investigation needs to be performed to determine if any of these advances are having a positive impact of patient morbidity and therapeutic effectiveness of the radiation therapy.

Use of PET in Pediatric Patients

Pediatric malignancies are distinct from cancers in adults due to their relative infrequency, differences in treatment strategies as compared to adult malignancies and prognosis. While there are many studies examining the role of PET-CT in adults, the evidence for use in pediatrics is sparse. Interestingly, FDG-PET has been studied for many years for use in pediatric brain tumors with good success⁸⁴. There is, however, interest in PET-CT for use in pediatric patients as a single session study in non-CNS malignancies. A recent review by Kumar suggests that there may be some role for PET-CT in common pediatric malignancies, including lymphoma, soft-tissue tumors, neuroblastoma, malignant bone tumors and germ cell tumors⁸⁵.

Tatsumi et al attempted to evaluate the use of PET-CT in various pediatric malignancies⁸⁶. The authors enrolled 55 patients in whom 151 PET-CT studies were performed for non-CNS tumors. 71% were performed for lymphoma and only 16 of 151 studies were performed for initial staging and diagnosis. In the setting of post-treatment follow-up, PET-CT had a sensitivity and specificity of 97% and 99%, respectively, compared with 74% and 91%, respectively for conventional imaging. The data for utilization of PET-CT for initial staging and diagnosis was limited by small sample size.

A major concern for the use of PET in the pediatric population is radiation exposure. This is especially true for studies that are to be used serially for post-treatment response and surveillance. Murano et al examined the difference in radiation exposure to children with malignancies from current imaging plans as compared with PET-CT⁸⁷. This study found that PET-CT had lower doses of radiation compared to current imaging plans such as conventional CT (64–68 mSv compared to 127–169 mSv). At a dose of 100 mSv or greater

it is estimated that the risk of a secondary cancer is 1 in 100 individuals⁸⁸. In another study specifically looking at serial PET-CT in pediatric malignancies, Chawla et al showed that the cumulative radiation dose per patient with PET-CT was 79 mSv (range 6.2 to 399)⁸⁹. Importantly, the study showed that the vast majority of the radiation dosage came from the CT portion of the study, suggesting that the FDG-PET added little to the total radiation exposure. In summary, while studies are showing that PET-CT may have a role in pediatric malignancies, prospective studies examining specific malignancies are needed to justify widespread clinical use.

Benign Disease

While the vast majority of the literature on PET-CT has investigated its role in oncology, several authors are looking into the uses of PET-CT for non-neoplastic disease. Given that FDG uptake occurs preferentially in neoplastic, inflammatory, and infectious processes, one application that is being studied is in patients with fever of unknown origin (FUO). FUO is defined as a recurrent fever of 38.3°C or higher, lasting 2–3 weeks and undiagnosed after appropriate work-up⁹⁰. In a review by Meller, sensitivity and specificity of PET in diagnosis of FUO is reported as 81% and 86%, respectively⁹¹. The authors report that 25–69% of PET scans are helpful in the diagnosis of FUO. While there is a paucity of research on this specific topic, preliminary studies indicate that PET may be an improvement upon gallium scans currently in use.

Another area in which the use of FDG-PET is being actively studied is in patients with inflammatory bowel disease. Halpenny reports sensitivities of 59–98% and specificities of 50–100% for the use of PET-CT in inflammatory bowel disease⁹². The author discusses monitoring of disease response to therapy, cancer surveillance, and diagnosis of areas of active inflammation all in one noninvasive test as the benefits of this modality.

PET-CT is being increasingly applied in the field of cardiology. PET perfusion scans have been studied for use in patients with coronary artery disease. Knaapen reports sensitivity and specificity from nine pooled studies to be 90% and 89%, respectively⁹³. These results are superior to currently used thallium-SPECT (single photon emission CT) images.

Finally, PET is gaining acceptance as a functional study for use in clinical practice in neurologic disease. While not indicated as a primary imaging technique, PET is finding use in conditions such as stroke, epilepsy, dementia, and movement disorders⁹⁴.

Summary

As outlined in this article, there is evidence to suggest a role for the use of PET-CT in patients with a variety of solid tumors including lung, colorectal and head and neck. PET-CT also has utility in patients with hematologic malignancies, including lymphoma. PET-CT is quickly becoming a complementary imaging modality for radiation therapy treatment planning and is also being considered for use in the pediatric cancer population.

The current literature of the performance characteristics of PET-CT are limited in several important ways. First, measurements of sensitivity, specificity as well as positive and negative predictive value are limited in that in many instances there is a lack of histologic confirmation. In the instance of lesions which are determined to be PET negative, clinical follow-up of lesions to confirm benign biology are utilized. In addition, although PET-CT is an imaging modality, the relative endpoint of future studies should be the proportion of instances in which clinical decision-making changes as a result of the test. Finally, the morbidity and cost of false positive results are rarely studied and reported in PET-CT studies, and may be the most important factor in terms of determining the cost-effectiveness

of this modality. The National Oncology PET registry is an attempt by insurers as well as Centers for Medicare and Medicaid Services to follow patients who have undergone PET to determine whether medical care and outcomes are improved.

Despite these questions, the development of new probes for use with PET are essentially unlimited. The ability to develop probes which are more sensitive and specific than FDG will only increase the clinical utility of functional imaging. Properly controlled studies will yield the results that can demonstrate how PET should be incorporated into evidence-based medicine.

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Figure 1. PET-CT Images in a patient with known left superficial inguinal lymph node metastasis

A. Whole body PET CT demonstrating hypermetabolic left inguinal lymph node (arrow) consistent with metastatic melanoma. **B.** Coronal view of PET-CT demonstrating hypermetabolic left inguinal lymph node (arrow) and showing anatomic relationship of surrounding muscles and blood vessels. **C.** Coronal view of PET-CT demonstrating a deep iliac lymph node (arrow) suspicious for metastasis in the same patient. The large hypermetabolic focus in the central pelvis is the urinary bladder. **D.** Coronal view of PET-CT demonstrating hypermetabolic focus within the right scapula (arrow) in the same patient. The detection of this bone lesion prompted a biopsy and ultimately altered the treatment plan of the patient.

Table 1
Operating Characteristic for PET-CT in Evaluation of Solitary Pulmonary Nodules

Author	Sensitivity	Specificity	Accuracy	PPV	NPV
Chang 2010	88	89	89	84	92
Bar-Shalom 2008	96	83	89	84	96
Kim 2007	97	85	93	94	93
Yi 2006	96	88	93	94	92

Table 2

Preoperative Mediastinal Lymph Node Staging by PET-CT

Author	Sensitivity	Specificity	Accuracy	PPV	NPV
Shim 2005	85	84	84	32	98
Tasci 2009	72	94	93	49	98
Liu 2009	65	97	92	79	90
Camochan 2009	52	83	75	53	82

Table 3

Staging of Axilla in Breast Cancer with PET-CT or PET

Author	Sensitivity	Specificity	Accuracy	PPV	NPV
Taira 2009	48	92		72	81
Chae 2009	49	84	73		
Greco 2001	94	86	89	84	95
Schirmeister 2001	79	92			

Table 4

PET-CT in Breast Cancer Recurrence

Author	Sensitivity	Specificity	Accuracy	PPV	NPV
Pan 2010	95	86	93	95	88
Radan 2006	90	71	83		
Veit-Haibach 2007			91		

Table 5

PET-CT in Colorectal Cancer Recurrence

Author	Sensitivity	Specificity	Accuracy	PPV	NPV
Chen 2007	95	83		96	77
Votrubova 2006	89	92	90		

Table 6

PET-CT in identification of primary head and neck tumor					
Author	Sensitivity	Specificity	Accuracy	PPV	NPV
Branstetter 2005	98	92	94	88	99
Hannah 2002	88	100			
PET-CT in detection of metastatic head and neck lymph nodes					
Author	Sensitivity	Specificity	Accuracy		
Schoder 2004	87–90	80–93	90–96		
Hannah 2002	82	94			
Baillet 1992	71	98			
Braams 1995	91	88			
PET-CT for the detection of 2nd primary and distant metastases					
Author	Sensitivity	Specificity	Accuracy	PPV	NPV
Kim 2007	98	93	93	63	99