PET/CT and Occult Primary Tumors

Donald A. Podoloff, MD, Houston, Texas

**Abstract**

Within the past 5 years, F-18 fluorodeoxyglucose (FDG) PET/CT has become one of the more frequent imaging modalities in the management of patients with cancer of unknown primary origin. FDG PET/CT detects more sites of metastasis than other modalities, and in 20% to 40% of cases it discloses the site of the primary tumor. Its exact role is yet to be defined because of a lack of prospective clinical trials comparing the performance of PET/CT with conventional anatomic imaging modalities. This article reviews the available literature, attempts to place PET/CT using F-18–labeled FDG in clinical perspective and compares the combined modality with conventional anatomic imaging technologies. (JNCCN 2009;7:239–244)

This article focuses on the current literature and reviews the indications and efficacy of PET/CT imaging in this vexing clinical situation of CUP; PET/CT and PET imaging will not be distinguished further.

An estimated 2% to 4% of all cancers reported in 2008 were of unknown primary origin for which a primary site will never be detected. Because appropriate treatment requires exact diagnosis and staging, these presentations are problematic for multiple reasons.

The recognition of lymph node involvement is still among the most challenging topics in diagnostic radio-oncology. In addition to its size, shape, and contour, the intrinsic architecture of the node, its vessels, metabolic activity, and more recently, histochemical characteristics must be assessed to reach specific diagnostic conclusions that can lead to more specific therapy. Conventional ultrasound has high sensitivity for detecting enlarged lymph nodes, but only moderate specificity. Tumor-associated alterations of intranodal blood vessel architecture are not specific enough for reliable differential diagnosis of lymphadenopathy with color-coded Doppler ultrasound. Power Doppler ultrasound improves distinction between inflamed, reactive, and metastatic nodes but is also imperfect.

CT is used to detect and characterize lymph nodes in regions inaccessible to ultrasound. However, diffuse lymph node enlargement secondary to infectious or granulomatous diseases cannot be distinguished from that caused by cancer.

MRI is comparable to CT in identifying lymph nodes. However, assessment of signal intensity does not permit reliable follow-up of disease activity. MR lymphography has promise for avoiding understaging as a result of microscopic tumor invasion and overstaging as a result of peritumoural inflammation. However this technique is new and has not been widely validated.

PET provides superior staging information because it offers functional information on tissue activity and

**Key Words**

PET/CT, cancer of unknown origin, unknown primary site, unknown primary and PET/CT
Detection of Primary Tumors

Seve et al. conducted a comprehensive review of the efficacy of 2-deoxy-2-[F-18]fluoro-D-glucose PET (FDG-PET) in the detection of primary tumors in patients with disseminated carcinoma of unknown primary origin. This review involved 10 studies (a total of 221 patients) published between 1998 and 2006. Each study evaluated the role of FDG-PET in the detection of unknown primary tumors after a conventional diagnostic workup. Although 94% of patients had a single site of metastases, the studies were otherwise very heterogeneous in the population studied, study design, and additional diagnostic workup. In 41% of patients, FDG-PET detected primary tumors that were not apparent after conventional workup. In this group of patients, the overall sensitivity, specificity, and accuracy rates of FDG-PET in detecting unknown primary tumors were 91.9%, 81.9%, and 80.5%, respectively.

F-18–labeled FDG-PET imaging also led to the detection of previously unrecognized metastases in 37% of patients. Lung cancers represented 59% of the detected tumors. FDG-PET had a high false-positive rate (58.3%) in tumors of the lower digestive tract, which is not unexpected because of the normal bowel regional glucose metabolism that can be quantified and has better sensitivity and specificity than CT for showing neoplastic foci. Dual-modality scanners (CT + PET) aid precise localization of diseased lymph nodes and provide unique information on the metabolism of residual tumor tissue.

A review of the literature since 2003 (excluding case reports) shows fewer than 40 articles focusing on PET and/or PET/CT in the setting of an unknown primary tumor, translating into fewer than 850 patients. Most of the studies retrospectively assess the efficacy of these techniques in the clinical setting of unknown primary tumors.

FDG-PET has not been well studied in patients with noncervical metastases. Although Delgado-Bolton et al. performed a meta-analysis of the literature to evaluate the accuracy of FDG-PET for detecting primary tumors in patients with CUP, they did not distinguish between patients with squamous carcinoma isolated to the head and neck and the general population of those with CUP.
el activity seen on PET imaging with F-18-labeled FDG. FDG-PET altered the clinical management in 35% of patients. Most of those patients (53%) underwent specific chemotherapy for lung and pancreatic cancers, whereas 12% underwent specific therapy for breast, ovarian, and prostate cancers and 14% underwent surgery with curative intent. Seve et al. concluded that FDG-PET was a satisfactory method for detecting primary tumors that were undetected with other conventional imaging modalities, and was sensitive for detecting previously unrecognized metastases. FDG-PET significantly changed clinical management in approximately one third of the patients studied.

In a retrospective evaluation of 41 patients without history of known cancer (18 women and 23 men; average age, 64.1 years) with metastatic disease confirmed with histopathology, Alberini et al. compared the clinical performance of conventional diagnostic procedures and PET. Compared with conventional diagnostic imaging procedure, PET detected all known metastatic lesions, with 26 true-positive and 2 false-negative results. Primary tumor remained undetermined in 8 patients after conventional investigations and PET. PET was superior to the conventional diagnostic procedure in 11 patients and led to treatment modification in these patients. Sensitivity of PET was superior to that of CT in detecting abdominal primary tumors. The investigators concluded that FDG-PET was useful in patients with unknown primary tumor. Its sensitivity was good and it modified disease management in approximately one third of the patients. PET improved evaluation of disease extent and could monitor treatment response.

In a retrospective analysis of 190 patients, 82 with histologically proven malignancy (HPM) and 108 with clinical suspicion of the presence of

Figure 2  PET/CT of a 79-year-old woman diagnosed with an unknown primary presenting with hoarseness. PET/CT scan shows intense nodal hypermetabolism in the left paratracheal space. A) No definite primary site was identified. B) The primary tumor is the retropharyngeal space. The primary tumor was seen only on PET/CT.
Changes in Management

Johansen et al. reported on 67 patients undergoing standardized diagnostic workup according to national guidelines, including panendoscopies, multiple mucosal biopsies, and diagnostic CT/MRI scans. Median follow-up was 40 months (range, 2–65 months). In 60 eligible patients, FDG-PET showed a primary tumor or metastatic disease in 30 patients (50%). In 18 patients, additional investigations confirmed a primary tumor in the hypopharynx (n = 5), oropharynx (n = 5), nasopharynx (n = 2), lung (n = 1), axilla (n = 1), bone (n = 1), and rectum (n = 1), and 2 patients had multiple sites of metastatic disease. In retrospect, MRI was able to detect 1 of the PET-detected primaries, leading to an overall detection rate of PET of 29% in CUP. A treatment change was made in 25% as a consequence of FDG-PET. PET before panendoscopy showed fewer false-positive pathologic foci. The investigators concluded that FDG-PET was valuable in addition to conventional extensive workup in CUP and neck metastases. Consequently, FDG-PET is now recommended as an early diagnostic modality in the workup of these patients.

Joshi et al. retrospectively studied patients with unknown primary tumors presenting with metastases external to the neck. In 63 cases with known metastases, all were FDG avid except for 1. PET scans were retrospectively classified as positive for a primary tumor in 29 patients, which was confirmed in 16, either through histology (n = 10) or radiologic and clinical follow-up (n = 6). Results were false-positive in 4 cases and the primary tumor was never confirmed in 9. Of the remaining 33 negative PET scans, the primary tumor was never found in 18. Follow-up and additional pathology investigations showed the primary tumor in 15. A survey on clinical usefulness of PET (response rate, 83%) suggested that PET positively contributed to diagnostic evaluation in 29 of 52 evaluable cases.

Prognosis in Patients With PET/CT-Negative Results

In a cohort of 31 patients with squamous cell carcinoma confirmed through fine-needle aspiration and biopsy, Miller et al. considered the long-term follow-up of those with negative PET results. They prospectively entered the patients into a diagnostic protocol to identify the occult primary tumor. The diagnostic...
protocol included a comprehensive head and neck examination (including flexible endoscopy) and CT and/or MRI. If the initial diagnostic evaluation failed to identify a primary tumor, patients underwent whole-body PET imaging followed by staging endoscopy with biopsy of the at-risk occult tumor sites. The outcome measures included the accuracy of PET to predict the presence of occult tumor at staging endoscopy and the accuracy of the negative PET and panendoscopy in predicting the subsequent development of a primary tumor in the upper aerodigestive tract during follow-up. PET detected 9 occult primary tumors in 31 patients (detection rate, 29%), and 5 (2 base of tongue and 3 palatine tonsils) were detected during panendoscopy despite a negative PET. Combination PET and panendoscopy detected 45.2% of the unknown primary tumors.

No primary tumor was detected in 17 patients (N1 = 7; N2a = 4; N2b = 2; N3 = 4), and they were treated as having an unknown primary carcinoma, with primary neck dissection with or without radiation therapy with or without chemotherapy. In this series of patients, 3 experienced neck recurrences (17.6%), and 1 (5.8%) developed a primary tumor of the upper aerodigestive tract with a mean follow-up of 31.1 months (range, 21–60 months). Miller et al. concluded that a negative PET study in patients with an occult primary head and neck carcinoma does not preclude the need for panendoscopy with biopsy to detect the occult primary tumor. The risk for development of a subsequent primary tumor seems to be low in patients with a negative PET and panendoscopy (< 6%).

Efficacy of PET/CT in the Setting of Lymph Node Metastases

Stoeckli et al. concluded that PET had a high specificity in the setting of unknown primary carcinoma presenting as lymph node metastatic disease and could be used as an initial diagnostic procedure.

Wartski et al. reported on 38 consecutive patients with cervical node metastasis whose primary tumor site had not been identified using conventional imaging and endoscopy, but in 26 of whom (68%) PET/CT identified focal uptake. Subsequent biopsy using rigid panendoscopy in 17 of the 26 patients identified 13 primary tumors that were proven with histology, and PET/CT identified distant lesions in 3 patients. PET/CT prompted treatment-related changes in 23 of 38 patients (60%), including changes in radiotherapeutic or surgical planning.

Conclusions

A MEDLINE search of PET and PET/CT in the clinical setting of CUP shows a benefit for PET/CT in identifying sites of primary tumor and distant unsuspected metastasis with reasonably high accuracy. It also indicates a role for PET/CT in radiotherapy treatment planning and the evaluation of therapeutic response earlier than with conventional imaging.

The role of PET/CT in CUP is currently evolving. It seems to have defined roles in identifying the primary tumor site and the site from which cervical lymph nodes arise. It also seems to have some prognostic efficacy. The introduction of more specific radiopharmaceuticals, such as F-18–labeled FLT (a marker of cell proliferation), may lead to greater efficacy in the future. However, comparative prospective clinical imaging trials are urgently needed to more fully evaluate its efficacy and determine the effect of PET/CT on overall patient survival.

References


