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DISCUSSIONS IN PET IMAGING

CONTINUING EDUCATION FOR MEDICAL PROFESSIONALS

PET and PET/CT for Colorectal Cancer

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LEARNING OBJECTIVES

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

- Explain the complementarity of anatomical and functional imaging, the importance of correlative imaging, and image coregistration.
- Describe the performance and indications of FDG-PET and PET/CT imaging in the staging, restaging, and therapy monitoring of patients with colorectal carcinoma.
- Summarize the promising applications of FDG-PET for monitoring regional therapy to hepatic metastases.
- Discuss the incremental value of PET/CT compared with PET alone in patients with colorectal carcinoma.

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Colorectal cancer is the third most common cancer in men and women, and it affects 5% of the population in the U.S. and most Western countries. The American Cancer Society estimates that approximately 135,000 new cases of colorectal cancer occur and about 57,000 patients die per year from this disease in the U.S., representing 10% of all cancer deaths. The diagnosis of colorectal carcinoma is based on colonoscopy and biopsy.

Approximately 70% to 80% of patients are treated with curative intent, and the overall survival at five years is less than 60%. About one-third of patients have recurrence within two years, and 25% of these patients have recurrence to one site and are potentially curable by surgical resection.

About 14,000 patients per year with colorectal carcinoma present with isolated liver metastases as their first recurrence, and about 20% die with metastases exclusively to the liver. Hepatic resection is the only curative therapy in these patients, but it is associated with a mortality of 2% to 7% and significant morbidity. Early detection and prompt treatment of recurrences may lead to a cure in up to 25% of patients. Accurate noninvasive detection of inoperable disease with imaging modalities therefore plays a pivotal role in selecting patients who would benefit from hepatic surgery.

Colorectal carcinoma is associated with elevated serum levels of carcinoembryonic antigen in approximately two-thirds of patients. Monitoring CEA serum levels is helpful in the surveillance of these patients, but when CEA serum level is rising, the site(s) of recurrence/metastases need to be identified and localized.

METHODS OF DIAGNOSIS

Diagnostic issues include early detection of these tumors; differentiation of malignant from benign tumors (lesion characterization); staging for resection that includes lesion localization; evaluation of proximity to vessels, invasion of adjacent structures, and metastasis to regional lymph nodes and distant sites; and assessment of therapeutic response. Some of these goals are better achieved with the high resolution of anatomical imaging techniques and others with molecular imaging using PET.

Rapid advances in imaging technologies present a challenge for both radiologists and clinicians who must integrate these technologies for optimal patient care and outcomes at minimal cost. Since the early 1990s, numerous technological improvements have occurred in radiological imaging. These include multislice spiral CT, which permits fast acquisition of angiographic images and multiphase enhancement techniques, and PET using FDG as a radiopharmaceutical that provides the capability for imaging tumor metabolism.

The clinical utility of FDG imaging was first established using dedicated PET scanners

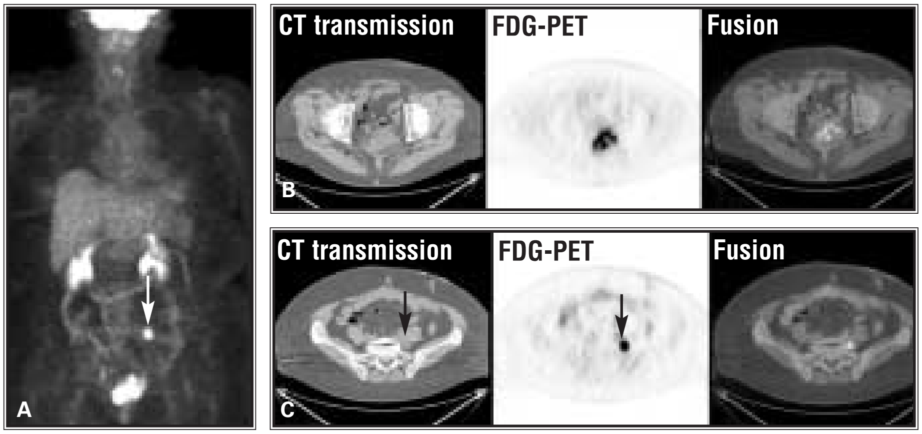

Figure 1. A 61-year-old woman with a history of sigmoid colectomy for colon carcinoma presented with pelvic pain. She underwent PET/CT imaging to assess local recurrence and restaging. A: FDG-PET maximum intensity projection image demonstrates FDG uptake in posterior lower pelvis masked by the bladder on anterior projection, which is displayed, and a focus of FDG uptake in left upper pelvis (arrow). B: Transaxial views just above the bladder and through upper portion of the focus of FDG uptake in lower posterior pelvis demonstrate that the focus of FDG uptake corresponded to a presacral mass in region of anastomosis indicating local recurrence. C: Transaxial views through focus of FDG uptake in left upper pelvis demonstrate that the focus of FDG uptake corresponded to a left presacral lymph node, indicating a lymph node metastasis (arrow). This lymph node was detected only retrospectively on the CT images. The finding of a metastatic lymph node in addition to local recurrence has an impact on management of the patient.

equipped with multiple rings of bismuth germanate oxide (BGO) detectors, but a spectrum of equipment is now available for positron imaging,[1] and modality combinations have become possible.

• *Anatomical and functional imaging are complementary.* Although numerous studies have shown that the sensitivity and specificity of FDG-PET are superior to those of CT in many clinical settings, the inability of FDG-PET to provide accurate anatomical localization remains a significant obstacle to maximizing its clinical utility. Because FDG is a tracer of glucose metabolism, its distribution is not limited to malignant tissue. To avoid misinterpretations, the interpreter must be familiar with the normal pattern and physiologic variations of FDG distribution and with clinical data relevant to the patient.[2,3] The limitations of anatomical imaging with CT and MRI are related to size criteria for differentiation of benign from malignant lymph nodes, difficulty differentiating post-therapy changes from tumor recurrence, and difficulty differentiating nonopacified loops of bowel from metastases in the abdomen and pelvis.

Close correlation of FDG-PET studies with conventional CT scans helps to minimize these difficulties. In practice for the past 10 years, dual interpretation has been accomplished by visually comparing corresponding FDG-PET and CT images. To aid in this interpretation, computer software has been developed to coregister the FDG-PET scans with the high-resolution anatomical maps provided by CT.[4] These methods offer acceptable fusion images for the brain, which is surrounded by the rigid skull. For the body, however, coregistration of two image sets often obtained at different points in time is technically more difficult. Identical positioning of the patient on the imaging table is critical. Shifting internal organ movement and peristalsis compound the problem.

Another approach that has gained wider acceptance is hardware for image fusion using multimodality imaging with integrated PET/CT systems.[1]

• *Integrated PET/CT systems.* The recent development of integrated PET/CT systems provides CT and FDG-PET images obtained in a single setting, allowing optimal coregistration of images. The fusion images provided by these systems allow the most accurate interpretation of both CT and FDG-PET studies. Because of the high photon flux of x-rays, CT attenuation maps from these integrated PET/CT systems also allow for optimal attenuation correction of the PET images.

FDG-PET FOR EVALUATION OF COLORECTAL CARCINOMA

Preoperative staging with imaging modalities is usually limited because most patients will benefit from colectomy to prevent intestinal obstruction, and the extent of the disease can be evaluated during surgery. FDG-PET imaging has demonstrated good performance in initial staging of colorectal cancer, however.[5]

A meta-analysis of 11 clinical reports encompassing 577 patients determined that the sensitivity and specificity of FDG-PET for detecting recurrent colorectal cancer were 97% and 76%, respectively.[6] A comprehensive review of the PET literature (2244 patients' studies) has reported a weighted average for FDG-PET sensitivity and specificity of 94% and 87%, respectively, compared with 79% and 73% for CT.[7] A meta-analysis performed to compare noninvasive imaging methods for the detection of hepatic metastases from colorectal, gastric, and esophageal cancers demonstrated that FDG-PET had a higher sensitivity (90%) than MR (76%), CT (72%), and ultrasound (55%), with an equivalent specificity of 85%.[8]

In the meta-analysis of the literature, FDG-PET imaging changed the management in 29% (102/349) of patients.[6] The comprehensive review reported a weighted average change of management related to FDG-PET findings in 32% of 915 patients.[7] Although survival is not an end point for a diagnostic test, Strasberg et al[9] demonstrated improved three-year survival of patients who underwent FDG-PET imaging in their preoperative evaluation for resection of hepatic metastases compared with historical series (77% versus 30% to 64%). Figure 1 illustrates detection of extrahepatic disease precisely localized on PET/CT in a patient with a history of colorectal carcinoma and recently diagnosed with hepatic metastases.

• *FDG-PET for monitoring therapy of hepatic metastases.* Hepatic metastases can be treated with systemic chemotherapy or regional therapy to the liver. Various procedures to administer regional therapy to hepatic metastases have been investigated, including chemotherapy administered through the hepatic artery using infusion pumps, selective chemoembolization, radio-frequency ablation, cryoablation, alcohol ablation, and radiolabeled yttrium-90 microspheres administered via the hepatic artery.[10-13] Preliminary reports suggest that the response to chemotherapy in patients with hepatic metastases can be predicted with PET. Responders may be distinguished from nonresponders after four to five weeks of chemotherapy with fluorouracil by measuring FDG uptake before and during therapy.[14]

Regional therapy to the liver by chemoembolization can also be monitored with FDG-PET imaging.[15] FDG uptake decreases in responding lesions, and the presence of residual uptake in some lesions can help guide further regional therapy (Figure 2). Langenhoff et al[16] have prospectively monitored 23 patients with liver metastases following RF ablation and cryoablation. Three weeks after therapy, 51/56 metastases became FDG-negative, with no recurrence during 16 months of follow-up, whereas among the five lesions with persistent FDG uptake, four recurred. Wong et al[17] have compared FDG-PET imaging, CT or MR imaging, and serum levels of CEA in monitoring the therapeutic response of hepatic metastases to Y-90 glass microspheres. They found a significant difference between the changes seen with FDG-PET imaging and the changes on CT or MR imaging. The changes in FDG uptake correlated better with the changes in serum levels of CEA.

In summary, preliminary data suggest that FDG-PET imaging may be able to effectively monitor the efficacy of regional therapy to hepatic metastases, but these data need to be confirmed in larger series of patients.

• *PET/CT versus PET for evaluation of colorectal carcinoma.* Published data regarding the incremental value of integrated PET/CT images compared with PET alone, or PET correlated with a CT obtained at a different time, are limited. But they have found improvement of lesion detection on both CT and FDG-PET images, improvement of the localization of foci of FDG uptake resulting in better differentiation of physiologic from pathologic uptake, and precise localization of the malignant foci (for example, skeleton versus soft tissue, or liver versus adjacent bowel or node). PET/CT fusion images affect clinical management by guiding further procedures, excluding the need for further procedures, and changing both inter- and intramodality therapy.[18] Precise localization of metastatic lymph nodes, for example, could result in a less invasive, more efficient surgical procedure. PET/CT fusion images have the potential to provide important information to guide the biopsy of a mass to more metabolically active regions of the tumor and to provide better maps than CT alone to modulate field and dose of radiation therapy.[19]

Concurrent PET/CT imaging with an integrated system may be especially important in the abdomen and pelvis.[20] PET images alone may be difficult to interpret because of the absence of anatomical landmarks other than the kidneys and bladder; the presence of nonspecific uptake in the stomach, small bowel, and colon; and urinary excretion of FDG. If possible, images of the abdomen and pelvis should be obtained with the arms elevated to avoid artifacts due to motion and beam-hardening artifacts on the CT transmission images. Concurrent PET/CT imaging is helpful, for example, for differentiating focal retention of urine in the ureter from an FDG-avid lymph node. A review of PET/CT for gastrointestinal tumors has recently been published.[21]

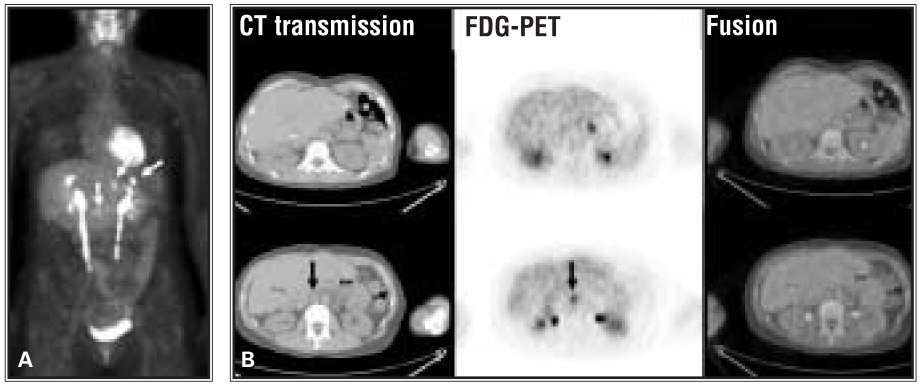

Figure 2. A 37-year-old woman with a history of colorectal carcinoma underwent a right hepatic lobectomy for hepatic metastases and presented with rising serum CEA levels. FDG-PET imaging was performed for detection of the site of recurrence and restaging. A: FDG-PET MIP image demonstrates physiologic FDG uptake in the myocardium, kidneys, ureters, and bladder. In addition, three foci of FDG uptake can be identified in the upper abdomen (arrows). B: Transaxial views through the foci of FDG uptake in the abdomen demonstrate that these foci of uptake correspond to mesenteric metastases (arrows). These metastases were detected only retrospectively on the CT images.

A study of 204 patients performed at Rambam Medical Center[22] using an integrated PET/CT system concluded that it improved the diagnostic accuracy of PET in approximately 50% of patients. Thirty-four of the patients had gastrointestinal tumors. PET/CT fusion images improved characterization of equivocal lesions as definitely benign in 10% of sites and definitely malignant in 5% of sites. Fusion images precisely defined the anatomic location of malignant FDG uptake in 6% and led to retrospective lesion detection on PET or CT in 8%. The results of fusion PET/CT images had an impact on the management of 14% (28/204) of patients, and seven of those patients with a change of management had colorectal cancer, representing 20% of patients with gastrointestinal tumors. The changes in management in the seven patients with colorectal cancer included guiding colonoscopy and biopsy for a local recurrence (n = 2), guiding biopsy to a metastatic supraclavicular lymph node (n = 1), guiding surgery to localized metastatic lymph nodes (n = 3), and referral to chemotherapy (n = 2).

A study of 45 patients with colorectal cancer referred for FDG-PET imaging using an integrated PET/CT system concluded that PET/CT imaging increases the accuracy and certainty of locating lesions. The frequency of equivocal lesion findings was reduced by 50% and the characterization of lesion increased by 30% with PET/CT compared with PET alone. The number of definite locations was increased by 25%, and the overall correct staging increased from 78% to 89%.[23]

Most institutions acquire CT transmission images without intravenous contrast to permit optimal attenuation correction, but such images do not allow visualization of many hepatic metastases. Therefore, although hepatic metastases are commonly seen as FDG-avid on the PET images, no corresponding lesions are seen on the noncontrast CT transmission images. A standard of care CT scan with intravenous and oral contrast needs to be performed if surgery is contemplated. Concurrent PET/CT fusion images have the potential to provide better maps than CT alone to modulate field and dose of radiation therapy, including in patients with colorectal carcinoma.[19]

LIMITATIONS OF FDG IMAGING

Small lesions (less than 5 to 10 mm, according to the resolution of the PET system and degree of FDG uptake) may yield false-negative results due to partial volume averaging, leading to underestimation of the uptake. The sensitivity of FDG-PET for detection of mucinous adenocarcinoma is lower than for nonmucinous adenocarcinoma (41% to 58% versus 92%), probably because of the relative hypocellularity of these tumors.[24]

High uptake of FDG by activated macrophages, neutrophils, fibroblasts, and granulation tissue results in FDG activity in inflammatory tissue. Mild to moderate FDG activity seen early after radiation therapy or along recent incisions, infected incisions, biopsy sites, drainage tubing, and catheters, as well as colostomy sites, can lead to errors in interpretation if the history is not known. Some inflammatory lesions, especially granulomatous ones, may be markedly FDG-avid. These include inflammatory bowel disease and abscesses.[25]

FDG uptake normally present in the gastrointestinal tract can occasionally be difficult to differentiate from a malignant lesion. Premalignant adenomatous polyps are FDG-avid and detected incidentally. The clinical history, physical examination, pattern of uptake, and correlation with anatomy as seen on the CT images are more helpful in avoiding false-positive interpretations than is semiquantitative evaluation by standardized uptake value.

SUMMARY

Evaluation of patients with known or suspected recurrent colorectal carcinoma is now an accepted indication for FDG-PET imaging. FDG-PET does not replace imaging modalities such as CT for preoperative anatomic evaluation, but it is indicated as the initial test for diagnosis and staging of recurrence, and for preoperative staging (node and metastasis) of known recurrence that is considered to be resectable. FDG-PET is valuable for differentiation of post-treatment changes from recurrent tumor, differentiation of benign from malignant lesions (indeterminate lymph nodes, hepatic and pulmonary lesions), and evaluation of patients with rising tumor markers in the absence of a known source.

FDG-PET has an impact on the treatment of 25% to 30% of patients. Addition of FDG-PET to the evaluation of these patients reduces overall treatment costs by accurately identifying patients who will and will not benefit from surgical procedures. FDG-PET imaging seems promising for monitoring patient response to therapy, including regional therapy to the liver, but larger studies are necessary.

FDG-PET imaging is complementary to morphological imaging with CT, and integrated PET/CT imaging thus provides optimal images for interpretation. The diagnostic implications of integrated PET/CT imaging include improved detection of lesions on both the CT and FDG-PET images, better differentiation of physiologic from pathologic foci of metabolism, and better localization of the pathologic foci.

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