Gastrointestinal Tract Malignancies and Positron Emission Tomography: An Overview

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^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) imaging is highly accurate in restaging colorectal cancer, esophageal cancer, and gastrointestinal stromal tumors. Overall, it compares favorably with anatomical imaging in the evaluation of tumor recurrence because metabolic abnormalities usually precede a structural change. Initial staging of these malignancies with PET is best used in patients with locally advanced disease who may benefit from curative resection if distant metastases are not found. It also appears to have great potential in predicting histopathologic response to neoadjuvant therapy and in monitoring the success of radiofrequency ablation and ^{90}Y microspheres radioembolization soon after intervention. FDG-PET can be used in other gastrointestinal malignancies as a prognostic tool and to detect distant disease but its role has not yet been well defined.
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^{18}F-Fluorodeoxyglucose positron emission tomography (FDG-PET) imaging has been used in clinical oncology since late 1980s. At that time, the complexity and cost of operating a PET center, added to a lack of reimbursement, limited the availability of this technology to academic institutions. Compelling scientific data from the 1990s consolidated the utility of PET in diagnosing and managing patients with malignancies, particularly lung cancer, colorectal cancer, lymphoma, and melanoma. During the past 8 years, the Centers for Medicare and Medicaid Services have gradually expanded the coverage for PET imaging in oncology. This led to proliferation of clinical PET facilities and commercial radiopharmacies, today allowing most metropolitan centers in the United States to provide FDG-PET imaging.

The interpretation of PET abdominal images often is challenging because of the biodistribution of FDG. Although background FDG activity in the chest usually is negligible, physiologic uptake in a variety of abdominal/pelvic organs can make it difficult to distinguish benign from malignant uptake. FDG is filtered but not reabsorbed in the kidneys, so activity is expected in the urinary system. Stomach wall uptake is common and colonic uptake may be intense, especially in the cecum and rectosigmoid. The liver has a typical

mottled appearance and moderate uptake. The spleen has a more homogeneous pattern, and the degree of uptake is less than the liver. Intense focal ovarian uptake may be physiological in premenopausal women. Paraspinal and perinephric fat uptake can be observed. Lymphoid tissue and skeletal muscle often demonstrate increased uptake. This article focuses on colorectal and esophageal carcinomas with brief mention of other gastrointestinal malignancies, including gastric carcinoma, gastrointestinal stromal tumors (GIST), hepatocellular carcinoma, cholangiocarcinoma, gallbladder, and pancreatic cancers.

Colorectal Cancer

Diagnosis and Preoperative Staging

Colorectal cancer ranks second as a cause of cancer death in the United States. Nearly 57,000 patients died of colorectal cancer in 2004. Early diagnosis is the key to long-term survival. The American Cancer Society screening guidelines suggest yearly fecal occult blood test plus flexible sigmoidoscopy every 5 years beginning at age 50 for asymptomatic individuals with no risk factors. All positive tests are followed up with colonoscopy and biopsy if needed.

Surgical resection is the optimal treatment for colorectal cancer, which is a highly curable disease if detected in its early stages. Preoperative imaging with abdominal computed tomography (CT) and endorectal ultrasound is the standard of care for rectal carcinomas to determine the need for neoadjuvant treatment. However, routine use of anatomical im-

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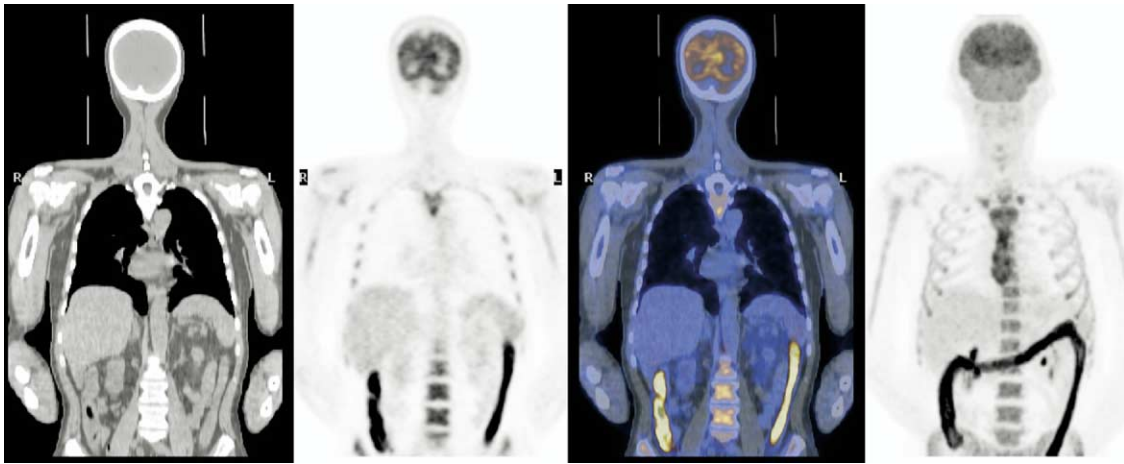
Figure 1 From left to right: coronal CT, attenuation corrected PET, fused image, and whole-body PET maximum intensity projection (MIP) in a 55-year-old man with active pancolitis. Note diffusely increased uptake in the imaged portions of the colon. MIP image also shows marrow activation from recent chemotherapy for nasopharyngeal carcinoma.

aging in the preoperative management of patients with cancer of the intraperitoneal colon remains controversial. CT often is used to assist in operative planning of colon cancers, but its cost-effectiveness is unclear.[1,2] This lack of clarity is largely attributable to the fact that most patients will benefit from surgical resection of the tumor to prevent colonic obstruction or bleeding. Therefore, accurate staging can take place intraoperatively with excision of pericolonic and mesenteric lymph nodes along with peritoneal exploration. Furthermore, the assessment of tumor involvement of regional lymph nodes with anatomical imaging is solely based on size and number of nodes present, limiting its diagnostic accuracy.

Several studies have shown the ability of FDG-PET imaging in the detection of primary carcinomas and premalignant lesions of the large bowel.[3-6] Sensitivity is highly dependent on both the size of the lesion, reaching 72% if the tumor is larger than 1 cm, and grade of dysplasia, ranging from 33% in low-grade lesions up to 76% in high-grade lesions and 89% in carcinomas.[6] There is a wide range of nonmalignant conditions in which increased FDG uptake is observed in the colon, such as inflammatory bowel disease, diverticulitis, and physiologic uptake in colonic mucosa, lymphoid tissue, and smooth muscle. Differentiation between benign and malignant uptake is predominantly based on the focal nature of hypermetabolism. Inflammatory bowel disease (Fig. 1) and physiologic uptake tend to be diffuse or segmental, whereas the accumulation of FDG in premalignant and malignant lesions is focal. Despite a low positive predictive value for malignancy, focally increased uptake of FDG in the large bowel should not be ignored, particularly in light of the high incidence of premalignant adenomas and colorectal cancer in the age group that typically undergoes FDG-PET imaging. Focally increased uptake in the colon should lead to further investigation with colonoscopy and, when necessary, biopsy/polypectomy.

Few studies have focused on the usefulness of FDG-PET scanning in the initial staging of colorectal carcinomas.[7-9] Overall, the sensitivity for detection of nodal metastasis is poor and is not significantly different from CT imaging. These results are not surprising because of the inability of FDG-PET to identify micrometastases and the resolution capabilities of the scanners currently used. The degree of uptake in lymph nodes smaller than 1 cm is often underestimated because of intrinsic resolution limitations of the PET systems. The observed accumulation of FDG in small lesions (measuring less than twice the full width at half maximum of the scanner) is not representative of their true metabolic activity. This decreases the sensitivity of the test in detecting early tumor spread to regional lymph nodes.

The use of FDG-PET imaging in the preoperative staging of colorectal cancers has been advocated,[9] but a substantial impact on clinical management has not been demonstrated. It is unlikely that initial treatment decision making will be significantly altered on the basis of PET imaging. Today, there is no established role for the systematic use of PET in the preoperative staging of colorectal cancer. It often helps the oncologic surgeon decide against operation when distant metastases are found, especially in patients with increased surgical risk because of significant comorbidities. FDG-PET imaging also can serve as a baseline scan for patients who present with advanced stage disease before chemotherapy. Assessment of the overall tumor burden and degree of FDG uptake before starting chemotherapy is a powerful tool to determine appropriate response to treatment on follow up scans. Figure 2 is a baseline whole body FDG-PET scan in a patient who was about to start chemotherapy for recently diagnosed colon cancer.

Detection of Tumor Recurrence

Most recurrences after surgical resection for colorectal cancer occur within the first 4 years. The likelihood of tumor recurrence is related to several factors, including tumor penetra-
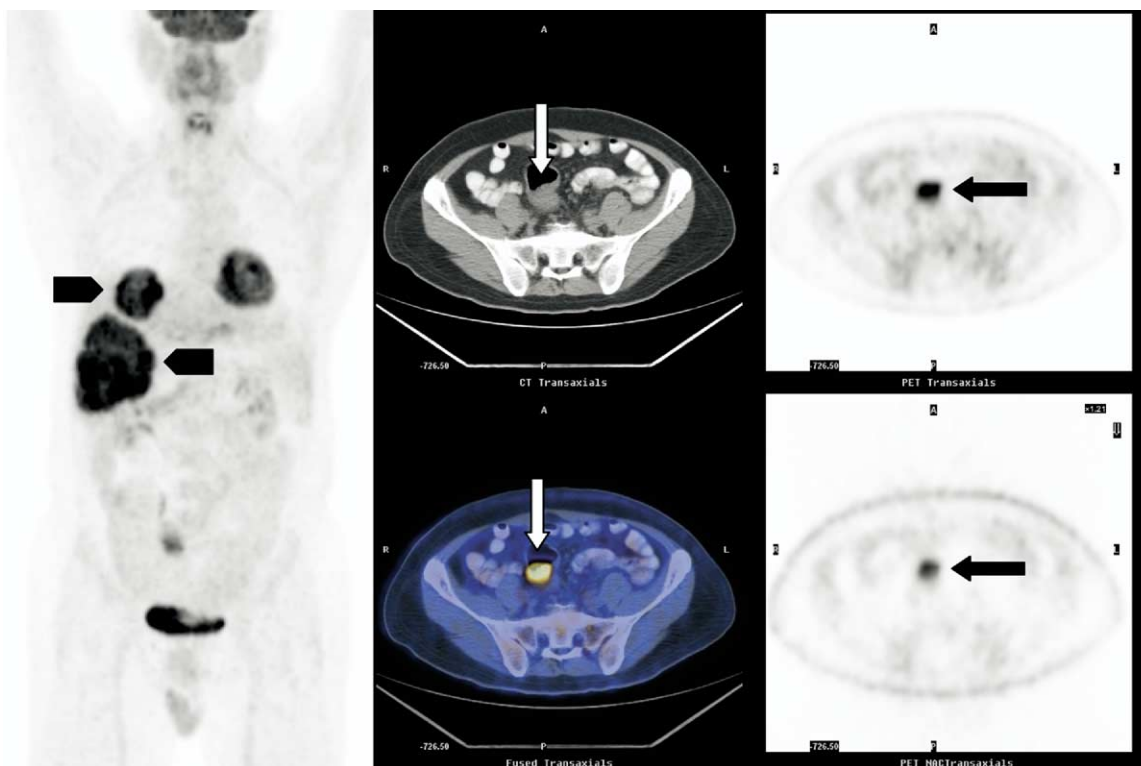
Figure 2 Whole-body PET MIP (left), transaxial CT (top left), attenuation-corrected PET (top right), fused image (bottom left), and nonattenuation-corrected PET (bottom right) in a 56-year-old man with rectosigmoid adenocarcinoma (arrows) and extensive liver metastases (arrowheads).

tion through the bowel wall into the pericolic fat, poorly differentiated histology, tumor extension to adjacent organs/vessels, number of involved lymph nodes, and a preoperative elevation of carcinoembryonic antigen (CEA) levels.

Accurate restaging of patients with colorectal carcinoma plays a pivotal role in guiding further treatment. Approximately 25% of recurrences are isolated to the liver[10] and curative resection is feasible but it is highly dependent on the number, size and location of the hepatic metastases. The presence of extrahepatic disease typically precludes surgery.

Ultrasound of the upper abdomen is an inexpensive and valuable screening tool for detecting liver metastasis and identifying patients who are not eligible for curative treatment. Some parts of the liver may not be well visualized with ultrasound, and its overall sensitivity is poor. CT commonly is used as a first-line imaging modality for the detection of colorectal tumor recurrence. Its diagnostic accuracy, however, is far from ideal. CT often underestimates the number of liver lesions, and postsurgical changes can be difficult to distinguish from local tumor recurrence. Several studies have described the additional value of FDG-PET imaging over anatomical imaging in recurrent colorectal cancer.[11-20] Metabolically active tumors can be detected before a morphologic change is noted on anatomical imaging. A meta-analysis of 11 studies with 577 patients[21] showed an overall sensitivity of 97% and specificity of 76% for FDG-PET detecting recurrent colorectal cancer. A more recent meta-analysis of 61 studies evaluating colorectal liver metastases[11] showed that FDG-PET had a sensitivity of 95% on a per-patient basis, signifi-

cantly better than CT (65%) and magnetic resonance imaging (MRI) (76%).

Elevated serum CEA levels are detected in two-thirds of patients with colorectal carcinoma. Abnormal CEA levels can be observed in a variety of benign conditions, but an increase in CEA levels is strongly associated with tumor recurrence with a reported specificity of 70% to 84%.[22,23] Frequent monitoring of CEA postoperatively may allow identification of patients with disease recurrence in whom curative surgical resection or other localized therapy might be attempted.

Serial CEA measurements appear to be more effective than clinical evaluation to detect recurrent disease from colorectal cancer. Its sensitivity is not as high for locoregional recurrence or pulmonary metastases as it is for liver metastases. Patients with rising CEA levels but no detectable disease on anatomical imaging pose a clinical challenge. It takes on average 3 to 9 months for conventional methods to localize disease relapse after elevation of CEA levels has been documented.[22,24,25] Few studies have demonstrated the value of FDG-PET in patients with rising CEA levels and no identifiable lesions on conventional imaging. Flanagan and coworkers[26] reported a positive predictive value of 89% (15/17) and a negative predictive value of 100% (5/5) in patients with CEA measurements of 10 to 45 ng/mL. Valk and coworkers[14] showed a positive predictive value of 95% (18/19) and a negative predictive value of 85% (11/13). The positive impact of PET on management decision in this clinical scenario is evident. Curative therapy may be attempted for patients with localized disease, whereas unnecessary surgery may be
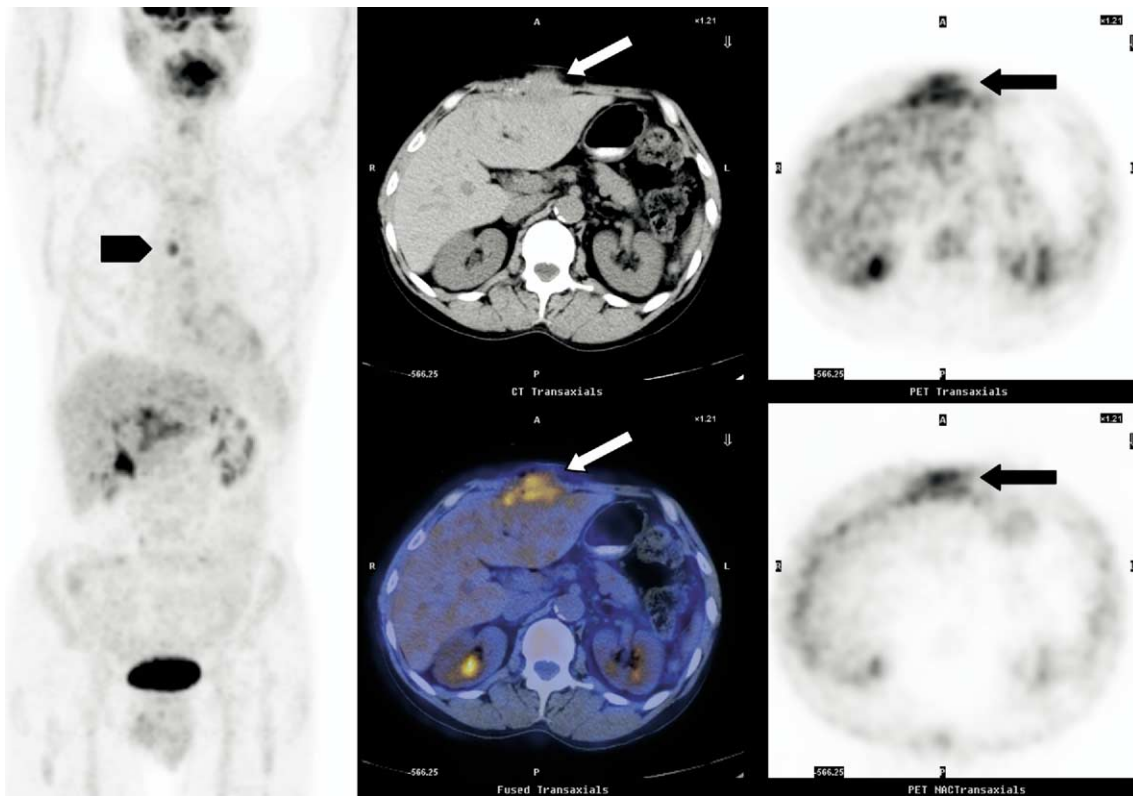
Figure 3 Whole-body PET MIP (left), transaxial CT (top left), attenuation-corrected PET (top right), fused image (bottom left), and nonattenuation-corrected PET (bottom right) in a 57-year-old man with recurrent colorectal liver metastasis invading the abdominal wall (arrows) with unsuspected nodal disease in the right internal mammary chain (arrowhead). This lymph node was biopsy-proven adenocarcinoma from colon cancer.

prevented in patients with advanced stage disease. Figure 3 is an example of how PET influenced management by identifying extra-hepatic disease in a patient with liver metastasis from colon cancer.

FDG-PET imaging has been shown to significantly alter patient management when compared with conventional imaging modalities. A prospective study by Ruers and coworkers[27] demonstrated a change in clinical management in 20% of patients being evaluated for resection of colorectal liver metastasis. A change in patient management based on FDG-PET findings was determined to be 29% in a meta-analysis of 11 articles with 577 patients.[21] In a prospective study of 102 patients with suspected or confirmed regional recurrence of colorectal cancer,[20] FDG-PET influenced management decision in 59% of cases. The high impact on treatment planning in this particular study was predominantly due to avoiding surgery in patients with widespread disease. In a subset of 20 patients with rising CEA levels but no obvious site of recurrence on conventional imaging, FDG-PET localized recurrence in 13 (65%).

Monitoring Response to Therapy
Chemotherapy and Radiation Therapy
The mainstay of adjuvant chemotherapy for colorectal cancer is 5-fluoruracil (5-FU). 5-FU is an effective palliative treatment in colorectal cancer, improving quality of life and survival.[28] The drug is usually well tolerated but response rates are only 10% to 20% in patients with advanced disease. Findlay and coworkers[29] studied 18 patients with colorectal cancer liver metastases before and during the first month of chemotherapy. By using a 15% reduction in the pretreatment tumor to liver ratio by 4 to 5 weeks, they were able to separate responders from nonresponders with a sensitivity of 100% and specificity of 90%.

The combination of 5-FU and local radiation therapy also is associated with increased survival in patients with unresectable disease. Post-therapeutic response evaluation is particularly problematic in rectal cancer patients. Endorectal ultrasound, CT, and MRI provide detailed morphological information, but functional characterization of treated lesions is poor. Radiation-induced inflammation, necrosis, and desmoplastic reactions may induce contrast enhancement of treated lesions, making it difficult to distinguish postradiation changes from residual tumor,[30] which hampers adequate assessment of disease status by means of anatomical imaging alone.

FDG-PET imaging can be particularly useful in patients with advanced stage colorectal cancer who are treated with neoadjuvant chemoradiotherapy. The ability to differentiate benign from malignant lesions based on their metabolic activity and biological aggressiveness allows early assessment of response to treatment. Guillem and coworkers[31] showed that FDG-PET imaging can predict long-term outcomes in patients with advanced colorectal cancer who undergo neoad-

juvant chemoradiotherapy. This study prospectively included 15 patients who had FDG-PET imaging before and 4 to 5 weeks after chemoradiotherapy. At a median follow up of 42 months, a metabolic tumor response of greater than 62.5% (as measured by a decrease in maximum standardized uptake value [SUV]) predicted disease-specific survival and recurrence-free survival. Similarly, in a prospective study of 20 patients, Amthauer and coworkers[32] used a cut-off SUV reduction of 36.1% to differentiate responders from nonresponders. The patients were imaged before and 2 to 4 weeks after the completion of treatment. The cutoff value of 36.1% yielded a sensitivity of 100% (13/13), specificity of 86% (6/7), positive predictive value of 93% (13/14), and a negative predictive value of 100% (6/6). Reliable monitoring of neoadjuvant treatment response is pivotal for risk stratification and treatment refinement. If these findings are confirmed on a larger series, FDG-PET imaging may prove useful in identifying patients at high risk for recurrence and those in whom less aggressive resection may be attempted. Standardized interval from completion of chemoradiotherapy to imaging as well as a cutoff percent decrease in SUV still need to be established to overcome transient tumor "stunning" and radiation induced inflammation, optimizing the diagnostic accuracy of FDG-PET.

Minimally Invasive Interventional Therapies

Several interventional therapies have emerged in the past few years as an alternative to more invasive surgical procedures, particularly for patients with liver metastases. Radiofrequency (RF) ablation and yttrium-90 (^{90}Y) microspheres radioembolization are increasingly becoming the interventional techniques of choice for patients with unresectable liver disease.

RF Ablation

RF ablation is typically performed percutaneously and guided with CT or ultrasound. The radiofrequency generator provides current and energy that is deposited in tissues through the RF ablation probe tip. The liver tissue is destroyed as temperatures reach 55°C.[33] Larger tumors may require multiple sessions with repositioning of the probe. This procedure is usually indicated for patients with less than 5 liver lesions measuring less than 5 cm in diameter.

RF ablation has been used with both palliative and curative intent. Median survival rates have been reported to improve with RF ablation of colorectal liver metastasis when compared with historical data.[34] Ablative treatment success depends on complete tumor destruction. Anatomical evaluation of residual tumor after the ablation procedure is limited because contrast enhancement in the periphery of the ablative necrosis may be caused by post-treatment hyperemia or tissue regeneration.[35] This decreases the specificity of ultrasound, CT, and MRI to detect residual tumor soon after RF ablation. Some authors[36,37] propose waiting a minimum 6 to 12 weeks before performing anatomical imaging to decrease the false-positive rate secondary to physiologic contrast enhancement.

FDG-PET appears to have great potential in identifying residual tumor soon after RF ablation. In a prospective study of 23 patients with a mean follow-up of 16 months, Langenhoff and coworkers[38] showed that FDG-PET has a positive predictive value of 80% (4/5 lesions) and a negative predictive value of 100% (51/51 lesions) when performed soon (less than 3 weeks) after the ablative procedure (RF ablation or cryoablation). Donckier and coworkers[39] reported on the value of FDG-PET imaging when performed at 1 week and 1 month after RF ablation of 28 liver metastases from different solid tumors. Residual hypermetabolism in the periphery of ablated sites detected by FDG-PET scans correlated well with incomplete tumor destruction in 4/28 lesions. CT imaging performed at the same time interval failed to demonstrate residual hypervascularized tumor in these patients. After a median follow up of 11 months, 0/24 lesions with negative postoperative FDG-PET scans developed local recurrence.

The ideal time interval between the ablative procedure and FDG-PET imaging has not been defined. Inflammatory changes from the procedure and regenerating liver tissue in the periphery of the necrotic zone may show increased uptake, making interpretation of the images difficult. Antoch and coworkers[40] have recently suggested that FDG-PET imaging should be performed immediately after RF ablation. None of 19 ablated liver sites in 10 pigs showed increased rim of uptake within 90 minutes after completion of the therapy. Furthermore, no tissue regeneration was found on histopathologic examination. These results are encouraging but prospective studies in treated patients are needed to establish the role and time of FDG-PET imaging as a first line modality to assess adequate response to ablative procedures. A more accurate imaging modality applied soon after therapy will allow early reintervention if residual tumor is present, potentially minimizing the spread of tumor.

^{90}Y Microspheres Radioembolization

Intra-arterial hepatic radioembolization with ^{90}Y microspheres is a new treatment option for unresectable hepatocellular carcinoma and liver metastasis. ^{90}Y microspheres are administered by selective hepatic artery canalization under fluoroscopic guidance. Treatment strategy is based on the same principle that guides hepatic chemoembolization; liver metastases depend primarily on the hepatic arteries for their nutrition and growth. When administered intraarterially, the microspheres (measuring approximately 30 μm in diameter) are trapped in the capillary bed and stop blood flow to the hepatic artery. ^{90}Y decays by beta emission with a half-life of 64 hours and an average 2.5 mm penetration depth in soft tissue.[41] Therefore, in addition to the mechanical occlusion by the microspheres, the embolized tissues receive a substantial radiation dose from beta rays, maximing tumor cell damage.

^{90}Y microsphere treatment is preceded by hepatic arteriography via the femoral artery on a separate day to assess the vascular anatomy of the liver and to exclude significant liver-lung shunting. The liver-lung shunt fraction is studied by administering ^{99m}Tc-macroaggregated albumin particles in the hepatic artery with subsequent scintigraphic imaging. Since the average size of ^{99m}Tc-macroaggregated albumin

particles is similar to that of microspheres, the calculated liver-lung shunt fraction estimates the patient's potential for developing radiation pneumonitis. Radioembolization with ^{90}Y microspheres is usually contraindicated for patients with liver-lung shunt fractions greater than 20%. Larger shunt fractions are typically observed in patients with unresectable hepatocellular carcinoma when compared with patients with metastatic liver disease.

Anatomical imaging appears insensitive in monitoring early response to ^{90}Y microspheres treatment when compared with metabolic imaging.[42] This is in part caused by edema, hemorrhage, and cystic/necrotic changes after therapy. In a prospective series of 8 patients with liver metastases from colorectal cancer, Wong and coworkers[42] reported on the superiority of FDG-PET over anatomical imaging (CT or MRI) to monitor response to ^{90}Y microspheres 3 months after treatment. All patients with a good metabolic response as judged by FDG-PET imaging had a drop in serum CEA levels, whereas none of these patients showed a significant anatomical response. Similar findings were again described by Wong and coworkers[43] in 27 consecutive patients.

FDG-PET imaging does appear to be a promising tool for early assessment of tumor response to ^{90}Y microspheres radioembolization. Larger prospective studies are needed to determine the best time interval from treatment to imaging, since it takes several days for the full radiation effect of ^{90}Y and inflammatory changes are likely to be present soon after therapy. Preliminary data suggest however that there are no significant changes in FDG uptake in treated versus untreated liver tissue at 4 weeks after therapy.[44] Figure 4 shows whole body FDG-PET imaging before and 7 weeks after ^{90}Y microspheres treatment of liver metastasis from colon cancer.

Integrated PET/CT Imaging

The use of CT as the attenuation map to correct the FDG emission data has become the standard of oncologic PET imaging in recent years. Combined PET/CT imaging is particularly beneficial when interpreting abdominal/pelvic images because focally increased uptake of FDG may be observed in a variety of benign conditions. These include incisions, ostomies, abscesses, fistulas, granulomas, diverticulitis, as well as physiologic uptake in colonic mucosa, lymphoid tissue, and muscle. The anatomic detail provided by CT helps differentiate benign from malignant uptake, increasing the confidence of the reader and yielding a better and more specific report.

Lesion characterization on CT also can increase the suspicion for malignancy even in the setting of mild FDG uptake. For example, the sensitivity of FDG-PET to detect mucinous adenocarcinomas is low, presumably because of the hypocellularity of these tumors.[15] The ability to identify cystic changes and calcifications that are characteristic of mucinous lesions on CT scan should increase the index of suspicion of the reader even if the degree of FDG uptake is low.

Precise measurement of small structures is yet another advantage of combined PET/CT imaging. The identification of small lesions (typically less than 1 cm) on CT may help pre-
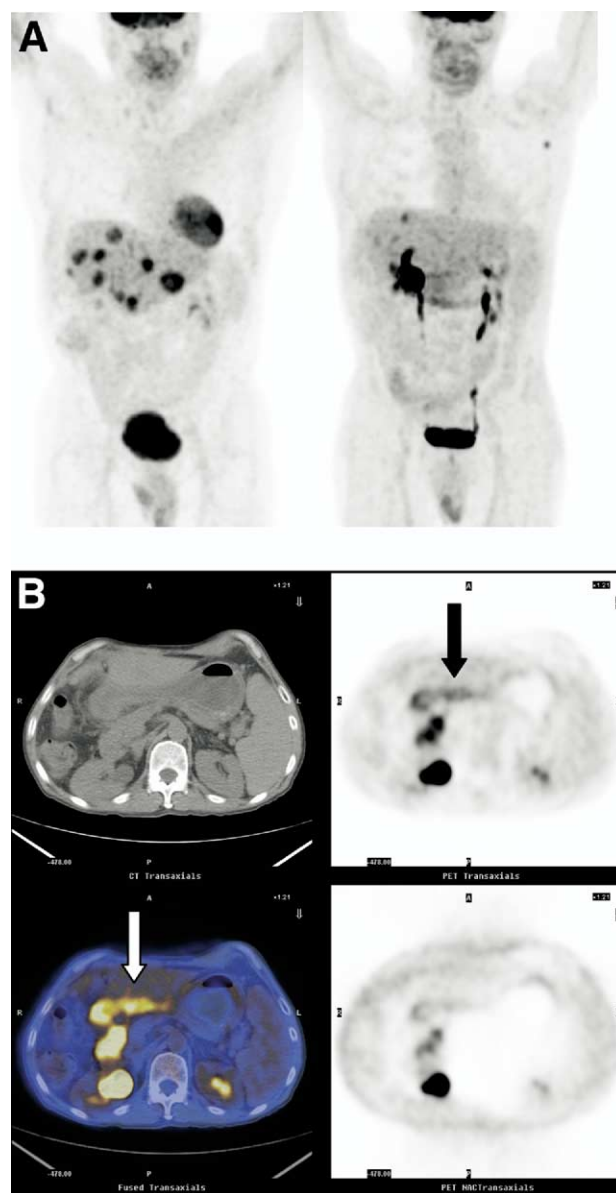

Figure 4 (A) Whole-body PET MIP before (top left) and 7 weeks after (top right) ^{90}Y microspheres radioembolization in a 53-year-old man with colorectal liver metastasis. Note the hypermetabolic liver metastasis improved significantly on the posttherapy scan. (B) Transaxial CT (top left), attenuation-corrected PET (top right), fused image (bottom left), and nonattenuation-corrected PET (bottom right) showing interval development of increased FDG uptake in the stomach and duodenum (arrows), representing gastroduodenitis from ^{90}Y microspheres reflux into the gastroduodenal artery.

vent excluding malignancy on the basis of low FDG uptake, since the metabolic rate in subcentimeter lesions is often underestimated because of resolution limitations of the PET scanners.

Finally, the use of integrated PET/CT imaging also improves intensity modulated radiation therapy planning in patients with rectal carcinoma.[45] These patients can be imaged prone on a flat bed to exactly match the position of planned intensity-modulated radiation therapy sessions. Better delineation of target volumes can be accomplished, lim-

iting higher tumoricidal doses to areas of increased FDG uptake and sparing normal adjacent structures.

Esophageal Cancer

In 1995, Yasuda and coworkers reported on whole body PET in the imaging of a patient with esophageal cancer.[46] This paper and other early literature[47,48] suggested that FDG-PET could be useful in the evaluation of esophageal cancer. Effective July 1, 2001, CMS approved FDG-PET for the diagnosis, staging, and restaging of patients with esophageal cancer.[49] The National Comprehensive Cancer Network 2005 guidelines[50] describe PET scanning as useful if available and a "recommended staging procedure for patients who are thought to have localized cancer." Although PET has proven itself valuable in the initial evaluation and follow-up of esophageal cancer, its precise role and applicability continues to evolve as more research is made available. Other PET radiotracers have been studied for esophageal cancer, but results have been disappointing compared with FDG.[51,52]

Diagnosis

PET has high sensitivity (90-100%) in the detection of primary esophageal cancer, and higher than that of CT, although most of the studies have been performed in patients with known cancer.[53-61] False-positive uptake may be caused by esophagitis or other inflammation, although most esophagitis manifests as mild linear diffuse uptake whereas that of neoplasia is more focal and intense. In addition, false-negative results are more likely with small or flat mucosal lesions as well as adenocarcinoma at or near the GE junction, possibly because of a diffuse growth pattern and/or mucinous histopathology.[62,63] Barium swallow and endoscopy are the methods of choice for initial detection of esophageal cancer, though PET may be useful in problem solving situations.

Staging

Esophageal cancer is often detected at a later stage, and overall survival is poor, although early disease has a better prognosis.[64] Esophageal cancer usually is treated with radical resection in limited disease. Chemotherapy and/or radiotherapy after surgery is advocated for more advanced locoregional disease depending on surgical and pathologic findings, and palliative techniques are used for unresectable tumors or with distant metastases.[63,65] Alternatively, patients with advanced locoregional disease may be treated with neoadjuvant chemoradiation and, depending on response, may then undergo curative surgery or palliation. The presence of involved locoregional lymph nodes has important prognostic implications but will not obviate surgery. Distant metastases will preclude curative therapy and often are undetected by conventional imaging.[66,67]

Staging typically is performed with endoscopic ultrasound (EUS) and CT; yet, these modalities over and understage as many as 30% to 40% of patients.[63] MRI has not been widely used or studied in this regard.[64] Thoracoscopy and laparoscopy are accurate but are invasive and expensive. EUS, espe-

cially combined with fine-needle aspiration (EUS-FNA), is considered the primary modality in the preoperative determination of depth of tumor invasion (T stage) and nodal status (N stage). PET is limited in its ability to determine depth of tumor invasion, and there is not a clear correlation between intensity of uptake and T stage.[56,66] Yet, EUS also has limitations because it is dependent on the operator and the probe may not be passed in as many as 30% of patients secondary to stenosis. Lymph nodes that are distant from the esophagus or with intervening air containing structures may also not be detected.[62,63,66]

In 2 early reports on esophageal cancer staging with PET, it was noted that, of a group of 58 patients, 17 of 17 had metastases seen with PET whereas only 5 of 17 had metastases detected with CT.[60] Although PET had greater accuracy than CT for N staging (76% versus 45%), both were not optimal.[59] However, the addition of PET led to a change in management in 17% and 20% of patients, respectively.[59,60]

Luketich and coworkers[68] determined that PET had higher accuracy (84%) than CT (63%) for distant metastases and that most PET misses were subcentimeter liver and lung lesions. In a later paper,[69] this group concluded that while PET can't replace CT for initial locoregional and distant staging, it is complementary to CT. PET is limited by minimal uptake in microscopic disease, poor conspicuity in nodes adjacent to intense primary tumor uptake, and the possibility of false-positive uptake in inflammatory lymph nodes.[70] PET/CT has been shown to improve on these results with 90% accuracy (96% sensitivity, 81% specificity) in detecting sites of disease, leading to upstaging in 10% of patients.[71] In the future, the majority if not all of PET will be performed as PET/CT, which may obviate the need for a separate CT, especially if the PET/CT is performed with oral and IV contrast.

Lerut and coworkers[72] looked at preoperative staging in 42 patients, comparing CT plus EUS to coregistered PET/CT. Although PET had lower overall accuracy for N staging than CT-EUS (48% versus 69%; mainly the result of lower sensitivity though higher specificity), accuracy for distant metastasis was much higher than for CT-EUS (86% versus 62%). It was concluded that PET adds value to conventional staging by increased detection of distant metastases and by its higher specificity for locoregional nodal disease. Although some researchers[53,56,62,69] have reported decreased sensitivity but increased specificity for N staging by PET, others[54,58,70] have found improved sensitivity for PET compared with CT and even EUS when incomplete endoscopies were included in the analysis. Combining PET with EUS-CT leads to optimal sensitivity, specificity, and accuracy for locoregional and distant metastases over any single modality alone, even compared with CT and EUS.[62]

Almost all researchers note the superiority of PET in detecting distant metastases compared with conventional modalities. In a recent study of 74 patients[71] PET correctly upstaged 20% of patients (missed by CT AND EUS) and downstaged 5%. False upstaging was present in 7% and downstaging in 3%, which mostly occurred with lower T-stage tumors. The authors note that PET had most value with
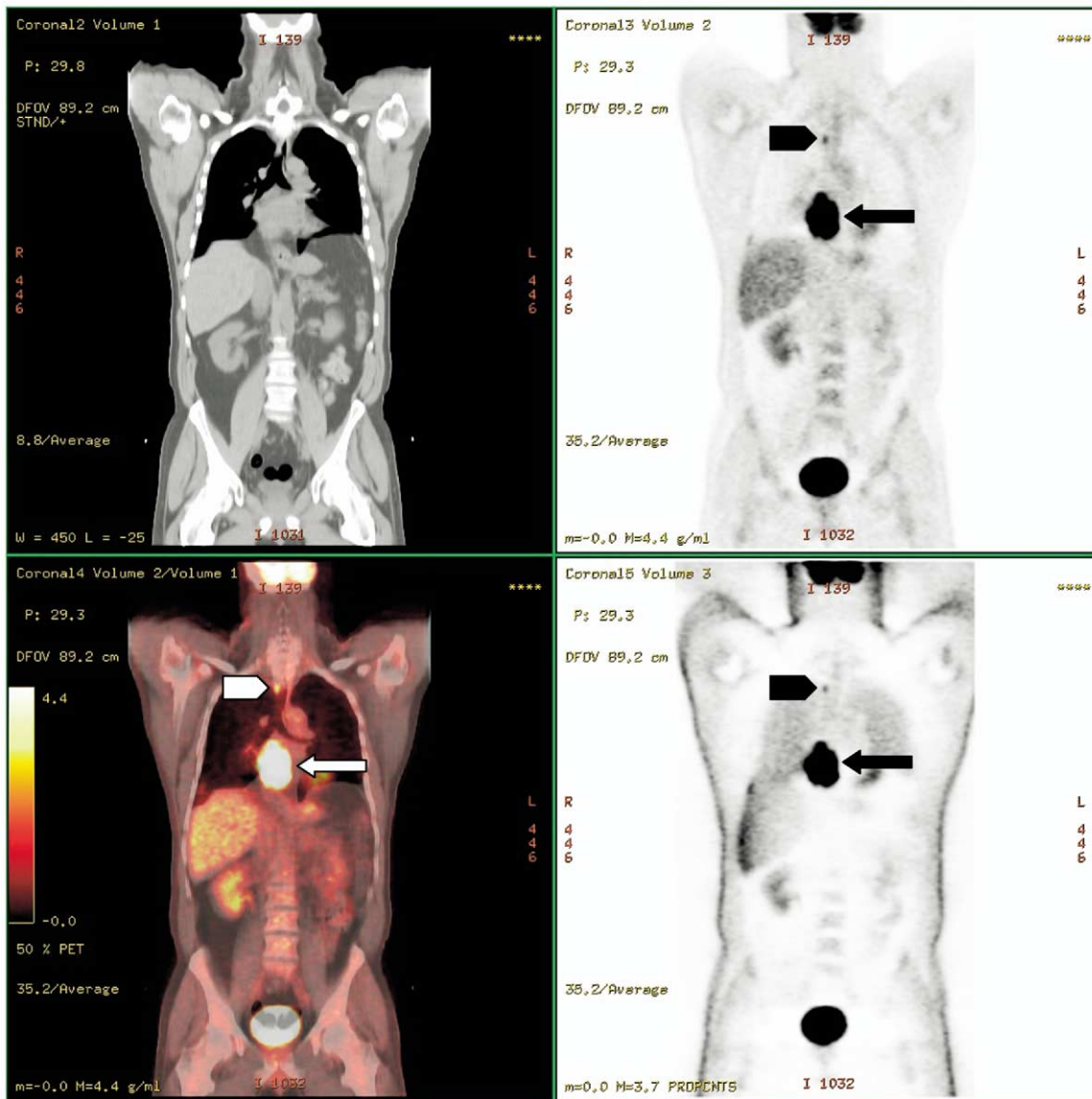
Figure 5 Coronal CT (top left), attenuation-corrected PET (top right), fused image (bottom left), and nonattenuation-corrected PET (bottom right) in a 57-year-old man with a large lower esophageal cancer (arrows) and a malignant right paratracheal lymph node (arrowheads). Uptake resolved in both regions after neoadjuvant chemotherapy and only minimal residual microscopicdisease was present in the esophagus after resection.

T3 or T4 disease and that PET should be performed in higher stage groups who are candidates for curative surgery.

Wallace and coworkers[73] examined multiple staging modalities based on published literature for esophageal cancer including CT, PET, EUS-FNA, and thoracoscopy/laporascopy and concluded that the combination of PET followed by EUS-FNA, if the PET was negative for distant metastases, was the preferred staging procedure.

With PET, the patient may serve as his or her own control. If the primary tumor does not take up FDG, then PET would likely not be useful for staging. Any positive site on PET should have pathological confirmation. Suspected brain metastases are best evaluated by MRI. Small lung nodules are optimally seen with CT if PET/CT is unavailable. Though there is little data, PET can likely replace bone scanning for

suspicion of skeletal involvement. Studies to define the exact role of PET and PET/CT in the staging of esophageal cancer are ongoing.[64] Figure 5 is an example of a PET positive primary tumor and paratracheal lymph node.

Prognosis and Response to Therapy

In early work by Fukunaga and coworkers,[57] SUV correlated highly with hexokinase activity in resected esophageal tumors. An SUV greater than 7 was associated with poor survival in all stages of disease. A significant difference in survival with PET stage rather than CT stage has also been described.[68] Other authors have not shown a significant difference between eventual response and initial SUV.[74,75]

Response to neoadjuvant therapy has been demonstrated

by some researchers to improve the rate of local tumor control and complete resection, as well as prevention of distant metastases. PET has added value due to its ability to determine metabolic response apart from that of anatomic response. But studies examining treatment response are not always directly comparable due to differences in type of neoadjuvant therapy, time course of PET, and criteria for response.

Brucher and coworkers[74] studied 27 patients with esophageal cancer above the carina before and 3 weeks after chemoradiation. Responders were defined as those patients with less than 10% viable tumor cells on pathology. At a 52% cutoff for decrease in SUV there was 100% negative predictive value and 72% positive predictive value for response to therapy. Thus, even a 52% reduction in SUV from baseline did not guarantee a total or near-total pathologic response likely due to small foci of tumor not optimally detected with PET. But PET was noted to perform better than clinical evaluation, CT, endoscopy and EUS in this regard. Weber and coworkers[76] found that for preoperative chemotherapy alone in patients with metabolically active adenocarcinoma of the GE junction with PET performed 2 weeks after initiation of therapy, a 45% reduction in SUV predicted a pathologic response with 89% sensitivity and 86% specificity. Cerfolio and coworkers[77] noted that PET/CT predicted a pathologic complete response with 88% accuracy versus EUS or CT alone (approximately 70% accuracy).

Yet, other researchers[78-80] report that absolute SUV or changes in SUV did not correspond to pathologic tumor regression. Song and coworkers[81] found only a 71% NPV for patients showing a complete response on PET and that a decrease in SUV only correlated well with pathologic response when highly metabolically active tumors (SUV >4) were selected. In a recent meta-analysis,[82] it was determined that the maximum joint sensitivity and specificity for response to therapy is 54% for CT, 86% for EUS, and 85% for PET. EUS was not possible in 6% of cases posttherapy.

Thus, the appropriate use of PET for response to therapy has not been well defined. There is no widely accepted cutoff value for SUV response, and the timing of PET after therapy has not been standardized. Although response on PET cannot definitely predict a complete microscopic pathologic response, it does correlate with clinical response and survival.[63,74,75,83] False positive uptake especially due to radiation esophagitis may also be present. Yet, by helping to separate responders from nonresponders, chemotherapy and surgical approach may be altered. Early reports also note the utility of PET for radiation treatment planning.[84,85]

Recurrence and Restaging

For recurrence and restaging there is a general consensus that conventional techniques such as endoscopy are best suited to detect perianastomotic recurrence but once recurrence is detected, PET and PET/CT provide the most accurate whole body restaging tools. Flamen and coworkers[86] studied 41 patients after resection with suspicion of recurrence and found that nonoptimized PET had 100% sensitivity but only

57% specificity for perianastamotic recurrence (mostly due to false positive uptake at sites of endoscopic dilation of recurrent stenoses), but had 90% accuracy for distant metastases, significantly greater than conventional imaging (CT and EUS), and provided additional information in 11/41 patients.

In a recent study[77] in which EUS-FNA, CT, and PET/CT were compared in restaging 41 patients after neoadjuvant chemoradiotherapy, optimized PET/CT performed before and approximately 3 weeks after chemoradiation had an accuracy of 80% in distinguishing T4 (invading adjacent structures which may be unresectable) from T1 to 3 status and a higher negative predictive value (95%) than CT (90%) or EUS (87%). It also was noted that PET/CT was more accurate (93%) than CT (78%) or EUS-FNA (78%) in predicting N status. In distinction to other literature, this study did not demonstrate much of an advantage of PET/CT in the detection of distant metastases.

Gastric Carcinomas

The diagnosis of gastric carcinomas is made by endoscopy and tumor biopsies. Local extension of the tumor is typically assessed by endoscopic ultrasound, whereas abdominal ultrasound and CT are used for metastatic workup. The sensitivity of FDG-PET to detect locally advanced gastric carcinomas is dependent on the microscopic growth type of the tumor. Stahl and coworkers[87] showed that distinct increased uptake of FDG is more commonly seen in the intestinal growth type (15/18, 83% sensitivity) than in nonintestinal type carcinomas (9/22, 41% sensitivity), probably because of the abundance of intra and extracellular mucous content and lack of expression of the glucose transporter Glut-1 on the cell membrane of the latter.

Both FDG-PET and CT appear insensitive to detect regional lymph node metastasis from gastric carcinomas. In a retrospective study of 81 patients, Yun and coworkers[88] showed a sensitivity of 34% for N1 and N2 disease and 50% for N3 disease using FDG-PET. The sensitivity of CT for detection of N1 disease (58%) was significantly better than that of FDG-PET.

A retrospective analysis of 33 patients[89] with suspected recurrence of gastric carcinoma showed a sensitivity of only 70% (14/20) and a specificity of 69% (9/13) for FDG-PET. However, the mean survival for the PET negative group (18.5 months) was significantly higher than the PET positive group (6.9 months), suggesting that PET may serve as a prognostic rather than diagnostic tool in gastric carcinomas.

Ott and coworkers[90] prospectively evaluated patients with locally advanced gastric carcinomas with FDG-PET at baseline and at 2 weeks after initiation of cisplatin-based chemotherapy. Thirty-five of 44 primary tumors (80%) were PET positive. By using a cutoff SUV reduction of 35%, FDG-PET correctly predicted histopathologic response after 3 months of therapy in 10 of 13 responders and in 19/22 nonresponders. The identification of nonresponders early in the course of chemotherapy will allow optimization of neoadjuvant strategies in locally advanced gastric carcinomas potentially minimizing progression of disease.

Gastrointestinal Stromal Tumors (GIST)

GISTs are uncommon tumors of the GI tract and are now believed to be not sarcomas and to be arising from interstitial cells of Cajal or primitive cells in the GI tract. The literature about GISTs remains confusing because tumor classification and terminology continually are refined. Furthermore, the exact definition of GISTs varies among authors. Some use the term to describe any GI submucosal mesenchymal tumor that is not myogenic (eg, leiomyosarcoma) or neurogenic (eg, schwannoma) in origin. Others are more restrictive and use the term when specifically referring to GI mesenchymal tumors that express the CD117 and/or CD34 antigen. The abnormality in a gene called c-kit is almost always found in patients with GISTs, and proteins known as KIT and PDGFRA have led to treatment with imatinib mesylate (Gleevac). Impressive response to targeted molecular therapy with Gleevac has increased the interest in GISTs. Approximately 15% of GISTs do not respond to Gleevac treatment and, hence, it is important to assess response to Gleevac treatment.

Only about 5000 cases are identified each year; 60% to 70% of them in the stomach and 20% to 30% in the small intestine. Grossly, GISTs are well-demarcated spherical masses that appear to arise from the muscularis propria layer of the GI wall. Intramural in origin, they often project exophytically and/or intraluminally, and they may have overlying mucosal ulceration. Larger GISTs nearly always outgrow their vascular supply, leading to extensive areas of necrosis and hemorrhage. GISTs are usually asymptomatic till they reach 5 cm in size and tumors more than 5 cm present with abdominal pain, bleeding, and intestinal obstruction. Thirty percent of GISTs are malignant and metastasize to liver and peritoneum.

Contrast-enhanced CT differentiates benign from malignant lesions. Heterogeneous enhancement, ulcerations, large size, direct invasion, and peritoneal spread favor malignant nature. Hersh and coworkers found that metastasizing lesions show increased FDG uptake and non metastasizing lesions did not show significant FDG uptake.[91] Goerres and coworkers in a prospective study compared contrast enhanced CT and PET/CT and found even though contrast enhanced CT showed more lesions and PET had variable FDG uptake, the prognostic information was better seen in FDG-PET images than in CT findings.[92] Gayed and coworkers showed similar findings in a retrospective analysis of 54 patients treated with Gleevac.[93]

Hepatocellular Carcinoma

Hepatocellular carcinoma is a tumor that is relatively uncommon in the United States, although its incidence is increasing, principally in relation to the spread of hepatitis C infection. It is the most common cancer in some parts of the world, with more than 1 million new cases diagnosed each year. Hepatocellular carcinoma is potentially curable by surgical resection, but surgery is the treatment of choice for only a small fraction of patients with localized disease. Prognosis depends on the degree of local tumor replacement and the extent of liver function impairment.

FDG-PET has a poor sensitivity to detect primary hepatocellular carcinoma because well-differentiated tumors may retain the capacity gluconeogenesis (to convert FDG-6-phosphate to FDG). Lee and coworkers showed that GLUT1 (glucose transporter 1) concentration is low and HKII (Hexokinase II) is high in hepatocellular carcinoma.[94] In a small series of 12 patients (4 untreated and 8 treated) Lin and coworkers showed improvement in sensitivity from 56% to 62.5% between images obtained at 1 hour and 2- to 3-hour delay.[95] Ho and coworkers used C11 acetate PET in 32 patients and showed a sensitivity of 87% compared with that of 47% with FDG-PET.[96] Hence the importance of FDG-PET in the management of hepatocellular carcinoma is mainly in detecting extrahepatic spread. In 18 patients Sugiyama and coworkers showed that FDG-PET contributed to the management of patients by detecting extra hepatic metastases.[97]

Cholangiocarcinoma and Gallbladder Cancer

In the United States, 2,500 cholangiocarcinomas and 5,000 gallbladder cancer cases are reported each year. Lee and coworkers have shown that cholangiocarcinomas have increased GLUT1 expression and decreased HKII.[94] Cholangiocarcinomas can be intrahepatic, perihilar (Klatskin tumor), and extrahepatic (90% adenocarcinoma and 10% squamous). Chronic inflammatory processes such as sclerosing cholangitis and parasitic infestation have been attributed to cause hyperplasia that leads to malignancy. FDG is not excreted in the bile, and any uptake in the biliary tree or gallbladder is a sign of malignancy or inflammation in the gallbladder or biliary tree. Anderson and coworkers reviewed retrospectively 50 patients with cholangiocarcinoma (n = 36) and gallbladder carcinoma (n = 14) and concluded that even though FDG-PET imaging changed the management in 30% of cases, granulomatous disease, sclerosing cholangitis and stents can show FDG uptake and mimic malignancy.[98]

Pancreatic Cancer

Although pancreatic cancer accounts for just 2% of new cancer cases in the United States, it is the fourth leading cause of all cancer deaths. FDG-PET certainly plays a role in the detection of nonlocoregional and extra abdominal metastases, but the role of FDG-PET in the initial diagnosis is questionable. A meta-analysis to check the cost-effectiveness and usefulness of FDG-PET in the management of pancreatic cancer showed a need for a well designed prospective study.[99] Pancreatic tumors of endocrine origin (insulinoma, glucogonoma, and VIPoma) are usually well differentiated and often are not FDG avid, and the recommendation is to use In111-OctreoScan or I-123 MIBG imaging for localization or pre treatment evaluation for Sandostatin or I-131 MIBG.[100]

Summary

FDG-PET imaging is highly accurate in restaging colorectal cancer, esophageal cancer and GISTs. It also appears to have great potential in predicting treatment response early in the course of therapy. Initial staging of these malignancies with PET is usually restricted to patients with locally advanced disease who may benefit from curative resection if distant metastases are not found. FDG-PET can be used in other GI malignancies as a prognostic tool and to detect distant disease but its role has not been established.

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