Positron emission tomography in neoplasms of the digestive system

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SUMMARY

PET/CT has proven to be extremely useful in studying neoplasms of the colon and esophagus. It has been less promising for lesions of the stomach, pancreas and hepatobiliary tract. Colorectal cancer is the third most common non-cutaneous cancer representing 13% of all malignancies. The use of colonoscopy has significantly contributed to the earlier detection and higher cure rate. PET/CT is not a screening procedure. It is very good for staging, recurrence detection and monitoring therapeutic interventions. It is excellent for detecting distant metastases, e.g. liver lesions, but is less accurate for detecting nodal involvement. The CT portion of the study enhances certainty of lesion localization and characterization. Esophageal cancer is less common in the U.S. in that it represents 7% of G-I cancers, but only 1% of all cancers. The major problem is that often it is advanced to Stages III or IV before it comes to clinical recognition. A 5-year survival has been improved from 3% to 10% by the use of induction chemoradiotherapy. PET has proven useful in staging and determining resectability, monitoring response to therapy, radiotherapy treatment planning and distinguishing between post-op scar and residual or recurrent disease on CT. Gastric cancer results have been more variable. The intestinal (tubular variety) shows better uptake than the non-intestinal (signet ring cell) variety because of the greater mucous content of the latter which is associated with more false negatives. FDG uptake in pancreatic cancer is also variable. Attempts at distinguishing carcinoma from pancreatitis have been limited. When lesions do show uptake, PET/CT has been helpful in monitoring therapeutic interventions. Hepatocellular cancer demonstrates significant FDG uptake in only 50-70% of cases. Cholangio carcinomas; particularly the peripheral variety, do show significant FDG uptake.

Key words: *Positron-Emission Tomography and Computed Tomography; Gastrointestinal Neoplasms; Colorectal Neoplasms; Esophageal Neoplasms; Stomach Neoplasms; Pancreatic Neoplasms; Carcinoma, Hepatocellular*

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PET IMAGING IN ESOPHAGEAL CARCINOMA

Esophageal carcinoma is a relatively rare disease with approximately 13,200 new cases detected in 2001 in the United States (1). It is most common between 50 and 60 years of age with a male to female ratio of 4:1 (2). According to the SEER database, an annual age-adjusted incidence rate is 4.5 per 100,000 men and women. Esophageal cancer is a highly lethal neoplasm with the reported annual age-adjusted mortality rate of 4.3 per 100,000 men and women (3). For the period between 2001 and 2007, in less than 25% of patients who were diagnosed without nodal involvement, the 5-year relative survival was 37.3%; while in 32% of those diagnosed with regional nodal involvement or documented metastatic disease, the 5-year survival was 18.4%, and 3.1%, respectively (2).

The gold standard for conventional staging in esophageal cancer includes CT and endoscopic ultrasound (EUS) with associated biopsy of the mucosa. The depth of tumor invasion is usually assessed by combination of esophagogastroduodenoscopy and endosonography. This approach evaluates extent of mucosal involvement and peritumoral nodal metastases, but is limited in patients with stenoses and strictures due to incomplete passage of the endoscope. CT may detect both local invasion of neighboring mediastinal structures and regional nodal and distal metastases (4). CT is less sensitive, however, for detection of regional and distant metastases compared to FDG PET. FDG PET or FDG PET/CT imaging has a significant role in primary staging of esophageal cancer (5-12). FDG PET provides more accurate staging and more accurate prognostic stratification than CT alone. It may alter the treatment strategy in more than 30% of patients (9, 12). Nevertheless, both FDG PET and CT are not able to detect small esophageal metastases. On CT examination, in most cases, a 10 mm cutoff is used for abnormal lymph nodes, while FDG PET usually cannot detect lesions smaller than 5 mm due to a spatial resolution of 3 mm-5 mm. Although FDG PET is not highly sensitive, with a reported range between 22%-76%, it has high specificity for detection of locoregional lymph node metastases (about 90%) (1). FDG PET and FDG PET/CT are limited in detection of peritumoral nodal disease (5, 8, 13). It is of limited value in assessment of regional lymph node involvement, whereas EUS has the highest sensitivity of 70%-90% (14).

It has been shown that ^{18}F-FDG is a good radiotracer to image esophageal cancer compared to other agents, such as ^{18}F-FLT and ^{11}C-choline (15, 16). Jager et al. compared FDG-PET with 11-C-choline PET for evaluation of mediastinal lymph nodes and reported FDG PET sensitivity of 100% versus 73% for ^{11}C-choline (15). In esophageal cancer, Westreenen et al. showed that the uptake of ^{18}F-FDG was significantly higher than ^{18}F-FLT. FLT is, however, useful to image signet ring cell gastric cancer whereas FDG-PET has reduced sensitivity (16).

Detection of distant metastases in esophageal carcinoma is a key fact in determining treatment strategy. Luketich reported FDG PET sensitivity and specificity of 69% and 93%, respectively, compared to only 46%, and 74%, respectively, for CT (17). FDG PET showed higher sensitivity and specificity of 78% and 90%, respectively compared to 46% and 69% for combined CT imaging and endosonography (13). Heeren et al. reported that the sensitivity of detecting distant nodal and systemic metastases was greater with FDG PET compared to CT/EUS alone (78% vs. 37%, respectively) (6). At the Third German Interdisciplinary Consensus Conference, FDG PET was classified as an essential component for the N and M staging in esophageal

carcinoma (18). FDG PET, however, has some limitations in the detection of distant metastases in some organs. For example, in case of brain metastases, it is likely that MRI is superior to FDG PET imaging. Lung metastases are also better imaged by CT than by FDG PET (1).

A frequent location of recurrent disease is at the anastomotic site. FDG PET has a reported sensitivity of anastomotic recurrence of 100% and a specificity of 57%, compared to endosonography (100%, and 93%, respectively). False positive FDG PET findings may be due to inflammatory changes, especially if endoscopic dilatation was previously performed. To detect recurrences that are distant from the anastomosis, FDG PET is more sensitive than morphologic imaging (94% vs. 81%, respectively), while both have the same specificity of 82%. After performing conventional morphologic imaging in the same patients, FDG PET identified additional lesions in 27% of cases, and excluded malignancy in cases reported as suspicious on conventional imaging. In summary, the combination of conventional diagnostic methods and FDG PET is the best approach to detect recurrent disease in esophageal cancer (2).

Krause et al. have reviewed the literature of FDG-PET and FDG PET/CT to assess treatment response in esophageal carcinoma. They divided studies into 2 groups, one, which evaluated response after the completion of the therapy and those with assessed response early in the course of the therapy. If late treatment response is evaluated, the initial FDG PET scan is correlated with the FDG PET scan at the end of treatment. FDG uptake in responders decreased to the background level, while residual FDG accumulation identified residual viable tumor (19). In the late assessment of response, the decrease in maximum SUVs after the completion of induction chemotherapy varied from study to study within the wide range of 50% (20), 52% (21), 60% (22), and more than 80% maximum SUV reduction (23,24). Flamen et al. detected that responders were shown to have a higher survival rate at 16 months versus non-responders with only a 6-month-survival rate. There is also a shorter disease-free interval in non-responders (23). The SUV reduction in responders correlates significantly with histopathological response and predicted clinical response. Patients with SUV reduction greater than threshold had a greater disease free survival and better long term outcome. Swisher et al. reported 76% accuracy in predicting histopathological non-response, with a corresponding sensitivity and specificity of 62% and 84%, respectively. They also showed that FDG PET was not able to rule out residual microscopic disease (25). Cerfolio reported that FDG PET was able to predict a complete response with a sensitivity of 87%, and both specificity and accuracy of 88% (26). Studies that assess late response to treatment are able to give information only on the prognosis of patients. They are not able, however, to alter the chemotherapy regimen in non-responding patients (19).

Early evaluation of the treatment response has been studied to predict response and subsequently modify and switch the therapy regimen early in the course of treatment. FDG PET should be performed as a baseline scan before treatment and a second scan should be obtained 2-4 weeks after the initiation of the first chemotherapy cycle (often within the first cycle of chemotherapy). In a study by Weber et al., FDG PET was performed before, and 2 weeks after the start of the chemotherapy regimen. The clinical response was evaluated by EUS and histology 3 months after the therapy. A cutoff value of 35% was effective in about 95% of cases delineating responders from non-responders. Those with grater decreases in FDG SUV uptake were more likely to achieve a complete response as well as having a longer time to progression and/or to recurrence, compared to those with minimal declines in FDG uptake (27). These results were updated in a prospective studies on a large number of patients (28,29). Another study also reported PET as a reliable tool in assessment of treatment response (30). Annovazi et al. obtained similar data in their study (31).

PET IN GASTRIC CARCINOMA

Staging of gastric carcinoma is usually performed with endoscopy and CT imaging (2). It is usually difficult to detect malignancy by FDG PET imaging due to low and variable glucose metabolism of the gastric mucosa, because of a large component of mucin in gastric carcinoma, particularly in the signet cell variety. FDG PET/CT is not sensitive enough to detect lymph node involvement in the initial staging of gastric cancer, preoperatively (32). On the other hand, FDG PET imaging has a role in detecting recurrent gastric tumor with a sensitivity of 70% and a specificity of 69% (33). Sun et al. reported accuracy of 82.6%, NPV of 77.7%, PPV of 85.7% in detection of recurrence postoperatively (34). FDG PET/CT changed clinical treatment decision in 30.4% of patients. In a study done by Sim et al., FDG PET was good as CT with the same sensitivity and specificity in detection of recurrence, but not for peritoneal seeding (35).

Imaging of gastric cancer is limited because a relatively high percentage of tumors are not FDG avid (4%-53%). The literature data for FDG PET sensitivity varies from 47%-96% (mean sensitivity 77%; mean specificity 99%) in detection of gastric cancer, with range of 23%-75% (mean sensitivity 45%, mean specificity 92%) in detection of lymph node involvement (36-39). Yoshioka demonstrated that FDG is useful in advanced, metastatic and recurrent gastric carcinoma but has low value in detection of peritoneal and pleural carcinomatosis as well as in bone metastases (40). Stahl reported 60% sensitivity for FDG PET in detection of locally advanced gastric cancer, while 22/40 tumors were non-intestinal growth type (signet cell variety) and were detected in only 41%. False negative findings (FN) were strongly correlated with whether tumor was of the intestinal (tubular) vs. non-intestinal (signet ring cell) growth type. Mucous content was much greater in the non-intestinal tumors (80%) and had more FN as compared to intestinal tumors (11%) (41).

FDG uptake is reported to be lower in non-intestinal types of gastric cancers such as cancers with signet ring cells, with high mucinous content and lower cellularity (33,38,41). Herrmann et al. compared FDG PET and FLT PET in detection of locally advanced gastric carcinoma and reported higher sensitivity in favor of FLT PET. They showed that FLT PET has a role in imaging of some histological subtypes of gastric carcinoma that are not expressing FDG uptake (42). Yun et al. reported that FDG PET is accurate just like CT in detection of primary early or advanced gastric tumors. They reported low sensitivity of both PET and CT in decision making on the extent of lymphadenectomy, although PET may detect some additional nodal involvement which is missed by CT. However, both PET and CT have high specificity for nodal disease (43).

PET IN PANCREATIC CANCER

In staging of adenocarcinoma of the pancreas the reported diagnostic accuracy of CT is 85%-95% (44, 45). There are some data suggesting that FDG PET has a role in preoperative diagnosis and staging, especially when CT is not able to make a definite diagnosis of malignancy (46, 47). FDG PET may also help in differentiating between benign and

malignant pancreatic lesions found on CT, with a sensitivity of 85%-100%, specificity of 67%-99% and accuracy of 85%-93% (48). Sperti reported equal sensitivity of both FDG PET and CT of 94%, while FDG PET alone showed higher specificity than CT (49). FDG PET was classified as the 1a indication for differentiation between inflammation and malignant pancreatic lesion, according to the 3rd German Interdisciplinary Consensus Conference (18).

CT imaging is better for detection of lymph node involvement, while FDG PET is superior for detection of distant metastatic disease (48). FDG PET has been shown to have low sensitivity in locoregional lymph node staging and is surpassed by endosonography. Moreover, markedly, intrahepatic cholestasis results in false-positive results which have been reported as hepatic metastases (50). FDG PET may help also to detect other areas of involvement and therefore prevent unnecessary surgery. In one report, FDG PET altered clinical treatment in 41% of cases (51). Heinrich et al. stated that treatment strategy was changed in 16% by using fusion FDG PET/CT (52). Maisey et al. detected decreased or absent FDG uptake after one month of chemotherapy which correlated with a longer survival (53). FDG PET imaging is also strongly recommended in patients with rising tumor marker levels (54, 55).

FDG PET imaging is of limited value in patients with diabetes mellitus due to elevated glucose levels and consequently decreased FDG uptake on PET scans. Zimny reported a lower FDG PET sensitivity (60%-63%) in diabetic patients compared to euglycemic patients (more than 90%) (56). The ^{11}C-labeled amino acid methionine (^{11}C-MET) PET may provide an alternative to FDG PET in diabetic patients (57).

Most neuroendocrine tumors like carcinoids, paragangliomas and islet cell tumors express somatostatin receptors. In these tumors, CT has lower sensitivity in detection of extrahepatic and extra-abdominal metastatic disease. Imaging with ^{111}In-octreotide plays an important role in imaging of these tumors. Somatostatin-receptor-negative tumors show high uptake of FDG and can be evaluated by FDG PET (18). FDG PET, however, may result in false negative scans in well-differentiated somatostatin-receptor-positive tumors (58). ^{68}Ga-octreotide PET provides imaging of endocrine pancreatic tumors (59-63).

PET IN LIVER CARCINOMA

FDG PET has sensitivity of 55% in detection of hepatocellular carcinoma (HCC), versus 90% of CT (64). Higher sensitivity rates on delayed FDG PET images have been reported. While FDG PET shows better results in poorly differentiated HCCs, (^{11}C) acetate PET is superior to FDG PET to detect well-differentiated tumors (65). Yamamoto et al. evaluated the utility of ^{11}C-choline PET, compared with ^{18}F-FDG PET, for detection of hepatocellular carcinoma. They reported that ^{11}C-choline PET had a better detection rate for moderately differentiated HCC lesions but not for poorly differentiated tumors (75% vs. 25%, respectively). In contrast, ^{18}F-FDG PET exhibited the opposite behavior, with corresponding detection rates of 42% and 75%, respectively (66).

FDG PET has a reported 83% sensitivity to detect extrahepatic metastases from HCC, which is comparable with the data obtained with CT (67). FDG PET/CT improves sensitivity in detection of liver metastases but only in FDG PET-positive lesions. FDG PET/CT can differentiate between intrahepatic and adjacent lesions of the liver (68).

Cholangiocellular carcinoma (CCC) expresses marked FDG uptake on PET images (69,70). FDG PET imaging showed high sensitivity specificity (92% and 93%, respectively) in detection of the primary tumor. FDG PET/CT has a sensitivity of 70% in detection of distant metastases, but has a low sensitivity of only 13% in detection of regional or hepatoduodenal lymph node metastases (71).

PET IN GASTROINTESTINAL STROMAL TUMORS (GISTs)

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract (2). Some authors have shown that FDG PET and CT have a similar sensitivity of 90% in the staging of GIST (72). FDG PET imaging was also shown to be useful for assessment of treatment response. GIST tumors are known to be chemoresistant and insensitive to irradiation. A tyrosine kinase inhibitor, imatinib, however, showed impressive results in treatment of GIST (73). Often authors have shown that FDG PET is superior to CT in assessing of early tumor response induced by imatinib therapy (74-76). FDG PET may detect a positive tumor response 8 days after the start of the imatinib therapy while CT needs approximately 7 weeks to detect a treatment response (74). Antoch et al. suggested that tumor response to imatinib should be assessed with a combination of morphologic and functional imaging. They performed separate FDG PET and CT scans and fused the FDG PET/CT images before treatment and 1, 3, and 6 months after the start of imatinib therapy. FDG PET/CT accurately diagnosed tumor response in 95%, versus 85% and 44%, respectively (77).

PET IN SMALL BOWEL CARCINOMA

Small bowel carcinomas are rare and frequently are of neuroendocrine origin. ^{68}Ga-DOTATOC PET is most commonly used for imaging of the somatostatin-receptor-positive tumors (78). FDG PET is also used in differentiation between sarcomas and benign tumors of the small bowel (79). Freudenberg et al. showed that FDG PET/CT is superior in detection of small bowel carcinomas, comparing to FDG PET alone (80).

PET IN COLORECTAL CARCINOMA

Colorectal carcinoma represents 13% of all malignancies (1) in the United States and the Western Europe and in 2008 it was the third most common cancer in men and women. It is the third leading cause of cancer-related deaths in the United States. The 5-year survival rate is about 66% (81).

FDG PET has no role in screening, preoperative diagnosis or initial staging of colorectal carcinoma mainly due to difficulties in distinguishing focal physiologic activity from malignant bowel uptake; an exception would be the need to detect or exclude distant extrahepatic metastatic disease (82). In our institution, liver metastases were detected in two patients with rectal cancer referred to PET/CT for initial staging (Figure 1 and 2).

During the postoperative follow-up, CT has been shown to be not sufficiently accurate for early detection of local recurrence of colorectal carcinoma. Selzner et al. reported 53% sensitivity for CT whereas FDG PET had a considerably higher sensitivity of 93% (83).

FDG PET is highly accurate in detection of relapsing colorectal carcinoma. Consequently, the indication for FDG-PET in relapsing colorectal cancer was highly graded, as 1a indication according to the 3rd German Interdisciplinary Consensus Conference (18). Arulampalam et al. concluded that FDG PET

is more accurate than CT for detection and staging of recurrent colorectal cancer. They reported that FDG PET is more accurate than CT to stage local recurrence with a sensitivity of 100% and specificity of 86% for FDG PET, versus 75% and 100% for CT. For detection of liver metastases, FDG PET sensitivity was 100% versus only 45%, while specificity was 100% for both). FDG PET upstaged 38% of patients and changed the management in 38% (84).

In a meta-analysis, Zhang et al. reported that FDG PET, in the study of distant metastases or recurrent colorectal cancer, had a pooled sensitivity and specificity of 91% and 83% respectively (85). Huenber et al., however, reported FDG PET sensitivity of 97% and specificity of 76% to detect local recurrences (86). According to another study, FDG PET/CT improves staging accuracy in colorectal cancer from 78% to 89% compared to FDG PET alone (87).

FDG PET also shows excellent sensitivity in detection of local recurrence after radiation therapy. Morphologic imaging is not able to distinguish between viable tumor and non-viable post-irradiated tissue until the tumor shrinks. On the contrary, PET makes this distinction on the basis that FDG is accumulated in viable tissue but not in the fibrotic scar tissue (88). It was also reported that PET is more accurate (90%-100%) than CT (48%-65%) in distinguishing post-therapy scar from recurrent disease (89, 90). Wiering et al. performed systematic literature meta-analysis to assess the role of FDG PET in the management of liver metastases in patients with colorectal cancer. FDG PET is the accurate technique for the assessment of extrahepatic disease; the pooled sensitivity and specificity of FDG PET were 91.5% and 95.4%, respectively, compared to 60.9% and 91.1% for CT imaging. Their data also showed ≥25% change in patients' clinical management (91).

Other authors have demonstrated also that FDG PET is more accurate than CT for hepatic metastases. A comparison of FDG PET versus CT and CT portography has been reported (89, 92). It was shown that FDG PET has higher accuracy in detecting hepatic and extrahepatic metastases in comparison to CT and CT portography (92% versus 78% and 80%) in contrast to higher sensitivity of CT portography (92).

To determine an exact location and evaluation of the extent of local pathology, Vogel favored FDG PET/CT over FDG PET alone (93). Chen et al. reported the 94.6% sensitivity and 83.3% specificity of FDG PET/CT in diagnosis of colorectal cancer recurrence and/or metastasis; 96.4% positive predictive value and 76.9% negative predictive value. They also detected recurrence and/or metastasis in 91.7% patients with elevated serum CEA levels (94). In another study, Flanagan studied unexpected increase in CEA levels without abnormal findings on conventional evaluation including CT. FDG PET correctly detected recurrence in more than 30% of patients (95).

FDG PET is a promising tool in assessment of residual masses after the initial treatment. De Geus-Oei et al. concluded that there was a high predictive value of FDG PET in the therapeutic management of colorectal cancer. In primary rectal cancer, FDG PET is useful after neoadjuvant treatment preoperatively; it correlates better with pathology than morphologic imaging modalities. FDG PET has an important role in evaluating the local ablative treatment of liver metastases; unlike CT, it detects incomplete tumor ablation (96). Clinical management was altered due to FDG PET findings in 29% of patients (86) or in 28% of cases by avoiding surgery in two thirds and by initiating operation in one third of patients (89). FDG PET also plays a role in restaging of patients with colorectal cancer; it changes clinical stage in 42% with upstaging in 80% and downstaging in 20% of patients (97).

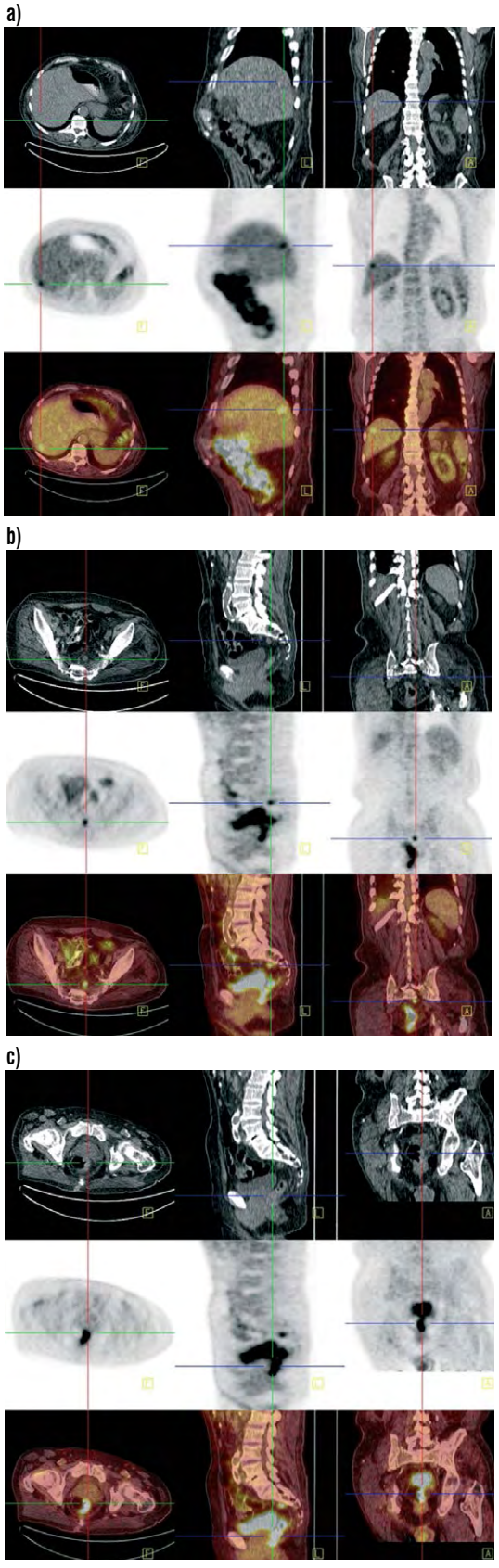

Figure 1. A 74 year-old male; Status post colonoscopy; biopsy detected adenocarcinoma recti a) FDG avid lesion in hepatic segment 7, SUV = 3.9, consistent with metastasis b) FDG avid presacral lymph node (on the left), SUV = 4.7, consistent with metastasis c) FDG avid focus, left lateral aspect, rectal area, SUV = 10.9, consistent with primary

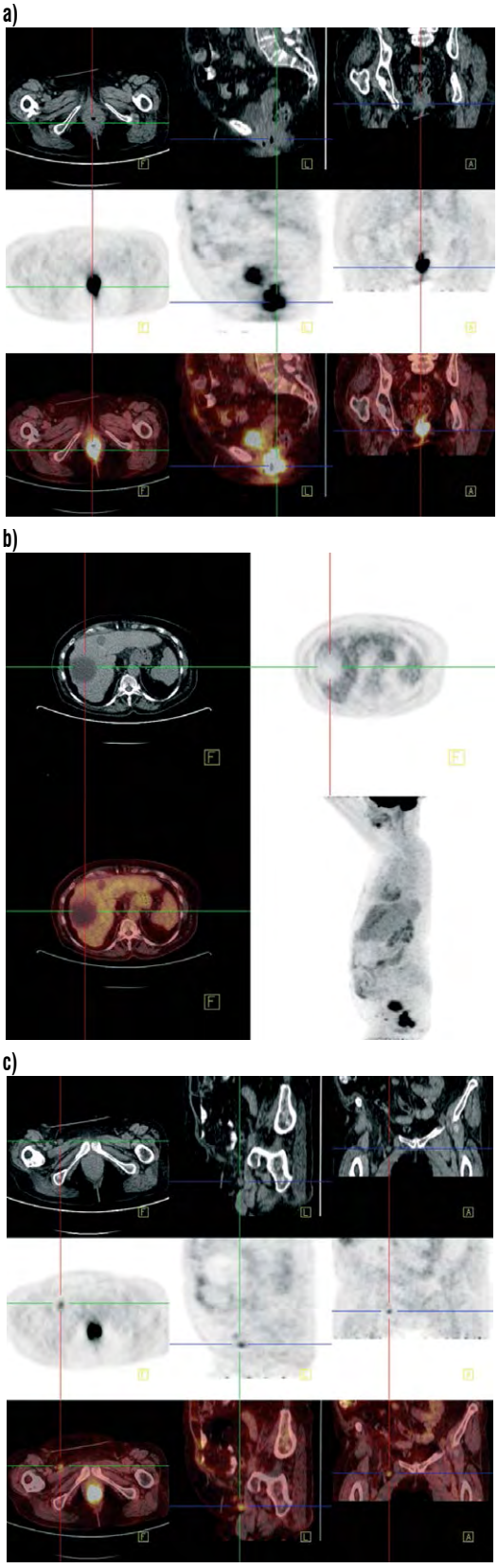

Figure 2. A 61 year-old female; Biopsy of an anal canal lesion was performed 4 months earlier; histology detected invasive carcinoma of the anus
a) Hypermetabolic focus in rectum and anal canal extending to the perineum. SUV = 19.5, indicative of locoregional tumor extension. b) There are 2 non-hypermetabolic foci in the liver, segment 4 and segments 7/8, c) Two hypermetabolic superficial inguinal lymph nodes, on the right, SUV = 3.63

CONCLUSION

FDG PET and particularly PET/CT has been found to be of great value in the management of the patient with gastrointestinal malignancies. Although not specifically relevant in screening of the initial diagnosis, it has a role in determining the extent of disease if there is reason to suspect or exclude local or distant metastases. Certainly, it is relevant during follow-up for detection of recurrence. FDG PET/CT is also useful to assess the efficacy of therapy although the criteria are different for different gastrointestinal tumors. These criteria are still being developed. Finally, nuclear medicine physicians and radiologists need to be alert to the incidental identification of foci in the gastrointestinal tract that may represent neoplasm when performing whole body FDG PET/CT for other reasons.

Conflict of interest

We declare no conflicts of interest.

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