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INTEGRATION OF PET IN THE CLINICAL MANAGEMENT OF GASTROINTESTINAL TRACT MALIGNANCIES

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INTRODUCTION

Positron emission tomography (PET) is a major paradigm shift in medical imaging as it is a molecular modality that images the metabolic activity of tissue. Recently, there has been a major expansion and move from research applications into clinical patient care. The majority of these PET scans are performed to evaluate cancer. Uses include cancer diagnosis, staging, restaging and monitoring response to therapy. There is evolving critical applications of PET in the management of Gastrointestinal (GI) tract malignancies. PET is highly sensitive in the detection of occult GIT tumors, nodal and metastatic involvement to liver and other distant sites, yet the role of CT is essential for anatomical delineation, defining tumor extent and resectability. This manuscript reviews the various indications of PET imaging in GI tract malignancies. This will demonstrate the literature and the wide clinical experiences of PET applications in esophagus, Stomach and colorectal. The primary tumors of abdominal solid organs like pancreas, liver ..etc were beyond the scope of this review. The fundamental role of CT imaging in GI tract malignancies is discussed with more emphasis on the added value of the recent fusion of PET and CT that leads to more precise and expansion of the molecular PET images.

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Esophageal cancer

Esophageal cancer has a very poor prognosis despite the advances in treatment because esophageal cancer is often diagnosed at advanced stage. There are two types of esophageal carcinoma, squamous cell type and adenocarcinoma which usually occur in the proximal and distal portion of the esophagus, respectively [1].

Staging work-up and imaging:

Staging methods include computed tomography (CT), endoscopic ultrasonography (EUS) and magnetic resonance imaging (MRI) [2]. These morphologic imaging modalities, however, rely on structural changes and are often inaccurate resulting in failure of surgery with curative intent. EUS has limitations in patients with stenosis of the lumen of the esophagus caused by the tumor. CT has limitations in differentiating benign from malignant causes of thickening of the wall of the esophagus. Positron emission tomography (PET) using fluorodeoxyglucose (FDG-PET) has now been integrated into the staging and restaging algorithm of esophageal cancer.

Patients with early disease have a good chance of survival as curative surgical resection of early stage esophageal cancer is the mainstay of therapy (figure 1). In advanced stages, however, neoadjuvant therapy is necessary prior to surgery to decrease tumor bulk and associated morbidity [1].

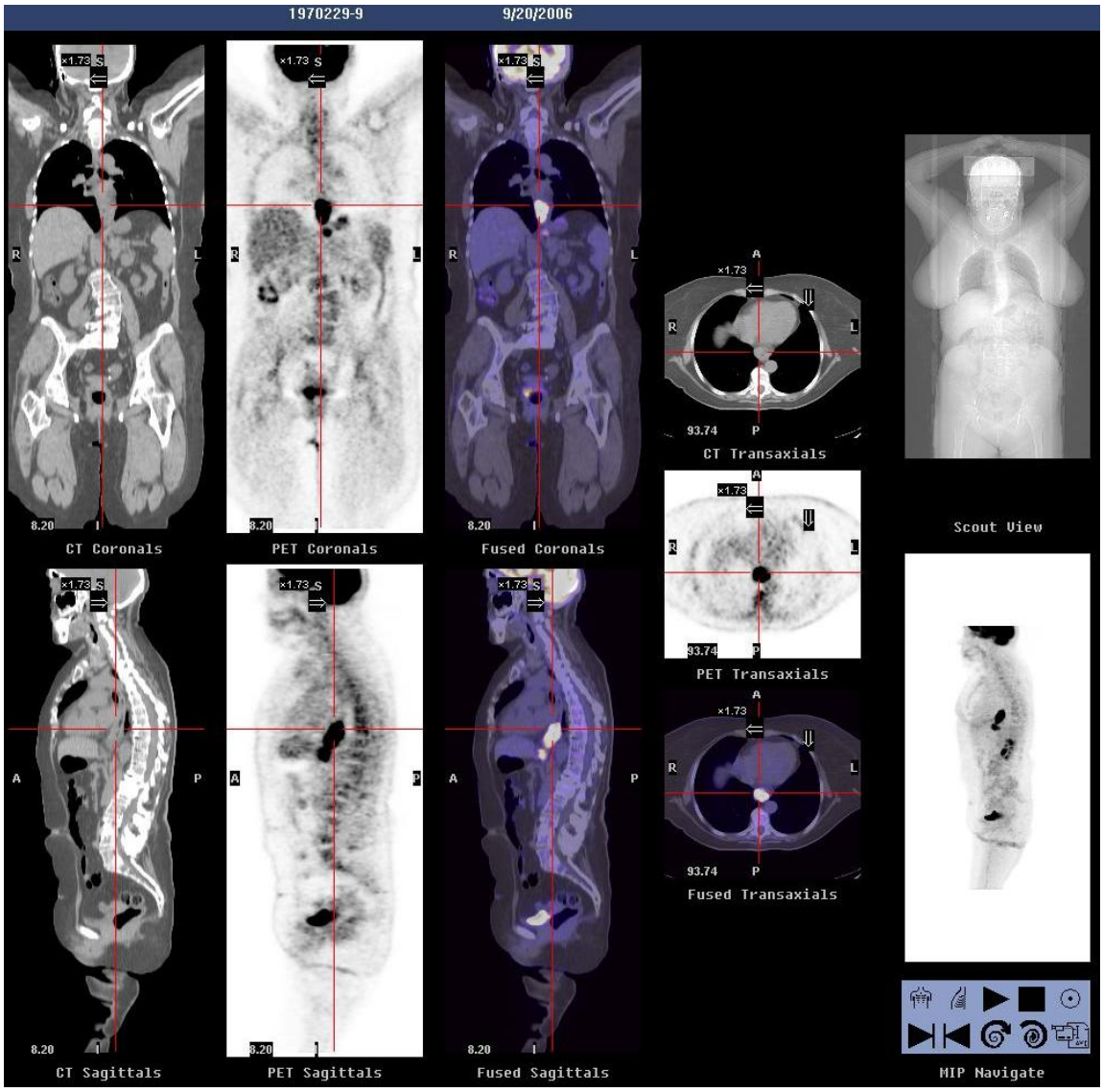

Figure (1): 65 years female patient with cancer esophagus, the PET showed high uptake in the primary that was already known from the CT examination. However, the combination of the PET and anatomical verification of CT showed the tumor extension distal to gastro-esophageal junction with early involvement of the stomach fundus. The rest of whole body showed no distant metastases.

Diagnosis and Staging by FDG-PET:

FDG PET became an established functional imaging modality for patients with esophageal cancer. FDG PET is highly sensitive in the detection of the primary esophageal tumors, hepatic and distant metastases [3-7].

Regional lymph node involvement in esophageal cancer is the most important prognostic factor. The sensitivity of both PET and CT appears limited for the detection of local lymph node involvement with small burden of tumor as well as lymph nodes that are in close proximity of the primary tumor. Nonetheless, studies have shown that FDG PET significantly improves preoperative lymph node staging. A meta-analysis of 12 studies has

demonstrated a pooled sensitivity and specificity of 51% and 84%, respectively for FDG PET in the detection of locoregional disease [8]. However, FDG PET is more sensitive than conventional imaging for detection of distant metastases therefore has an important role in M staging. The overall pooled sensitivity and specificity of FDG PET for detection of distant metastases was reported around 67% and 97%, respectively [8]. In a prospective study of 74 patients with esophageal carcinoma, FDG PET had a higher accuracy than the combination of CT and EUS for diagnosing stage IV disease (82% versus 64%) [9, 10]. EUS was more sensitive than FDG PET for local lymph node staging (81% versus 33%), but the specificity of FDG PET was superior to CT and EUS combined for staging local and distant lymph nodes. FDG PET changed the stage in 22% (16/74) of patients, by upstaging two thirds and downstaging one third [9]. Comparing different strategies for preoperative staging of patients with esophageal cancer, Wallace et al [11] found that the combination of PET + EUS with fine needle aspiration biopsy was the most effective strategy among various combination strategies.

Prognosis:

FDG PET is promising for the assessment of prognosis. In a study of 69 patients with esophageal cancer who were undergoing curative surgery, the SUV of the primary tumor, the number of positive lymph nodes on FDG PET, the length of the tumor and tumor stage were independent prognostic predictors compared to clinical features [12].

Assessment of response to therapy:

One of the strong predictors of long-term survival is the degree of response to chemotherapy and radiation therapy [13]. In a study on 100 patients, PET, CT and EUS were compared prior to and 3-5 weeks after completion of neoadjuvant therapy [14]. FDG PET imaging was superior to both CT and EUS with a sensitivity, specificity and accuracy of 62%, 84% and 76%, respectively. When the primary tumor, regional and distant metastatic disease were considered, the sensitivity, specificity and accuracy of PET was 69%, 78% and 75% respectively**.** In this study, a post-therapy SUV of the primary tumor (equal or greater than 4.0) was an independent predictor of long-term survival. Other studies showed that the response to therapy can be predicted early after the initiation of chemotherapy or chemoradiotherapy [15, 16]. Although, larger prospective trials are necessary, it appears that the degree of change in FDG uptake during or after therapy is predictive of the pathological response and has long-term prognostic significance.

Restaging:

Patients with esophageal carcinoma present with distant metastases more often at the time of recurrence than at the time of initial diagnosis. As a whole body metabolic imaging modality FDG PET is superior to other imaging techniques in the detection of distant metastases. Hence, FDG PET may be most helpful in restaging patients when they present with recurrence [17, 18].

Summary:

So, PET in ca aesophus may change the staging in up to 25% of patients because of its superiority in the detection of distant metastases when compared to CT and EUS. Locoregional nodal metastases are detected more accurately with FDG PET than CT, but not as compared to EUS. The utility of FDG PET may be more important in the evaluation of patients with recurrence or suspected recurrence and in the assessment of response to therapy.

Gastric Cancer:

Ninety-five percent of gastric cancers are adenocarcinomas. They have been classified into the intestinal and diffuse type. The diffuse type seems to have a genetic predisposition and affects younger individuals. Histologically, it is poorly differentiated and lacks glandular structures. The intestinal types develop in a transition from normal mucosa to dysplasia and adenocarcinoma, usually in the distal stomach. Histologically, the intestinal type forms gland-type structures [19, 20].

Staging:

The prognosis of patients with gastric cancer depends on the tumor extent and includes both nodal involvement and direct tumor extension beyond the gastric wall [21]. The diagnosis for the primary is usually made by endoscopy and biopsy, while CT and EUS are used for assessment of the locoregional extent of the disease [2]. For early gastric cancer, surgical resection with en bloc resection of the tumor and regional lymph nodes is associated with a 5-year survival of approximately 90% [22]. Unfortunately, most cases are diagnosed at an advanced stage and are treated with neoadjuvant chemotherapy with a poor survival of approximately 10% [2]. The role of FDG PET for staging of gastric cancer is still controversial, yet the PET is highly sensitive for showing hepatic and distant metastases [23-25], as with the case example shown in figure (2). Overall, for gastric carcinomas, the sensitivity, specificity and accuracy of PET for the detection of the primary tumor, loco-regional metastases, and distant metastases is in the same range as for esophageal carcinomas. The sensitivity for detecting locally advanced gastric carcinoma ranges from 60 to 80% [23, 26, 27]. Pathologic type (Nonintestinal type) and depth of invasion and tumor size have been reported as factors influencing the detection rate [23, 27]. The false negatives for FDG PET are for the detection of diffuse type of gastric adenocarcinoma with a high mucin content, in addition, normal diffuse physiological uptake in the stomach may obscure small tumors with low degree of FDG uptake.

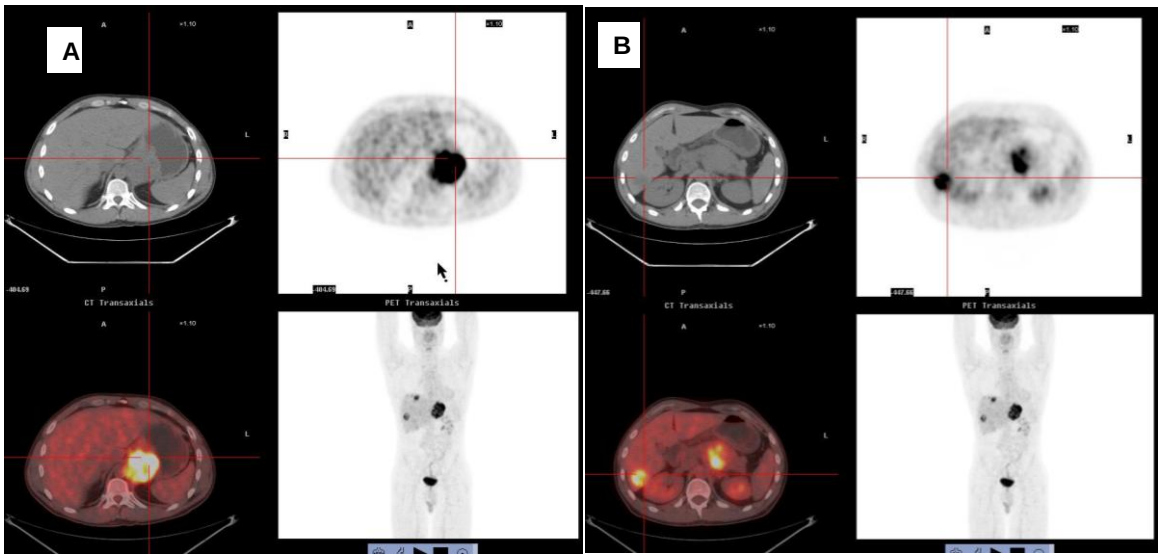

Figure (2): 70 years male patient with gastric cancer. The PET images showed the primary mass with intense uptake and 2 hepatic metastases. The fusion PET/CT images delineates the malignant lesions more precisely.

Restaging and Monitoring response to therapy:

There is scarce data on the role of FDG PET in the detection of recurrent gastric cancer, assessment of response to therapy and prediction of prognosis. The diagnostic performances of FDG-PET were limited for assessing recurrent disease and local nodal involvement, even though it may provide additional information as compared to CT and influence the patients' management [28, 29]. A prospective study of 44 patients with locally advanced gastric cancer demonstrated that FDG PET can correctly predict the response to therapy early, after initiation of chemotherapy, and the metabolic response was also predictive of survival. The metabolic response as measured after 14 days from chemotherapy, was correlated with both the pathologic response (in 29 of 35 patients) and the overall survival [26]. Mochiki et al., [27] reported a significantly lower survival rate in patients with high uptake tumors in a series of 85 patients, but conversely, Stahl et al [23] did not find any relation ship between intensity of uptake and survival.

It seems that both the diagnostic performances and the clinical impact of PET should be further investigated before using as a routine imaging modality in patients with gastric cancer. Nonetheless, FDG PET should be used as a problem solving tool in an adjunct setting in select patient populations.

Colorectal cancer:

Colorectal cancer is the third most common cause of cancer and affects 5% of the population in the United States and most western countries.

Approximately 70%-80% of patients are treated with curative intent and the overall survival at 5 years is less than 60%. [1].

The diagnosis is usually made by colonoscopy and biopsy. The prognosis of patients with colon cancer is clearly related to the degree of penetration of the tumor through the bowel wall, the presence or absence of nodal involvement, and the presence or absence of distant metastases.

FDG PET imaging in the diagnosis and staging of colorectal cancer:

Although both malignant and premalignant colon lesions can accumulate FDG, yet there is no role for the PET as a screening or diagnostic tool [30, 31]. In addition to cost and availability issues, the physiological bowel uptake frequently observed, is likely to lead to unacceptably high proportion of false positive results.

For the initial pre-operative staging of colorectal cancer, FDG PET imaging has been proposed as efficient test. It identified distant metastases and was superior to CT for detection of hepatic metastases (figure 3).

However, regarding the T stage (tumor depth) and the N stage FDG PET was as poor as CT for detecting tumor extent and involvement. The sensitivity for detecting nodal metastases was as low as 29%. The impact on patient management is marginal because most patients undergo surgery anyway with staging essentially performed during the surgery. In one study, FDG PET imaging changed the treatment management in 8% of patients and the range of surgery in 13% [32-34].

Recurrent Colorectal Cancer:

Most patients with colorectal cancer undergo surgery with curative intent in 70% of cases, however, the recurrence rate is close to 40% within 5 years following surgery. Up to 80% of the recurrences are in fact diagnosed

during the first 2 years. The primary site of recurrence is the liver (approximately 20% of all patients) followed by local site (12.5%) and the lungs (8%) [35, 36]. Twenty-five percent of these patients have recurrence limited to one site and are potentially curable by surgical resection [37]. For example, about 14,000 patients per year present with isolated liver metastases as their first recurrence, and about 20% of these patients die with metastases exclusively to the liver [38]. Hepatic resection is the only curative therapy in these patients, but it is associated with a mortality of 2%-7% and has the potential for significant morbidity [39]. The poor prognosis of extra-hepatic metastases is believed to be a contraindication to hepatic resection [40]. Therefore, accurate noninvasive detection of inoperable disease with imaging modalities plays a pivotal role in the selection of patients who would benefit from surgery.

A wide variety of surveillance strategies have been proposed including measurement of CEA serum levels has a sensitivity of 59% and specificity of 84% but does not localize recurrent lesions [41]. Barium studies have been used for detection of local recurrence with accuracy in the range of 80%. However, barium studies have been reported to be only 49% sensitive and 85% specific for overall recurrence [42]. CT has been the conventional imaging modality of choice used to localize recurrence but has limitations for detection of metastases in the peritoneum, mesentery and lymph nodes. In addition, the differentiation of post-surgical changes from local tumor recurrence is often equivocal [43-46]. The interest of frequent colonoscopy remains largely debated and there is no consensus regarding the optimal strategy for follow up because of the lack of benefit in survival for costly intensive follow up programs [30]. In this context, it is not a surprise to find a large amount of scientific data related to the use of FDG-PET for restaging of recurrent colorectal cancer.

FDG-PET imaging for recurrent colorectal cancer:

Early detection of recurrent disease is vital, as the recurrence must be staged as accurate as possible to orient patient management toward either re-surgery or medical treatments, both of which significantly improve the survival or quality of live. Significant number of studies has demonstrated the value of FDG PET as a functional imaging modality for detecting recurrent or metastatic colorectal carcinoma (figure 3). Overall, the sensitivity of FDG PET imaging is in the 90% range and the specificity is greater than 70%[47-52].

A meta-analysis reviewing 11 articles published up to 1999 reported pooled sensitivity and specificity of 97% and 76%, respectively, for detecting recurrent colorectal cancer The sensitivity was similar for detecting lesions throughout the body (281 patients), in the liver (393 patients), or local-pelvic recurrences (366 patients), but in these two latter situations, the specificity reached 99% and 98%, respectively. Change in management was evaluated to occur in 29% of the cases (102 of 349 patients) [53].

Several studies have compared FDG-PET and CT in the differentiation of post-therapy changes from local recurrence [47, 48, 54]. CT was equivocal in most cases and the accuracy of FDG PET imaging was greater than 90%. Lai et al in his study on 76 patients [54], reported that the accuracy of FDG PET and CT was 95% and 65%, respectively. Other studies have compared the accuracy of FDG-PET and CT for detection of hepatic metastases [48, 54-56]. Overall, the accuracy for FDG PET was higher than for CT.

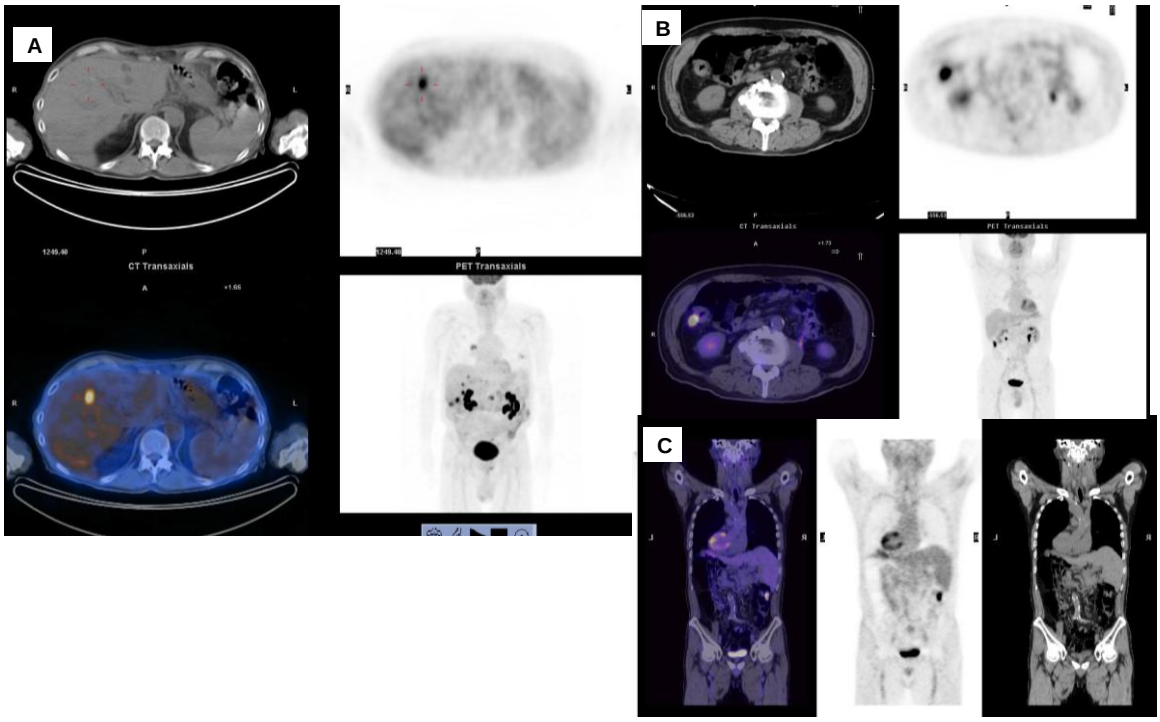

Figure (3): Restaging after detection of raised CEA levels, A) multiple liver metastases by PET and the some of them are not seen in CT as the one showed. B, C) The combinations of PET and CT showed the ability to definitely localize the colonic primary tumor and showed the absence of metastases. PS; the activity seen distal to heart in C is related to Gastric physiological uptake.

A meta-analysis performed to compare non-invasive imaging methods (US, CT, MRI and FDG PET) for the detection of hepatic metastases in colorectal, gastric and esophageal cancers demonstrated that at an equivalent specificity of 85%, FDG PET had the highest sensitivity at 90% compared to 76% for MRI, 72% for CT and 55% for US [57]. A comprehensive review of the PET literature (2,244 patient's studies) has reported a weighted average for FDG PET sensitivity and specificity of 94% and 87% respectively compared to 79% and 73% for CT [58].

One of the challenging clinical situations in which FDG-PET significantly contributes to patient management, is when CEA levels are increased, which strongly suggests tumor relapse, with a conventional work-up that fails to identify the site of recurrence. Flanagan et al., [49] reported 100% sensitivity and 89% positive predictive value in 22 patients in such a situation. Libutti et al., [59] studied 28 patients with increased CEA levels and a comprehensive conventional work-up, following which 13 patients had no lesion identified, and 15 had a single lesion. The overall sensitivity of PET was 89%.

Nevertheless, false-negative FDG PET findings have been reported with mucinous adenocarcinoma. Two studies reported that the sensitivity of FDG PET for detection of mucinous adenocarcinoma is significantly lower than for non-mucinous adenocarcinoma, with a sensitivity of 58% and 92% respectively (p=0.005) [60, 61]. This low sensitivity of FDG PET for detection of

mucinous adenocarcinoma is due to the relative hypocellularity of these tumors.

Assessment of response to therapy:

One of the earliest applications for FDG-PET was to differentiate scar tissue following therapy from recurrent tumor in the pelvic area [62, 63]. In cases of advanced cancer colon, systemic chemotherapy with 5-fluorouracil, often in combination with radiotherapy, has demonstrated effective palliation and improved survival [64]. A study on 44 patients demonstrated that FDG PET imaging can differentiate local recurrence from post-therapy changes (scarring) after radiation therapy, However, post radiation inflammatory changes many lead to increase in FDG uptake [65]. In fact, the longer the interval of time between completions of radiation therapy, the higher is the accuracy of PET for assessing recurrent or persistent disease [66]. The time course of post-irradiation FDG activity has not been studied systematically; it is, however, generally accepted that FDG activity present 6 months after completion of radiation therapy most likely represents tumor recurrence. A case-controlled study of 60 FDG-PET studies performed 6 months following external beam radiation therapy for rectal cancer found a sensitivity of 84% and specificity of 88% for detection of local pelvic recurrence [66]. Some data indicates that FDG PET assessment of locally advanced rectal cancer response to preoperative chemoradiation may predict long term outcomes [67-70].

Systemic chemotherapy or regional therapies are used to treat hepatic metastases. The regional therapy modalities for hepatic metastases include chemotherapy administered through the hepatic artery using infusion pumps, selective chemoembolization, radiofrequency ablation, cryoablation, alcohol ablation and radiolabeled ^{90}Y-microspheres [71]. There are preliminary reports suggesting that the response to chemotherapy in patients with hepatic metastases can be predicted using FDG PET. Responders may be discriminated from non-responders after 4 to 5 weeks of chemotherapy with fluorouracil by measuring FDG uptake before and during therapy [72]. Data suggest that FDG PET imaging accurately monitors the efficacy of radiofrequency ablation for treatment of hepatic metastases and it detects incomplete tumor ablation not detectable on CT. FDG uptake decreases in responding lesions and the presence of residual uptake in some lesions can help in guiding further regional therapy [73]. Overall, the current data suggest that FDG PET imaging may be able to effectively monitor the efficacy of regional therapy to hepatic metastases but, it seems that much a larger series of patients before considering FDG-PET as a routine clinical tool in this indication.

Impact of FDG PET on Patient Management:

The greater sensitivity of FDG PET compared to CT in the diagnosis and staging of recurrent tumor results from two factors: early detection of abnormal tumor metabolism, before changes become apparent by anatomic imaging, and the whole body imaging which permits detection of metastases in unusual and/or unexpected sites. FDG PET imaging allows detection of unsuspected metastases in 13%-36% of patients and has a clinical impact in 14%-65% [52, 56, 74-76]. In the study of Delbeke et al, [56] surgical management was altered by FDG PET in 28% of patients, in one-third by initiating surgery and in two thirds by avoiding surgery.

Kalff et al., [78] compared the treatment plan according to the results of the conventional work-up with the actual management, decided after performing PET. Treatment changes occurred in 60 (59%) of 102 patients; in particular, surgery was cancelled in 26 (60%) of 43

patients because PET found additional, unsuspected, lesions. Other groups found even higher figures, such as Staib et al., [74] who reported in a series of 100 patients additional information in 86% of the cases and modification of the surgical decision in 61%. Other investigators reported changes in management ranging from 21% to 48% [51, 79-81]. The comprehensive review of the FDG PET literature has reported a weighted average change of management related to FDG PET findings in 32% of 915 patients [58].

Fernandez et al., reported 5-year survival data after resection of metastasis from colorectal carcinoma [82]. They established a 5-year survival rate using conventional diagnostic imaging from the literature by pooling the data from 19 studies with a total of 6,090 patients. The 5-year survival rate was 30% and appeared not to have changed over time. These results were compared to their group of 100 patients with hepatic metastases, who were pre-operatively staged for resection with curative intent with the addition of FDG PET imaging. The 5-year survival rate improved to 58%, indicating that they were able to define a subgroup after conventional imaging that has a better prognosis. The main contribution was to be able to detect occult disease, leading to a reduction of unnecessary surgeries.

So; PET has established itself as an essential diagnostic tool in patients with colorectal cancer. It is valuable in these indications: diagnosis and staging of recurrence especially before re-surgery with curative intent, and differentiation of post treatment changes from recurrence, differentiate nature of indeterminate lymph nodes, hepatic and pulmonary lesions. Most importantly, evaluation of patients with rising CEA tumor marker levels with inconclusive work-up. FDG PET proves useful for assessing the response to treatment and as a systemic screening tool in follow-up after curative surgery especially in patients with high risks of recurrence.

The addition of FDG PET imaging reduces overall treatment costs by accurately identifying patients who will and will not benefit from surgical procedures. It is particularly useful if surgery can be avoided in cases where FDG PET demonstrates metastases.

Hybrid PET/CT in GIT malignancies:

Combined PET/CT imaging with an integrated system is especially important in the abdomen and pelvis. FDG PET images alone may be difficult to interpret. Bowel activity may be high, with various patterns that can either mimic disease or mask peritoneal or intestinal lesions. The absence of anatomical landmarks with physiological excretion by kidneys and ureteric activity make it difficult confidently to locate a focus of increased uptake as peritoneal, nodal, or even bony.

A study of 45 patients with colorectal cancer referred for FDG PET imaging using an integrated PET/CT system demonstrated that PET/CT imaging increases the accuracy of interpretation and certainty of locating lesions. In their study, the frequency of equivocal and probable lesion characterization was reduced by 50% with PET/CT compared to PET alone, the number of definite locations was increased by 25%, and the overall correct staging increased from 78% to 89% [83].

In 204 patients (34 with GIT tumors) studied with integrated PET/CT system, the diagnostic accuracy of PET is improved in approximately 50% of patients. The results of PET/CT images had an impact on management of 14% (28/204) of all patients, 7/28 patients with a change of management had colorectal cancer representing 20% (7/34) of patients with GIT tumors. The impact on management in the 7 patients with colorectal cancer included guiding

colonoscopy and biopsy for a local recurrence (n=2), guiding surgery to localized metastatic lymph nodes (n=3) and referral to chemotherapy (n=2) [84].

Selzner et al., [85] compared contrast CT and PET/CT imaging in 76 patients evaluated for resection of liver metastases. CT with contrast and PET/CT provide similar sensitivity in the detection of hepatic metastases (95% and 91% respectively). However, the specificity of PET/CT was superior for detection of intrahepatic recurrences in patients with prior hepatectomy (specificity of 50% versus 100%). The sensitivity of PET/CT was 93% for detection of local recurrence at the primary colorectal resection site compared to only 53% for contrast CT. The PET/CT findings changed the therapeutic strategy in 21% of patients.

The added value of PET/CT over dedicated PET was reviewed in 62 patients who underwent abdomino-perineal or low anterior resection for colorectal cancer. The sensitivity and specificity for FDG PET was 82% and 65% while it was much higher (98% and 96% respectively) for hybrid PET/CT [86].

Though, presently, there are no published literature regarding the incremental value of PET/CT for staging esophageal cancer, it is highly recommended based on the improved detection and characterization of equivocal and suspicious lesions [87, 88].

The CT addition to the PET have the marvelous advantages of using the superior CT data for attenuation correction, and the potential to provide better maps than CT alone to modulate field and dose of radiation therapy in GIT malignancies [89].

Limitations of PET in GIT Malignancies:

Interpretation of FDG PET images needs familiarity with the normal distribution of FDG, physiological variations, and benign conditions that accumulate FDG, which can mimic malignant processes. FDG uptake is normally present in the esophagus, stomach and bowel. Incidental colonic FDG uptake in 27 patients without colorectal carcinoma has been correlated with colonoscopic and/or histolopathologic findings [90]. In most patients, diffuse uptake was normal, segmental uptake was due to colitis, and focal uptake was associated with benign adenomas. Agress et al., [91] reviewed FDG PET studies of 1,750 patients referred for evaluation of known or suspected malignancies. The authors found 58 unexpected focal areas of FDG uptake and 42 lesions were pathologically confirmed, 30 (71%) of which were malignant or premalignant including 18 colonic adenomas and three colon carcinoma.

False positive high FDG uptake is seen in inflamed tissues due to the active metabolism in macrophages, neutrophils, fibroblasts and granulation tissue. Mild to moderate FDG activity seen early after radiation therapy, along recent incisions, infected incisions, drainage tubing and catheters, as well as colostomy sites can lead to errors in interpretation. Post-radiotherapy FDG high uptake may persist for several months and comparison with baseline FDG images and knowledge of the radiation port are imperative. Some inflammatory lesions, especially granulomatous ones, may be markedly FDG-avid and can be mistaken for malignancies; this includes inflammatory bowel disease, diverticulitis, acute cholangitis, acute cholecystitis, acute pancreatitis, tuberculosis, sarcoidosis, histoplasmosis and aspergillosis among others [92].

The size of the tumor and the degree of FDG avidity determine tumor delectability. False-negative lesions are caused by partial volume averaging,

leading to underestimation of the uptake in small lesions (less than twice the resolution of the imaging system) or in necrotic or mucinous lesions, falsely classifying these lesions as benign.

The FDG is extremely sensitive but the specificity can be compromised in various circumstances as noted. Other improvements may be expected from the development of alternative tracers that ideally retain the high sensitivity of FDG while improving the specificity for tumors. A review of these alternative PET tracers is beyond the scope of this article, but data obtained with ^{18}F-Deoxy-Fluorothymidine (FLT) are worth mentioning, given the high expectations generated by this compound. Francis et al., [93] demonstrated a strong correlation between FLT uptake in colorectal cancer lesions and their level of proliferation, as measured by immuno-histochemistry. In a series of 17 patients with colorectal cancer, the same investigators reported that both FDG and FLT demonstrated all primary tumors were visualized but FDG uptake was on average two-fold higher when compared to FLT. Pulmonary and peritoneal metastases were visualized with both tracers, but the sensitivity of FLT for hepatic metastases was only 34% compared to 97% for FDG due to the high physiologic hepatic activity with FLT [94]. Prognosis and therapy assessment should be the major indications for FLT tracer, provided further studies establish its clinical value.

CONCLUSIONS

The clinical applications of FDG-PET imaging in GIT tumors is now firmly established in various situations that include preoperative staging of esophageal cancer and revealing unexpected metastases in gastric and colorectal carcinoma. More importantly is the detection and staging of recurrent colorectal cancer when there is a clinical or biological suspicion with inconclusive conventional findings. The literature showed encouraging results in the evaluation of the therapeutic response of various gastrointestinal malignancies, either during the treatment or after its completion.

PET and CT are complimentary modalities and quite useful in the abdomen where there is abundant physiologic FDG uptake. The diagnostic implications of integrated PET/CT imaging include improved detection of lesions on both CT and FDG PET images, better differentiation of physiologic from pathologic foci, and better localization of pathologic foci. This advanced hybrid technology provides more accurate interpretation of both CT and FDG PET images and therefore affect the clinical management by guiding further procedures (biopsy, surgery, radiation therapy) or excluding unnecessary additional imaging leading to optimal patient care in GIT malignancies.

REFERENCES

1. Jemal, A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A, Feuer EJ, Thun MJ. Cancer statistics, 2005. *CA Cancer J Clin.* 2005, 55 , 10-30.
2. Dehdashti, F, Siegel BA. Neoplasms of the esophagus and stomach. *Semin Nucl Med.* 2004, 34 , 198-208.
3. Flanagan, FL, Dehdashti F, Siegel BA, Trask DD, Sundaresan SR, Patterson GA, Cooper JD. Staging of esophageal cancer with 18F-fluorodeoxyglucose positron emission tomography. *AJR Am J Roentgenol.* 1997, 168 , 417-24.
4. McAteer, D, Wallis F, Couper G, Norton M, Welch A, Bruce D, Park K, Nicolson M, Gilbert FJ, Sharp P. Evaluation of 18F-FDG positron emission tomography in gastric and oesophageal carcinoma. *Br J Radiol.* 1999, 72 , 525-9.

5. Luketich, JD, Friedman DM, Weigel TL, Meehan MA, Keenan RJ, Townsend DW, Meltzer CC. Evaluation of distant metastases in esophageal cancer: 100 consecutive positron emission tomography scans. *Ann Thorac Surg.* 1999, 68 , 1133-6; discussion 1136-7.

6. Rice, TW. Clinical staging of esophageal carcinoma. CT, EUS, and PET. *Chest Surg Clin N Am.* 2000, 10 , 471-85.

7. Hoegerle, S, Altehoefer C, Nitzsche EU. Staging an esophageal carcinoma by F-18 fluorodeoxyglucose whole-body positron emission tomography. *Clin Nucl Med.* 2000, 25 , 219-20.

8. van Westreenen, HL, Westerterp M, Bossuyt PM, Pruim J, Sloof GW, van Lanschot JJ, Groen H, Plukker JT. Systematic review of the staging performance of 18F-fluorodeoxyglucose positron emission tomography in esophageal cancer. *J Clin Oncol.* 2004, 22 , 3805-12.

9. Flamen, P, Lerut A, Van Cutsem E, De Wever W, Peeters M, Stroobants S, Dupont P, Bormans G, Hiele M, De Leyn P, Van Raemdonck D, Coosemans W, Ectors N, Haustermans K, Mortelmans L. Utility of positron emission tomography for the staging of patients with potentially operable esophageal carcinoma. *J Clin Oncol.* 2000, 18 , 3202-10.

10. Lerut, T, Flamen P, Ectors N, Van Cutsem E, Peeters M, Hiele M, De Wever W, Coosemans W, Decker G, De Leyn P, Deneffe G, Van Raemdonck D, Mortelmans L. Histopathologic validation of lymph node staging with FDG-PET scan in cancer of the esophagus and gastroesophageal junction: A prospective study based on primary surgery with extensive lymphadenectomy. *Ann Surg.* 2000, 232 , 743-52.

11. Wallace, MB, Nietert PJ, Earle C, Krasna MJ, Hawes RH, Hoffman BJ, Reed CE. An analysis of multiple staging management strategies for carcinoma of the esophagus: computed tomography, endoscopic ultrasound, positron emission tomography, and thoracoscopy/ laparoscopy. *Ann Thorac Surg.* 2002, 74 , 1026-32.

12. Choi, JY, Jang HJ, Shim YM, Kim K, Lee KS, Lee KH, Choi Y, Choe YS, Kim BT. 18F-FDG PET in patients with esophageal squamous cell carcinoma undergoing curative surgery: prognostic implications. *J Nucl Med.* 2004, 45 , 1843-50.

13. Thomas, CR, Jr. Biology of esophageal cancer and the role of combined modality therapy. *Surg Clin North Am.* 1997, 77 , 1139-67.

14. Swisher, SG, Maish M, Erasmus JJ, Correa AM, Ajani JA, Bresalier R, Komaki R, Macapinlac H, Munden RF, Putnam JB, Rice D, Smythe WR, Vaporciyan AA, Walsh GL, Wu TT, Roth JA. Utility of PET, CT, and EUS to identify pathologic responders in esophageal cancer. *Ann Thorac Surg.* 2004, 78 , 1152-60; discussion 1152-60.

15. Weber, WA, Ott K, Becker K, Dittler HJ, Helmberger H, Avril NE, Meisetschlager G, Busch R, Siewert JR, Schwaiger M, Fink U. Prediction of response to preoperative chemotherapy in adenocarcinomas of the esophagogastric junction by metabolic imaging. *J Clin Oncol.* 2001, 19 , 3058-65.

16. Wieder, HA, Brucher BL, Zimmermann F, Becker K, Lordick F, Beer A, Schwaiger M, Fink U, Siewert JR, Stein HJ, Weber WA. Time course of tumor metabolic activity during chemoradiotherapy of esophageal squamous cell carcinoma

and response to treatment. *J Clin Oncol.* 2004, 22 , 900-8.

17. Flamen, P, Lerut A, Van Cutsem E, Cambier JP, Maes A, De Wever W, Peeters M, De Leyn P, Van Raemdonck D, Mortelmans L. The utility of positron emission tomography for the diagnosis and staging of recurrent esophageal cancer. *J Thorac Cardiovasc Surg.* 2000, 120 , 1085-92.
18. Kato, H, Miyazaki T, Nakajima M, Fukuchi M, Manda R, Kuwano H. Value of positron emission tomography in the diagnosis of recurrent oesophageal carcinoma. *Br J Surg.* 2004, 91 , 1004-9.
19. Lauren, P. The Two Histological Main Types of Gastric Carcinoma: Diffuse and So-Called Intestinal-Type Carcinoma. an Attempt At a Histo-Clinical Classification. *Acta Pathol Microbiol Scand.* 1965, 64 , 31-49.
20. Zivny, J, Wang TC, Yantiss R, Kim KH, Houghton J. Role of therapy or monitoring in preventing progression to gastric cancer. *J Clin Gastroenterol.* 2003, 36 , S50-60; discussion S61-2.
21. Greene, FL. TNM staging for malignancies of the digestive tract: 2003 changes and beyond. *Semin Surg Oncol.* 2003, 21 , 23-9.
22. Roukos, DH. Current advances and changes in treatment strategy may improve survival and quality of life in patients with potentially curable gastric cancer. *Ann Surg Oncol.* 1999, 6 , 46-56.
23. Stahl, A, Ott K, Weber WA, Becker K, Link T, Siewert JR, Schwaiger M, Fink U. FDG PET imaging of locally advanced gastric carcinomas: correlation with endoscopic and histopathological findings. *Eur J Nucl Med Mol Imaging.* 2003, 30 , 288-95. Epub 2002 Nov 8.
24. Yoshioka, T, Yamaguchi K, Kubota K, Saginoya T, Yamazaki T, Ido T, Yamaura G, Takahashi H, Fukuda H, Kanamaru R. Evaluation of 18F-FDG PET in patients with a, metastatic, or recurrent gastric cancer. *J Nucl Med.* 2003, 44 , 690-9.
25. Mochiki, E, Kuwano H, Katoh H, Asao T, Oriuchi N, Endo K. Evaluation of 18F-2-deoxy-2-fluoro-D-glucose positron emission tomography for gastric cancer. *World J Surg.* 2004, 28 , 247-53. Epub 2004 Feb 17.
26. Ott, K, Fink U, Becker K, Stahl A, Dittler HJ, Busch R, Stein H, Lordick F, Link T, Schwaiger M, Siewert JR, Weber WA. Prediction of response to preoperative chemotherapy in gastric carcinoma by metabolic imaging: results of a prospective trial. *J Clin Oncol.* 2003, 21 , 4604-10.
27. Mochiki, E, Kuwano H, Katoh H, Asao T, Oriuchi N, Endo K. Evaluation of 18F-2-deoxy-2-fluoro-D-glucose positron emission tomography for gastric cancer. *World J Surg.* 2004, 28 , 247-53. Epub 2004 Feb 17.
28. De Potter, T, Flamen P, Van Cutsem E, Penninckx F, Filez L, Bormans G, Maes A, Mortelmans L. Whole-body PET with FDG for the diagnosis of recurrent gastric cancer. *Eur J Nucl Med Mol Imaging.* 2002, 29 , 525-9. Epub 2002 Feb 23.
29. Jadvar, H, Tatlidil R, Garcia AA, Conti PS. Evaluation of recurrent gastric malignancy with [F-18]-FDG positron emission tomography. *Clin Radiol.* 2003, 58 , 215-21.
30. Ohlsson, B, Palsson B. Follow-up after colorectal cancer surgery. *Acta Oncol.* 2003, 42 , 816-26.
31. Chen, YK, Kao CH, Liao AC, Shen YY, Su CT. Colorectal cancer screening in asymptomatic adults: the

role of FDG PET scan. *Anticancer Res.* 2003, 23 , 4357-61.

32. Abdel-Nabi, H, Doerr RJ, Lamonica DM, Cronin VR, Galantowicz PJ, Carbone GM, Spaulding MB. Staging of primary colorectal carcinomas with fluorine-18 fluorodeoxyglucose whole-body PET: correlation with histopathologic and CT findings. *Radiology.* 1998, 206 , 755-60.
33. Mukai, M, Sadahiro S, Yasuda S, Ishida H, Tokunaga N, Tajima T, Makuuchi H. Preoperative evaluation by whole-body 18F-fluorodeoxyglucose positron emission tomography in patients with primary colorectal cancer. *Oncol Rep.* 2000, 7 , 85-7.
34. Kantorova, I, Lipska L, Belohlavek O, Visokai V, Trubac M, Schneiderova M. Routine (18)F-FDG PET preoperative staging of colorectal cancer: comparison with conventional staging and its impact on treatment decision making. *J Nucl Med.* 2003, 44 , 1784-8.
35. Kievit, J. Follow-up of patients with colorectal cancer: numbers needed to test and treat. *Eur J Cancer.* 2002, 38 , 986-99.
36. Longo, WE, Johnson FE. The preoperative assessment and postoperative surveillance of patients with colon and rectal cancer. *Surg Clin North Am.* 2002, 82 , 1091-108.
37. August, DA, Ottow RT, Sugarbaker PH. Clinical perspective of human colorectal cancer metastasis. *Cancer Metastasis Rev.* 1984, 3 , 303-24.
38. Foster, JH, Lundy J. Liver Metastases. *Curr Probl Surg.* 1981, 18 , 157-202.
39. Holm, A, Bradley E, Aldrete JS. Hepatic resection of metastasis from colorectal carcinoma. Morbidity, mortality, and pattern of recurrence. *Ann Surg.* 1989, 209 , 428-34.
40. Hughes, KS, Rosenstein RB, Songhorabodi S, Adson MA, Ilstrup DM, Fortner JG, Maclean BJ, Foster JH, Daly JM, Fitzherbert D, et al. Resection of the liver for colorectal carcinoma metastases. A multi-institutional study of long-term survivors. *Dis Colon Rectum.* 1988, 31 , 1-4.
41. Moertel, CG, Fleming TR, Macdonald JS, Haller DG, Laurie JA, Tangen C. An evaluation of the carcinoembryonic antigen (CEA) test for monitoring patients with resected colon cancer. *Jama.* 1993, 270 , 943-7.
42. Chen, YM, Ott DJ, Wolfman NT, Gelfand DW, Karsteadt N, Bechtold RE. Recurrent colorectal carcinoma: evaluation with barium enema examination and CT. *Radiology.* 1987, 163 , 307-10.
43. Sugarbaker, PH, Gianola FJ, Dwyer A, Neuman NR. A simplified plan for follow-up of patients with colon and rectal cancer supported by prospective studies of laboratory and radiologic test results. *Surgery.* 1987, 102 , 79-87.
44. Steele, G, Jr., Bleday R, Mayer RJ, Lindblad A, Petrelli N, Weaver D. A prospective evaluation of hepatic resection for colorectal carcinoma metastases to the liver: Gastrointestinal Tumor Study Group Protocol 6584. *J Clin Oncol.* 1991, 9 , 1105-12.
45. Granfield, CA, Charnsangavej C, Dubrow RA, Varma DG, Curley SA, Whitley NO, Wallace S. Regional lymph node metastases in carcinoma of the left side of the colon and rectum: CT demonstration. *AJR Am J Roentgenol.* 1992, 159 , 757-61.
46. Charnsangavej, C, Whitley NO. Metastases to the pancreas and peripancreatic lymph nodes from

carcinoma of the right side of the colon: CT findings in 12 patients. *AJR Am J Roentgenol.* 1993, 160 , 49-52.

47. Falk, PM, Gupta NC, Thorson AG, Frick MP, Boman BM, Christensen MA, Blatchford GJ. Positron emission tomography for preoperative staging of colorectal carcinoma. *Dis Colon Rectum.* 1994, 37 , 153-6.

48. Ogunbiyi, OA, Flanagan FL, Dehdashti F, Siegel BA, Trask DD, Birnbaum EH, Fleshman JW, Read TE, Philpott GW, Kodner IJ. Detection of recurrent and metastatic colorectal cancer: comparison of positron emission tomography and computed tomography. *Ann Surg Oncol.* 1997, 4 , 613-20.

49. Flanagan, FL, Dehdashti F, Ogunbiyi OA, Kodner IJ, Siegel BA. Utility of FDG-PET for investigating unexplained plasma CEA elevation in patients with colorectal cancer. *Ann Surg.* 1998, 227 , 319-23.

50. Flamen, P, Stroobants S, Van Cutsem E, Dupont P, Bormans G, De Vadder N, Penninckx F, Van Hoe L, Mortelmans L. Additional value of whole-body positron emission tomography with fluorine-18-2-fluoro-2-deoxy-D-glucose in recurrent colorectal cancer. *J Clin Oncol.* 1999, 17 , 894-901.

51. Imdahl, A, Reinhardt MJ, Nitzsche EU, Mix M, Dingeldey A, Einert A, Baier P, Farthmann EH. Impact of 18F-FDG-positron emission tomography for decision making in colorectal cancer recurrences. *Langenbecks Arch Surg.* 2000, 385 , 129-34.

52. Kalff, VV, Hicks R, Ware R, Binns D, McKenzie A. 29. F-18 FDG PET for Suspected or Confirmed Regional Recurrence of Colon Cancer. A Prospective Study of Impact and Outcome. *Clin Positron Imaging.* 2000, 3 , 183.

53. Huebner, RH, Park KC, Shepherd JE, Schwimmer J, Czernin J, Phelps ME, Gambhir SS. A meta-analysis of the literature for whole-body FDG PET detection of recurrent colorectal cancer. *J Nucl Med.* 2000, 41 , 1177-89.

54. Schiepers, C, Penninckx F, De Vadder N, Merckx E, Mortelmans L, Bormans G, Marchal G, Filez L, Aerts R. Contribution of PET in the diagnosis of recurrent colorectal cancer: comparison with conventional imaging. *Eur J Surg Oncol.* 1995, 21 , 517-22.

55. Vitola, JV, Delbeke D, Sandler MP, Campbell MG, Powers TA, Wright JK, Chapman WC, Pinson CW. Positron emission tomography to stage suspected metastatic colorectal carcinoma to the liver. *Am J Surg.* 1996, 171 , 21-6.

56. Delbeke, D, Vitola JV, Sandler MP, Arildsen RC, Powers TA, Wright JK, Jr., Chapman WC, Pinson CW. Staging recurrent metastatic colorectal carcinoma with PET. *J Nucl Med.* 1997, 38 , 1196-201.

57. Kinkel, K, Lu Y, Both M, Warren RS, Thoeni RF. Detection of hepatic metastases from cancers of the gastrointestinal tract by using noninvasive imaging methods (US, CT, MR imaging, PET): a meta-analysis. *Radiology.* 2002, 224 , 748-56.

58. Gambhir, SS, Czernin J, Schwimmer J, Silverman DH, Coleman RE, Phelps ME. A tabulated summary of the FDG PET literature. *J Nucl Med.* 2001, 42 , 1S-93S.

59. Libutti, SK, Alexander HR, Jr., Choyke P, Bartlett DL, Bacharach SL, Whatley M, Jousse F, Eckelman WC, Kranda K, Neumann RD, Carrasquillo JA. A prospective study of 2-[18F] fluoro-2-deoxy-D-glucose/positron emission tomography scan, 99mTc-

labeled arcitumomab (CEA-scan), and blind second-look laparotomy for detecting colon cancer recurrence in patients with increasing carcinoembryonic antigen levels. *Ann Surg Oncol.* 2001, 8 , 779-86.

60. Whiteford, MH, Whiteford HM, Yee LF, Ogunbiyi OA, Dehdashti F, Siegel BA, Birnbaum EH, Fleshman JW, Kodner IJ, Read TE. Usefulness of FDG-PET scan in the assessment of suspected metastatic or recurrent adenocarcinoma of the colon and rectum. *Dis Colon Rectum.* 2000, 43 , 759-67; discussion 767-70.
61. Berger, KL, Nicholson SA, Dehdashti F, Siegel BA. FDG PET evaluation of mucinous neoplasms: correlation of FDG uptake with histopathologic features. *AJR Am J Roentgenol.* 2000, 174 , 1005-8.
62. Beets, G, Penninckx F, Schiepers C, Filez L, Mortelmans L, Kerremans R, Aerts R, De Roo M. Clinical value of whole-body positron emission tomography with [18F]fluorodeoxyglucose in recurrent colorectal cancer. *Br J Surg.* 1994, 81 , 1666-70.
63. Strauss, LG, Clorius JH, Schlag P, Lehner B, Kimmig B, Engenhart R, Marin-Grez M, Helus F, Oberdorfer F, Schmidlin P, et al. Recurrence of colorectal tumors: PET evaluation. *Radiology.* 1989, 170 , 329-32.
64. Bertino, JR. Biomodulation of 5-fluorouracil with antifolates. *Semin Oncol.* 1997, 24 , S18-52-S18-56.
65. Haberkorn, U, Strauss LG, Dimitrakopoulou A, Engenhart R, Oberdorfer F, Ostertag H, Romahn J, van Kaick G. PET studies of fluorodeoxyglucose metabolism in patients with recurrent colorectal tumors receiving radiotherapy. *J Nucl Med.* 1991, 32 , 1485-90.
66. Moore, HG, Akhurst T, Larson SM, Minsky BD, Mazumdar M, Guillem JG. A case-controlled study of 18-fluorodeoxyglucose positron emission tomography in the detection of pelvic recurrence in previously irradiated rectal cancer patients. *J Am Coll Surg.* 2003, 197 , 22-8.
67. Guillem, JG, Puig-La Calle J, Jr., Akhurst T, Tickoo S, Ruo L, Minsky BD, Gollub MJ, Klimstra DS, Mazumdar M, Paty PB, Macapinlac H, Yeung H, Saltz L, Finn RD, Erdi Y, Humm J, Cohen AM, Larson S. Prospective assessment of primary rectal cancer response to preoperative radiation and chemotherapy using 18-fluorodeoxyglucose positron emission tomography. *Dis Colon Rectum.* 2000, 43 , 18-24.
68. Guillem, JG, Moore HG, Akhurst T, Klimstra DS, Ruo L, Mazumdar M, Minsky BD, Saltz L, Wong WD, Larson S. Sequential preoperative fluorodeoxyglucose-positron emission tomography assessment of response to preoperative chemoradiation: a means for determining longterm outcomes of rectal cancer. *J Am Coll Surg.* 2004, 199 , 1-7.
69. Amthauer, H, Denecke T, Rau B, Hildebrandt B, Hunerbein M, Ruf J, Schneider U, Gutberlet M, Schlag PM, Felix R, Wust P. Response prediction by FDG-PET after neoadjuvant radiochemotherapy and combined regional hyperthermia of rectal cancer: correlation with endorectal ultrasound and histopathology. *Eur J Nucl Med Mol Imaging.* 2004, 31 , 811-9. Epub 2004 Feb 5.
70. Calvo, FA, Domper M, Matute R, Martinez-Lazaro R, Arranz JA, Desco M, Alvarez E, Carreras JL. 18F-FDG positron emission tomography staging and restaging in rectal cancer treated with preoperative chemoradiation. *Int*

J Radiat Oncol Biol Phys. 2004, 58 , 528-35.

71. Liu, LX, Zhang WH, Jiang HC. Current treatment for liver metastases from colorectal cancer. *World J Gastroenterol.* 2003, 9 , 193-200.

72. Findlay, M, Young H, Cunningham D, Iveson A, Cronin B, Hickish T, Pratt B, Husband J, Flower M, Ott R. Noninvasive monitoring of tumor metabolism using fluorodeoxyglucose and positron emission tomography in colorectal cancer liver metastases: correlation with tumor response to fluorouracil. *J Clin Oncol.* 1996, 14 , 700-8.

73. Langenhoff, BS, Oyen WJ, Jager GJ, Strijk SP, Wobbes T, Corstens FH, Ruers TJ. Efficacy of fluorine-18-deoxyglucose positron emission tomography in detecting tumor recurrence after local ablative therapy for liver metastases: a prospective study. *J Clin Oncol.* 2002, 20 , 4453-8.

74. Staib, L, Schirrmeister H, Reske SN, Beger HG. Is (18)F-fluorodeoxyglucose positron emission tomography in recurrent colorectal cancer a contribution to surgical decision making? *Am J Surg.* 2000, 180 , 1-5.

75. Strasberg, SM, Dehdashti F, Siegel BA, Drebin JA, Linehan D. Survival of patients evaluated by FDG-PET before hepatic resection for metastatic colorectal carcinoma: a prospective database study. *Ann Surg.* 2001, 233 , 293-9.

76. Ruers, TJ, Langenhoff BS, Neeleman N, Jager GJ, Strijk S, Wobbes T, Corstens FH, Oyen WJ. Value of positron emission tomography with [F-18]fluorodeoxyglucose in patients with colorectal liver metastases: a prospective study. *J Clin Oncol.* 2002, 20 , 388-95.

77. Meta, J, Seltzer M, Schiepers C, Silverman DH, Ariannejad M, Gambhir SS, Phelps ME, Valk P, Czernin J. Impact of 18F-FDG PET on managing patients with colorectal cancer: the referring physician's perspective. *J Nucl Med.* 2001, 42 , 586-90.

78. Kalff, V, Hicks RJ, Ware RE, Hogg A, Binns D, McKenzie AF. The clinical impact of (18)F-FDG PET in patients with suspected or confirmed recurrence of colorectal cancer: a prospective study. *J Nucl Med.* 2002, 43 , 492-9.

79. Arulampalam, T, Costa D, Visvikis D, Boulos P, Taylor I, Ell P. The impact of FDG-PET on the management algorithm for recurrent colorectal cancer. *Eur J Nucl Med.* 2001, 28 , 1758-65. Epub 2001 Oct 20.

80. Simo, M, Lomena F, Setoain J, Perez G, Castellucci P, Costansa JM, Setoain-Quinquer J, Domenech-Torne F, Carrio I. FDG-PET improves the management of patients with suspected recurrence of colorectal cancer. *Nucl Med Commun.* 2002, 23 , 975-82.

81. Desai, DC, Zervos EE, Arnold MW, Burak WE, Jr., Mantil J, Martin EW, Jr. Positron emission tomography affects surgical management in recurrent colorectal cancer patients. *Ann Surg Oncol.* 2003, 10 , 59-64.

82. Fernandez, FG, Drebin JA, Linehan DC, Dehdashti F, Siegel BA, Strasberg SM. Five-year survival after resection of hepatic metastases from colorectal cancer in patients screened by positron emission tomography with F-18 fluorodeoxyglucose (FDG-PET). *Ann Surg.* 2004, 240 , 438-47; discussion 447-50.

83. Cohade, C, Osman M, Leal J, Wahl RL. Direct comparison of (18)F-FDG PET and PET/CT in patients with

colorectal carcinoma. *J Nucl Med.* 2003, 44 , 1797-803.

84. Bar-Shalom, R, Guralnik L, Tsalic M, Leiderman M, Frenkel A, Gaitini D, Ben-Nun A, Keidar Z, Israel O. The additional value of PET/CT over PET in FDG imaging of oesophageal cancer. *Eur J Nucl Med Mol Imaging.* 2005, 32 , 918-24. Epub 2005 Apr 19.

85. Selzner, M, Hany TF, Wildbrett P, McCormack L, Kadry Z, Clavien PA. Does the novel PET/CT imaging modality impact on the treatment of patients with metastatic colorectal cancer of the liver? *Ann Surg.* 2004, 240 , 1027-34; discussion 1035-6.

86. Even-Sapir, E, Parag Y, Lerman H, Gutman M, Levine C, Rabau M, Figer A, Metser U. Detection of recurrence in patients with rectal cancer: PET/CT after abdominoperineal or anterior resection. *Radiology.* 2004, 232 , 815-22. Epub 2004 Jul 23.

87. Yuan, S, Yu Y, Chao KS, Fu Z, Yin Y, Liu T, Chen S, Yang X, Yang G, Guo H, Yu J. Additional value of PET/CT over PET in assessment of locoregional lymph nodes in thoracic esophageal squamous cell cancer. *J Nucl Med.* 2006, 47 , 1255-9.

88. Guo, H, Zhu H, Xi Y, Zhang B, Li L, Huang Y, Zhang J, Fu Z, Yang G, Yuan S, Yu J. Diagnostic and prognostic value of 18F-FDG PET/CT for patients with suspected recurrence from squamous cell carcinoma of the esophagus. *J Nucl Med.* 2007, 48 , 1251-8. Epub 2007 Jul 13.

89. Pan, T, Mawlawi O, Nehmeh SA, Erdi YE, Luo D, Liu HH, Castillo R, Mohan R, Liao Z, Macapinlac HA.

Attenuation correction of PET images with respiration-averaged CT images in PET/CT. *J Nucl Med.* 2005, 46 , 1481-7.

90. Tatlidil, R, Jadvar H, Bading JR, Conti PS. Incidental colonic fluorodeoxyglucose uptake: correlation with colonoscopic and histopathologic findings. *Radiology.* 2002, 224 , 783-7.

91. Agress, H, Jr., Cooper BZ. Detection of clinically unexpected malignant and premalignant tumors with whole-body FDG PET: histopathologic comparison. *Radiology.* 2004, 230 , 417-22. Epub 2003 Dec 29.

92. Kubota, R, Yamada S, Kubota K, Ishiwata K, Tamahashi N, Ido T. Intratumoral distribution of fluorine-18-fluorodeoxyglucose in vivo: high accumulation in macrophages and granulation tissues studied by microautoradiography. *J Nucl Med.* 1992, 33 , 1972-80.

93. Francis, DL, Freeman A, Visvikis D, Costa DC, Luthra SK, Novelli M, Taylor I, Ell PJ. In vivo imaging of cellular proliferation in colorectal cancer using positron emission tomography. *Gut.* 2003, 52 , 1602-6.

94. Francis, DL, Visvikis D, Costa DC, Arulampalam TH, Townsend C, Luthra SK, Taylor I, Ell PJ. Potential impact of [18F]3'-deoxy-3'-fluorothymidine versus [18F]fluoro-2-deoxy-D-glucose in positron emission tomography for colorectal cancer. *Eur J Nucl Med Mol Imaging.* 2003, 30 , 988-94. Epub 2003 May 9.