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REVIEW

Role of (^{18}F) 2-fluoro-2-deoxyglucose positron emission tomography in upper gastrointestinal malignancies

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Abstract

The role of whole-body FDG [(^{18}F) 2-fluoro-2-deoxyglucose] positron emission tomography (PET) scanning as an imaging modality in the management of patients with malignancy has evolved enormously over the past two decades. FDG-PET has demonstrated significant efficacy in the staging, prognostication and detection of occult metastatic disease in malignancies of the gastrointestinal tract, in addition to assessment of the response to cytotoxic chemotherapy in a more timely manner than has traditionally been possible by more conventional imaging tools. The sensitivity and specificity of FDG-PET for the detection and staging of malignancy depend not only on the site and size of the primary tumor and metastases, but also on histological cell type, reflecting underlying disparities in glucose metabolism. The metabolic response to neo-adjuvant chemotherapy or to chemo-radiotherapy in cancers of the gastro-esophageal junction or stomach has been demonstrated in several prospective studies to correlate significantly with both the histological tumor response to treatment and with consequent improvements in overall survival. This may offer a future paradigm of personalized treatment based on the PET response to chemotherapy. FDG-PET has been less successful in efforts to screen for and detect recurrent upper gastrointestinal malignancies, and in the detection of low volume metastatic peritoneal disease. Efforts to improve the accuracy of PET include the use of novel radiotracers such as (^{18}F) FLT (3-deoxy-3-fluorothymidine) or ^{11}C-choline, or fusion PET-CT with concurrent high-resolution computed tomography. This review focuses on the role of FDG-PET scanning in staging and response assessment in malignancies of the upper gastrointestinal tract, specifically gastric, esophageal and pancreas carcinoma.

Key words: Positron emission tomography; Gastric cancer; Esophageal cancer; Pancreas cancer

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INTRODUCTION

Whole-body positron emission tomography (PET) scanning after the administration of (^{18}F) 2-fluoro-2-deoxyglucose (FDG) has emerged as a promising new imaging modality in the management of patients with malignancy. The role of FDG-PET scanning in upper gastrointestinal (GI) malignancies has evolved tremendously over the past two decades. Like most imaging modalities, FDG-PET initially made its mark in staging for preoperative risk assessment, prognostication, and in evaluation of

distant metastatic disease. FDG-PET scanning has also improved our ability to identify occult metastatic disease in a number of malignancies, including malignancies of the upper GI tract. When considering glucose uptake as a surrogate for metabolic activity, another important application of FDG-PET scanning is therapeutic response assessment. Traditional computed tomography (CT) scanning has been the mainstay for assessment of the effectiveness of cytotoxic therapy in solid tumor oncology; however with the advent of FDG-PET, it has been increasingly apparent that this new modality may also provide an assessment of the therapeutic effectiveness of cytotoxic therapy, and possibly at an earlier time point.

This review focuses on the role of FDG-PET scanning in staging and therapeutic response assessment in malignancies of the upper GI tract, specifically gastric and esophageal carcinoma.

SCIENCE OF FDG-PET AND CHANGES IN FDG UPTAKE

FDG uptake is considered as a surrogate for the metabolic activity of a malignancy, specifically linked to glucose metabolism in malignant cells[1]. The role of FDG-PET imaging, in fact, may be related to the Warburg effect-the observation made by Otto Warburg in 1924 that suggested that cancer cells metabolize glucose differently from normal non-malignant cells[2]. Specifically, cancer cells tend to grow and metabolize nutrients independent of growth factor stimulus, but not in the most efficient manner for ATP generation, but rather in a manner that would support the acquisition of building blocks for continued, uncontrolled cell division and growth[2]. Central to this hypothesis is dysfunction of the phosphoinositide 3-kinase signaling pathway, commonly identified as pathologic in a majority of malignancies, and which is central to both growth control and glucose metabolism. A change in glucose metabolism, as identified by FDG-PET serial imaging, may therefore uniquely predict subsequent cell death[1].

Glucose uptake by malignant cells is largely mediated by the GLUT-1 transporter[3]. In a study of 60 patients with squamous cell carcinoma of the esophagus, Hiyoshi *et al*[4] demonstrated that GLUT-1 expression was correlated with the depth of tumor, lymph node metastasis and pathological stage, in addition to FDG avidity on PET imaging. Mu *et al*[5] correlated the standardized uptake value (SUV) with the expression of GLUT-1 and the Ki-67 proliferative marker, and found that with increasing clinical stage and pathological dedifferentiation, the expression of both markers increased concurrently, indicating an association with tumor aggressiveness. Tohma *et al*[6] demonstrated that FDG uptake may have a more significant association with the intracellular enzyme hexokinase-2 expression than with GLUT-1 expression. In contrast, FDG uptake is not associated with cyclin D1, p53, epidermal growth factor receptor or vascular endothelial growth factor expression in esophageal tumors[7].

ESOPHAGEAL CARCINOMA

Role of PET in staging the depth of disease-esophageal carcinoma

Clinical significance of T stage: Penetration of the primary tumor through successive layers of the walls of the esophagus is described using the T stage of the tumor. Deeper levels of mucosal involvement are associated with a higher risk of nodal and distant metastasis, and diminishing overall survival. The location of the primary tumor within the esophagus has particular relevance to the draining lymph node stations for that area. Nodal metastasis beyond the locoregional nodes may render the patient unresectable as a result. Early cancers (T2 or less) may undergo primary surgical resection. Those tumors with T3 or greater depth of penetration may undergo preoperative chemotherapy or chemoradiotherapy with a view to future resection, or definitive combined modality therapy.

FDG-PET and T stage

In an initial study of FDG-PET in the assessment of esophageal cancer by Flamen *et al*[8], FDG-PET detected 70 out of 74 esophageal lesions. It failed to detect 4 small (< 8 mm) T1 lesions. This study demonstrated no correlation between the SUV and the T stage. A retrospective series from Japan similarly demonstrated superior sensitivity of PET for the detection of T2 or greater disease; 25/25 patients with T2 or greater tumors had FDG uptake, compared to 0/7 with T1 tumors. Significant correlations with increased SUV uptake were seen with both the size of the primary and with the depth of tumor invasion[9].

In a prospective series of 81 patients who underwent surgery with no preoperative treatment, PET detected the primary lesion in 43% of pT1 tumors. Sensitivity was significantly better for pT1b disease at 61%, compared with 18% for pT1a. PET positivity increased with increasing levels of tumor invasion, being 83% at T2, 97% at T3 and 100% at T4[10]. Importantly, in another study examining patients with early stage tumors who underwent primary surgical treatment, PET-CT could not distinguish between those with carcinoma *in situ* (Tis) *vs* those with T1 disease, with FDG uptake in 5/11 (45%) and 26/47 (55%) respectively. The investigators noted a trend towards both increased frequency of FDG uptake and increased SUV with increasing depth of invasion.

It may be concluded from this data that PET, and indeed PET-CT, is an inadequate modality for assessing depth of tumor penetration within the mucosal wall of the esophagus, and also that it cannot distinguish adequately between carcinoma *in situ* and invasive disease. However, with increasing depth of invasion, an FDG-PET scan is increasingly likely to identify the malignancy.

In addition, FDG avidity on FDG-PET scans should be taken in context due to the small but real rate of false positive scans. Specifically, areas of increased FDG uptake within the esophagus may have an alternate cause such as chemotherapy or radiation-induced esophagitis, candida or other benign causes[11-14]. PET lacks the specificity to differentiate between these conditions, under-

Table 1 Prospective studies comparing the accuracy of positron emission tomography with computed tomography and/or endo-ultrasonography for the detection of lymph-node metastases

Ref.	Yr	Histology	*n*	Imaging	Sensitivity (%)	Specificity (%)
Flamen *et al*[114]	2000	SCC/AC	74	PET	39	97
				CT	63	88
				EUS	22	96
				EUS/CT	54	90
Lerut *et al*[115]	2000	SCC/AC	42	PET	22	91
				CT/EUS	83	45
Yoon *et al*[116]	2003	SCC	81	PET	30	90
				CT	11	95
Sihvo *et al*[18]	2004	AC	55	PET	35	91
				CT	42	45
				EUS	85	60
Lowe *et al*[19]	2005	SCC/AC	75	PET	82	60
				CT	84	67
				EUS	86	67
Shimizu *et al*[20]	2009	SCC	20	PET-CT	11-50	85-100
				Thin slice CT	22-100	69-100

PET: Positron emission tomography; CT: Computed tomography; EUS: Endoscopic ultrasound; SCC: Squamous cell carcinoma; AC: Adenocarcinoma.

scoring the inadequacy of this approach. Due to these factors, endoscopic ultrasound (EUS) is the preferred method for assessment of the depth of invasion of the primary tumor through the wall of the esophagus. This has been demonstrated in a meta-analysis of 49 studies to have a sensitivity of 81%-90% for T staging and a specificity of 99%[15]. EUS is limited by inability to pass through stenotic tumors in these cases, PET or PET-CT based imaging may serve as a useful adjunct.

Role of PET in staging nodal disease-esophageal cancer

Clinical significance of nodal stage: Nodal status in esophageal cancer is determined by the presence or absence of involved locoregional lymph nodes. The regional designation of a lymph node relates to its anatomical relationship to the primary tumor. Tumors of the upper third of the esophagus drain to superior mediastinal and cervical lymph nodes. Tumors of the middle third drain both superiorly and inferiorly to paratracheal, hilar, subcarinal, periesophageal, and pericardial lymph node stations. Tumors of the lower third of the esophagus drain to lymph node basins in the lower mediastinum and celiac areas Patients with non-regional lymph node spread have a worse prognosis than those with locoregional spread only, but better than those with distant metastases.

Initial reports of PET showed promise due to apparent increased sensitivity in the detection of lymph node metastasis when compared to CT[16]. However this may have been due to the use of outdated CT technology and techniques, and this initial promise with respect to increased sensitivity has not been sustained in well designed prospective studies.

In an initial report, Flamen *et al*[8] reported that 74 patients demonstrated a lower sensitivity of PET for the detection of regional lymph node metastasis when compared to EUS (81% *vs* 33%) but with a non-significant trend towards higher specificity (84% *vs* 69%). PET showed a higher specificity than CT and EUS combined when staging both regional and non-regional lymph node metastases for esophageal cancer. In a prospective study of 58 patients comparing CT and PET in the detection of lymph node metastasis within the abdomen by Kneist *et al*[17], the investigators observed a sensitivity of only 24% for PET compared to 73% for CT. Sensitivity of PET was significantly less in the area of the lesser curvature and the celiac trunk. Specificity was 75% and 95%, respectively. Within the thorax, PET demonstrated an improved but still inferior sensitivity (42% *vs* 75%) and again a superior specificity to CT. A prospective evaluation of CT, EUS and PET by Sihvo *et al*[18] demonstrated that EUS had a higher sensitivity for the detection of nodal disease (85%) than CT or PET (42% and 35%). The combination of CT, EUS and PET did not appreciably increase the sensitivity of the assessment. Neither was there any synergy between modalities with respect to specificity. A 2005 study performed by Lowe *et al*[19] comparing CT, PET and EUS for the staging of esophageal cancer showed comparable sensitivities between the three modalities for the detection of nodal disease (82%-86%). Specificity was also not significantly different at 67% for CT and EUS, and 60% for PET.

Progress in the development of both CT and PET imaging may lead to improvements in the diagnostic accuracy of both modalities. A recent study comparing thin slice CT to PET-CT in the detection of subclinical lymph node metastasis in patients with operable squamous cell carcinoma demonstrated the superiority of CT for the detection of disease at all lymph node stations, with the caveat that sensitivity appeared to decrease from the cervical area (100%) to the abdominal area (22%). Specificity was high for both CT and PET in the cervical and abdominal lymph node basins, with superior specificity for PET demonstrated only within the mediastinum[20].

The results of the above studies are described in Table 1. In order to better characterize these heterogenous results, a meta-analysis was performed by van Westreenan *et al*[50]. This included both prospectively and retrospectively obtained data. Pooled sensitivity for the detection of locoregional lymph node metastases was 51% (range, 8%-92%) with pooled specificity of 84% (range, 67%-100%)[21]. The low sensitivity of PET in prospective studies may be due to a selection bias in many cases. These results may be biased by the inclusion only of apparently early stage patients who proceeded immediately to surgery. Those who required preoperative chemotherapy and/or radiation were excluded, leading to an over-representation of solely micrometastatic foci, which are less reliably detected. For reasons of this relatively low sensitivity of PET for locoregional disease, and due to its excellent specificity, FDG-PET is better as an adjunct to conventional

Table 2 Prospective studies comparing the accuracy of positron emission tomography with computed tomography and/or endo-ultrasonography in the detection of distant metastases

Ref.	Yr	Histology	*n*	Imaging	Sensitivity (%)	Specificity (%)
Flamen *et al*[8]	2000	SCC/AC	74	PET	71	90
				CT	41	83
				EUS	42	94
				EUS/CT	47	78
Lerut *et al*[115]	2000	SCC/AC	42	PET	77	90
				CT/EUS	46	69
Sihvo *et al*[18]	2004	SCC	81	PET	35	91
				CT	42	45
Heeren *et al*[25]	2004	SC/AC	74	PET	71	98
				CT	21	98
				CT/EUS	29	96
Lowe *et al*[19]	2005	SCC/AC	75	PET	81	91
				CT	81	82
				EUS	73	76

PET: Positron emission tomography; CT: Computed tomography; EUS: Endoscopic ultrasound; SCC: Squamous cell carcinoma; AC: Adenocarcinoma.

imaging modalities for the detection of lymph node metastases rather than a comprehensive staging investigation in its own right.

Efforts to improve accuracy of PET in the detection of lymph node metastasis

The limited spatial resolution of PET may lead to difficulties due to the fact that uptake within lymph nodes close to the primary tumor may be difficult to distinguish from the tumor itself. Fusion PET-CT and correlation with metabolic and tumor-related parameters may offer superior sensitivity for the detection of nodal disease. A 2009 study by Roedl *et al*[22] compared fusion PET-CT with PET viewed side by side with CT images, in addition to axial tumor area, tumor width diameter and SUV uptake. Fusion PET-CT was more sensitive and more specific for the detection of lymph node metastasis at 70% *vs* 62% and 95% *vs* 91%, respectively. Sensitivity and specificity of 87% and 85% were increased by the addition of tumor diameter measurements. However when qualitative visual analysis was added to quantitative tumor dimension measurement in addition to PET-CT the sensitivity was 96% and the specificity 95%.

Dual time PET may assist in the differentiation between benign and malignant lesions, and may also improve the accuracy of detection of lymph node metastasis in esophageal cancer. Small malignant lesions and malignant lymph nodes show an increase in SUV uptake over time, whereas benign disease does not, and shows an early peak only. An improvement in diagnostic accuracy from 83% to 91% was seen with dual time imaging of squamous cell carcinomas of the thoracic esophagus. In addition, false positive uptake in the lung hilum due to inflammatory processes was distinguished from malignant disease in 19/42 (45%) of patients using this method[23].

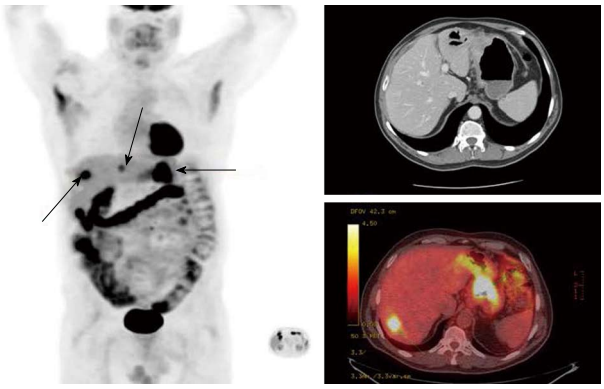

Figure 1 (^{18}F) 2-fluoro-2-deoxyglucose-positron emission tomography/computed tomography image of a patient with a proximal gastric cancer and occult liver metastasis. The liver lesion was not identified on the corresponding staging computed tomography.

DETECTION OF METASTATIC ESOPHAGEAL CANCER USING FDG-PET

PET finds a niche in the detection of metastatic disease, where its performance is superior than in the detection of the depth of the primary lesion or of locoregional lymph node involvement of esophageal carcinoma (Table 2).

An initial prospective study by Luketich *et al*[24] demonstrated a sensitivity of PET for detection of metastatic disease of 69% with a specificity of 93.4% and an overall accuracy of 84%. Following this, Flamen *et al*[8] demonstrated that FDG-PET had a superior accuracy for the detection of metastatic disease compared to combined CT and EUS (82% *vs* 64%), largely driven by the higher sensitivity of PET (74% *vs* 47%). PET correctly upstaged 15% of patients from M0 to M1 disease. The study by Lowe *et al*[19] demonstrated similar sensitivity of PET and CT at 81%, and superior specificity for PET. This may relate to improvements in CT scanning techniques in recent years.

A 2004 study by Heeren *et al*[25] demonstrated that PET upstaged up to 20% of patient to M1 disease. The accuracy of CT was 86% compared to CT/EUS at 69%. All three modalities combined provided an accuracy of 92%. In this study 13% of patients in whom M1 disease was detected on PET were spared an unnecessary surgical procedure, however 87% did require laparoscopy to confirm PET positive findings underscoring the importance of cytological confirmation of metastatic disease. In a combined analysis of 452 patients from 11 studies the pooled sensitivity and specificity for the detection of metastatic disease by PET was 67% (95% confidence interval (CI): 58%-76%) and 97% (90%-100%) respectively. Figures 1 and 2 demonstrate the detection of occult liver (Figure 1) and bone (Figure 2) metastases by FDG-PET/CT not seen on conventional CT imaging.

IS PET PREDICTIVE OF SURVIVAL IN ESOPHAGEAL CANCER?

Many studies have examined the relationship between

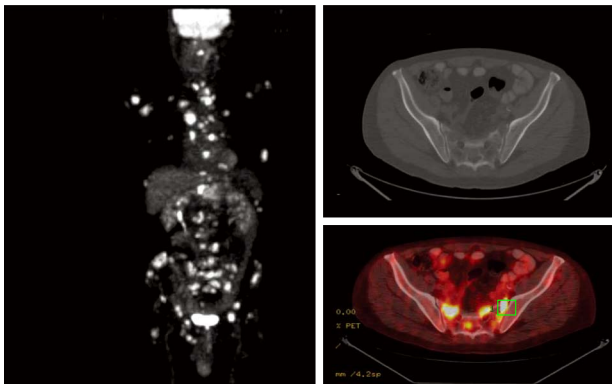

Figure 2 (^{18}F) 2-fluoro-2-deoxyglucose-positron emission tomography/computed tomography detects diffuse bony metastases not seen on staging computed tomography.

SUVmax and survival. In a recent systematic review, all 12 studies selected for inclusion demonstrated that a higher SUVmax of the primary tumor was associated with inferior survival, however only seven of these reached statistical significance. In a meta-analysis of disease-free and overall survival, the hazard ratios for disease recurrence and death were 2.52 and 1.86, respectively, for those with a higher than median SUV[26]. This correlation with peak SUV and survival may hold true even for those with apparently early stage disease[27].

SUVmax is also often significantly correlated with pathological stage, acting as a potential confounder. On multivariate analysis in several smaller studies, peak SUV was significantly associated with survival in univariate but not multivariate analysis, and thus did not emerge as an independent risk factor[28,29]. However in a large retrospective study of 184 patients with operable esophageal cancer, where SUVmax was significantly correlated with the stage of the primary tumor, lymph node status, and presence of metastasis in univariate analysis, on multivariate analysis SUV remained independently and significantly associated with overall survival when correcting for pathological stage of disease. The 5-year overall survival for those with an SUVmax $\geqslant$ 4.5 was 47% compared to 76% in those with an SUV $\leqslant$ 4.5[30]. It should be noted that the majority (91%) of patients in this study had a diagnosis of squamous cell carcinoma, and that these results contrast sharply with those published by Rizk *et al*[31] in a retrospective series of 189 patients with adenocarcinoma of the distal esophagus or gastro-esophageal (GE) junction who underwent chemoradiation as a primary treatment, in which they failed to show any association between survival for those with a high or a low SUVmax. Those with a high SUVmax did however show a superior response to chemoradiation This led the authors to conclude that although high SUVmax was correlated with inferior survival following resection in their earlier study, because high baseline SUVmax was also associated with a superior response to chemoradiation, this acted as an equalizing factor with respect to survival.

Altogether, these data suggest that high SUVmax is most likely to be associated with increased tumor stage and size of lesion. Whether SUVmax is an independent predictor of patient outcome (specifically independent of tumor stage) is not sufficiently validated.

ROLE OF FDG-PET IN RADIOTHERAPY TREATMENT PLANNING FOR ESOPHAGEAL CANCER

The gross tumor volume (GTV) must be accurately delineated in order to successfully treat the area of malignancy. However, conventional CT scanning has a low discriminatory value for this purpose. FDG-PET has been investigated in order to assess whether this improves the accuracy of this delineation. Excellent correlation has been demonstrated between preoperative FDG-PET and EUS measurements of tumor length and measurements of the same resected surgical specimen[32]. The addition of FDG-PET to conventional CT planning may lead to increases or reductions in the GTV of up to 20%, and changes in the planning target volume in over half of patients[33,34]. Modifications of GTV are most often seen in the longitudinal direction[35], however this may also change based on detection of suspicious lymphadenopathy outside the original planned treatment field[36]. Improved accuracy in GTV delineation may lead to changes in radiation dose intensity to critical structures such as the heart and lungs[33,37], whereas utilization of CT alone may lead to undertreatment of FDG-PET avid disease[34]. However, due to a lack of standardization of FDG-PET assessments of GTV and the presence of significant interobserver variation, the use of FDG-PET is not routine in radiotherapy treatment planning, nor has this been validated in terms of improved outcomes such as survival or locoregional tumor control. A prospective trial is ongoing in this regard (NCT01156831)[38].

DOES SUV PREDICT RESPONSE TO CHEMORADIOTHERAPY?

Several studies have examined whether the change in SUV of the primary tumor with chemotherapy or chemoradiotherapy is useful in determining the response to the intervening therapy. A large proportion of studies have been prospective, but were limited in their scope of analysis to some extent by small numbers. Each study evaluated a different treatment regimen. Most studies used pathological response as the gold standard for evaluation of chemotherapy efficacy. This is commonly measured using the Mandard system[39] or a simple modification of this system, where pathological response is classified according to the percentage of viable tumor cells remaining, with non-responders having > 10% tumor cells remaining, partial response 0%-10%, and complete responders 0% viable tumor cells.

A first prospective study in 2001 by Weber *et al*[40] of

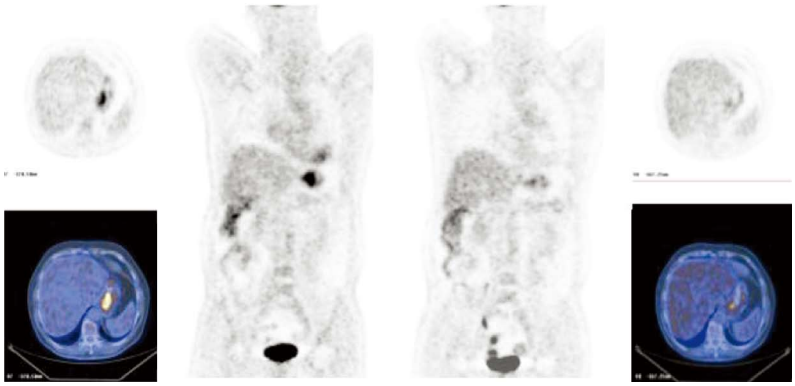

Figure 3 (^{18}F) 2-fluoro-2-deoxyglucose-positron emission tomography response in a patient with a proximal gastric cancer receiving chemotherapy.

40 patients with adenocarcinoma of the GE junction and gastric cardia demonstrated a median reduction in SUV of responders of more than three times that of non-responders and was significantly correlated with pathological response ($P < 0.001$). Response was also significantly associated with survival. Those with no response had a 2-year survival of 37% *vs* 60% in responders. Figure 3 demonstrates a sample FDG-PET/CT response for a patient with a proximal gastric adenocarcinoma.

A prospective trial by Ott *et al*[41] used a predetermined level of reduction in SUV to determine the cut-off point for metabolic responder *vs* non-responder. This had been previously determined to be a reduction of 35% from baseline, which had been demonstrated to have a sensitivity and specificity of 93% and 95%, respectively, for the detection of a pathological response[40]. Sixty five patients with locally advanced GE junction tumors undergoing preoperative chemotherapy were enrolled. Baseline tumor FDG uptake was 8.1 ± 3.4 SUV for assessable patients. SUV uptake significantly decreased to 5.4 ± 2.0 (approximately 33%) in the follow-up scan. Eighteen patients were classified as metabolic responders and 38 as metabolic nonresponders. The pathological response was highly significantly correlated with the metabolic response ($P < 0.001$); 44% of patients with a metabolic response had a pathological response, compared to 5% of metabolic non-responders. Median overall survival for non-responders was 18 mo, significantly shorter than overall survival for the group as a whole at 32 mo. Median survival for metabolic responders had not yet been reached at the time of publication.

A similar study was performed at Memorial Sloan Kettering Cancer Center as a validation study, and reported in abstract form in 2007[42]. In this study, patients with locally advanced but resectable gastric/GE junction adenocarcinoma received preoperative chemotherapy with irinotecan and cisplatin for two cycles. An FDG-PET CT scan was performed at baseline and again at day 15 and day 35. This study confirmed the results initially reported by Weber *et al*, demonstrating that a significant drop in SUV from baseline was associated with the pathologic response to therapy as well as with patient survival[42].

The primary utility of a change in FDG-PET SUV from baseline as a marker for response to chemotherapy and subsequently survival is that this information is available early in the treatment plan, and thus could potentially be used in order to guide future management. This approach was taken by Lordick *et al*[43] in the MUNICON trial. This study recruited 119 patients with locally advanced tumors of the GE junction undergoing preoperative chemotherapy. Patients who did not meet a predefined metabolic response level on FDG-PET of a 35% reduction from baseline SUVmax 2 wk after commencing treatment did not continue with chemotherapy but proceeded directly to surgery. Metabolic responders completed the course of preoperative chemotherapy and then proceeded to surgery; 49% of patients were metabolic responders and 51% were metabolic non-responders. Of the metabolic responders, 58% achieved a major histological response, with 0% in the non-responders. R0 surgical resection was possible in 96% of metabolic responders and in 74% of metabolic non-responders. On pathologic assessment, metabolic responders demonstrated earlier stage tumors than metabolic non-responders. Metabolic non-responders had a median event-free survival of 14.1 mo compared to 29.7 mo in metabolic responders. It was noted that metabolic responders who did not have a pathological response had survival comparable to those who were metabolic non-responders, implying that a metabolic response was necessary but not sufficient for improved survival[43].

In a cross trial comparison between the original study by Ott *et al*, where chemotherapy was continued despite a metabolic non-response, and MUNICON where non-responders proceeded directly to surgery, amongst those patients that went on to complete surgical resection, survival between non-responders in both groups was similar. This suggests that, amongst metabolic non-responding patients, patient survival was unaffected (either adversely or positively) by continuing with ineffective chemotherapy or by stopping ineffective chemotherapy and proceeding early to surgery. These results have led to an ongoing clinical trial in which failure to respond to initial induction chemotherapy with a reduction in SUV on

PET is followed by introduction of a salvage regimen of non-cross resistant chemotherapy in an effort to improve outcome (NCT00737438 on clinicaltrials.gov; Memorial Sloan Kettering study, IRB 08-081).

In contrast, in a study of 32 patients with esophageal/GE junction adenocarcinoma, a FDG-PET scan performed following a week of chemoradiation failed to detect any significant difference between pathologic responders and non-responders with respect to changes of SUVmax on PET[44]. This may in fact be due to the timing of the PET as radiation is known to have a "stunning" effect with respect to FDG uptake, irrespective of further cell kill, which may cause bias in an interpretation performed at an early interval following radiation.

These studies suggest that the utility of FDG-PET in response assessment in esophageal/GE junction adenocarcinoma remains to be verified at this time, but that it is a potentially promising modality to begin "individualized" care for patients with upper GI malignancies (namely esophageal and gastric adenocarcinoma). It should be noted that the response of PET to chemotherapy when compared with that of CT may lead to clinical confusion, such as when a lesion improves by PET criteria, but fails to shrink or may even enlarge slightly by traditional RESIST criteria[45]. Recently proposed guidelines for response assessment in solid tumors suggest that PET progression may be defined as an SUV increase of $\geqslant$ 20% in a region 1 cm or larger in diameter, whereas a response be defined as a decline in SUV of $\geqslant$ 30% in such a region[46]. Such a guideline would seem to be a good starting point for evaluation of the PET response in many solid tumor malignancies, but will need prospective validation.

FDG-PET FOR THE DETECTION OF ESOPHAGEAL CANCER RECURRENCE

The accuracy of CT and magnetic resonance imaging (MRI) for the detection of recurrent disease, particularly within the area of the initial primary tumor may be decreased by post-surgical or post-chemoradiation related changes such as fibrosis, edema, and inflammation. Guo *et al*[47] followed 112 patients with resected squamous cell carcinoma of the esophagus for recurrence with FDG-PET/CT. PET demonstrated excellent sensitivity at local, regional and distant sites of metastases (96.9%, 85.9% and 90.5%, respectively), but lower specificity for local-regional recurrence (50%, 92.2% and 89.9%, respectively). Of note, five out of nine false positive FDG-PET scans were identified in the area of the surgical anastomosis. A French study examined the routine use of FDG-PET in the prospective follow-up of resected esophageal cancer patients[48]. This study demonstrated that for the detection of locoregional recurrence, PET had a higher sensitivity, slightly lower specificity and a superior accuracy than CT (100% *vs* 65%, 85% *vs* 91%% and 91% *vs* 81%, respectively). PET was also superior to CT in the detection of local metastasis. No patient had a negative PET and a recurrence detected by another modality, i.e., there were no false negative PET scans in this study, leading to a 100% negative predictive value. As this recently published study is the first examining the prospective use of PET to detect recurrence in asymptomatic patient, it is too early to comment on whether changes in management based on this strategy will lead to improvements in patient outcomes.

COMPARISON OF FDG-PET AND OTHER PET TRACERS IN THE DIAGNOSIS AND MANAGEMENT OF ESOPHAGEAL CANCER

FDG is not a tumor specific radiotracer, and this leads to the drawback of false positive uptake in areas of inflammation or infection by neutrophils and macrophages, i.e., when there is contamination of the malignancy with other actively dividing or metabolically active cells. An alternative to FDG-PET is (^{18}F) FLT (3-deoxy-3-fluorothymidine) which is trapped intracellularly following phosphorylation by thymidine kinase 1 into (^{18}F) FLT-monophosphate, forming the rationale for the use of FLT as a proliferation tracer[49]. A study by Westreenan *et al*[50] compared the efficacy of FLT *vs* FDG in the detection of esophageal cancer and demonstrated increased uptake for FDG rather than FLT (FLT-PET missed 20% of primary esophageal tumors in this study). FDG-PET also detected a synchronous primary rectal tumor in one patient, which was not detected by FLT-PET. In addition, there was no correlation between uptake of FLT and Ki-67, a marker of proliferation. For this reason, FDG remains the preferred radiotracer for use in the diagnosis and management of patients with esophageal cancer[50].

^{11}C-choline is a small molecule that is integrated into the cell membrane as phosphatidylcholine and serves as a marker of cell membrane metabolism. Because of late urinary excretion, it has been examined in genitourinary tumors such as prostate cancer[51]. ^{11}C-choline has been investigated in two studies of esophageal cancer. Kobori *et al*[52] studied squamous cell carcinoma of the upper esophagus and claimed a superior sensitivity for choline-PET in the detection of primary tumors and nodal metastases in the mediastinum (94% and 88%, respectively). Specificity was not reported. In this study the sensitivity of FDG-PET was 34% and 38% for the primary tumor and nodal involvement, which is somewhat lower than the literature median. These results contrast with those of Jager *et al*[53], who studied a more diverse group of esophageal and GE junction adenocarcinomas in addition to squamous cell carcinoma of the esophagus and GI stromal tumors. They demonstrated the superiority of FDG-PET, with a sensitivity of 100%, 67%, and 100% for the detection of primary tumor, locoregional and lymph node metastases, respectively, compared to 73%, 60%, and 75%, respectively, for choline-PET. Imaging in the abdominal area

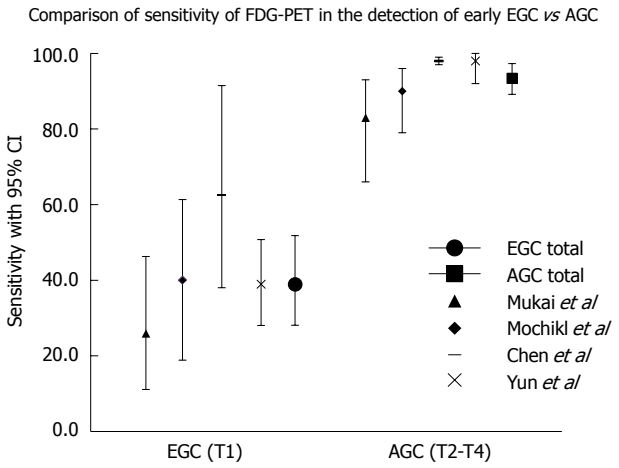

Figure 4 Sensitivity of (^{18}F) 2-fluoro-2-deoxyglucose-positron emission tomography to identify primary early and advanced gastric carcinoma. FDG-PET: (^{18}F) 2-fluoro-2-deoxyglucose-positron emission tomography; EGC: Early gastric cancer; AGC: Advanced gastric cancer; CI: Confidence interval.

using choline-PET is limited by the high background uptake of this agent by the liver.

GASTRIC ADENOCARCINOMA

Gastric cancer remains the most common GI malignancy worldwide, responsible for approximately 934 000 new diagnoses annually (8.6% of new cancer cases) and 700 349 deaths worldwide annually[54]. Gastric cancer may be distinguished anatomically such that proximal tumors (associated with chronic reflux and obesity) have worse prognosis than distal tumors which are more commonly associated with chronic infection by *Helicobacter pylori*[55]. Alternatively, gastric cancer may also be distinguished histopathologically as diffuse, intestinal, or mixed histology which describes the pattern of spread of the primary tumor[56]. Based on these distinctions, an emerging concept in understanding the biology and physiology of gastric cancer is that it likely reflects not one disease, but several[55]. How these distinctions impact on FDG-PET imaging is still evolving.

IMAGING PRIMARY GASTRIC CARCINOMA WITH FDG-PET

Unlike esophageal carcinoma, in which the majority of tumors (particularly T2-T4) are identified on FDG-PET imaging, the primary gastric lesion is less well imaged by FDG-PET. This has been demonstrated in several series with sensitivity for detection of gastric lesions ranging from 21% to 100%[57-65]. Specificity ranged from 78% to 100%. There are several factors that affect the sensitivity and specificity to detect a primary gastric carcinoma. Significantly, there is a variable and occasionally intense uptake of FDG of a physiological nature within the gastric wall[61,63,66]. FDG uptake may also correspond to acute inflammation such as superficial or erosive gastritis[67]. This leads to two disadvantages in the detection of gastric cancer. Firstly, an awareness of this phenomenon must exist in order to avoid a high number of false positive diagnoses. Conversely, over-awareness may lead to failure to detect weakly enhancing and diffuse malignant lesions.

TUMOR SIZE AND DEPTH (T STAGE) AND FDG-PET

Tumor size and T stage may influence the sensitivity of PET imaging in the detection of the primary gastric lesion. In one study, sensitivity was as low as 21% for detecting tumors < 30 mm in size, and increased to 76% for lesions over 30 mm[62]. Gastric cancer limited to the mucosa or submucosa (T1 lesions), are less likely to be detected by PET than more advanced T2-T4 lesions. Sensitivity for detection of early gastric cancers (T1) ranges from 26% to 63%, whereas that for more advanced disease (T2-T4) ranges from 83%-98%[57,61,62,65]. Figure 4 graphically depicts the range of sensitivity in diagnosis of early and advanced gastric cancer.

Histological subtype variants also influence glucose uptake and therefore the ability of PET to detect the primary lesion. The ability of FDG-PET to detect non-intestinal gastric primary tumors can range from 0% for T1 non-intestinal primaries to 77% for advanced non-intestinal disease. For intestinal type tumors, sensitivity ranges from 44% for T1 tumors to 92% for T2 or greater disease[62,63,68]. This may relate to the fact that the GLUT-1 transporter has been shown to be preferentially expressed on the intestinal type gastric carcinoma cell subtype, with decreased expression on mucous-secreting and signet ring type cells[69,70]. GLUT-1 expression has been shown in multivariate analysis to be the most influential factor relating to FDG uptake in gastric carcinoma, although the relationship between histological subtype and SUV uptake and sensitivity of FDG-PET has not been consistent across studies[71,59-61].

TECHNIQUES TO IMPROVE DETECTION OF THE PRIMARY GASTRIC LESION

Simple measures such as distention of the stomach by water or, less commonly, food have been shown to improve the accuracy of detection of gastric lesions both pre-operatively and in the post-operative remnant stomach[72-74]. In an effort to improve detection of gastric cancer by PET, the pyrimidine analog FLT has been used as an alternative radiotracer. One study demonstrated increased sensitivity of FLT-PET for detection of gastric tumors, especially if those tumors which were not FDG avid[58]. This may improve detection of previously difficult-to-detect tumor types such as mucin-producing and signet ring cell tumors. A second smaller study showed comparable efficacy between the two moieties[59]. In both studies, mean SUV uptake was lower for FLT-PET than for FDG-PET. Additional improvements may be made

Table 3 Gastric cancer lymph node staging by positron emission tomography

Ref.		*n*	Sensitivity (%) PET	Specificity (%) PET	Sensitivity (%) CT	Specificity (%) CT
Chen *et al*[57]		61	61	92	77	62
Kim *et al*[60]		73	40	95	71	71
Mochiki *et al*[61]		85	23	100	65	77
Mukai *et al*[62]		62	34.50	97	62.10	87.90
Yeung *et al*[64]		23	22	97		
Yoshioka *et al*[75]	Low resolution	42	47	62		
	High resolution	41	73	78		
Yun *et al*[65]		81	35	97	52	94
Tian *et al*[78]		38	60	100		
Yang *et al*[79] (PET-CT)		78	37	97.20	60.50	83.30

PET: Positron emission tomography; CT: Computed tomography.

possible by improving spatial resolution of the imaging equipment[75].

SCREENING FOR GASTRIC CARCINOMA WITH FDG-PET

FDG-PET has not been shown to be an effective screening tool for the diagnosis of gastric cancer. In one study, combined with endoscopy in asymptomatic individuals, PET-CT detected 2/20 cancers from 2861 patients screened giving a sensitivity of only 10% and a positive predictive value of 8.3%; 18/20 cancers were early gastric cancers (T1). There were 22 false positives on this study. There was no significant difference between the SUV values of the false positives and the true positives[76]. A second study of 1336 asymptomatic patients detected two gastric cancers in addition to nine other malignancies. The rate of false positive in this study was three times the rate of true positive findings[77]. Therefore, the screening sensitivity of FDG-PET in an asymptomatic population is less again than that in a diseased population.

FDG-PET AND LYMPH NODE STATUS: GASTRIC ADENOCARCINOMA

Survival in gastric cancer patients decreases with lymph node involvement, and with the number of lymph nodes involved. Knowledge of lymph node status therefore is not only of importance with respect to prognosis, but may also guide surgical treatment planning and which patients may benefit from neoadjuvant chemotherapy.

FDG-PET has been examined both alone, in comparison with CT imaging, and combined as CT-PET, in the preoperative assessment of the nodal status of gastric cancer (see Table 3). The sensitivity of PET is generally low for the detection of lymph node metastases, ranging from 22% to 60% for normal resolution scans[57,60-62,64,65,75,78,79]. It is possible that this may reflect the low spatial resolution of PET at 7 mm-9 mm which leads to difficulty discriminating perigastric lymph nodes from the gastric primary tumor, as sensitivity has been shown to increase to up to 73% with a higher resolution scan[75]. This compares poorly with the sensitivity of CT which ranges from 52% to 77% in the same series. By contrast the specificity of PET is higher than that of CT, ranging from 62%-100%, compared to CT (range, 62%-94%)

The sensitivity and specificity of PET are also influenced by lymph node staging status (i.e., N1, N2, or N3 nodal metastases). In three studies which stratified sensitivity by lymph node status, CT was significantly more sensitive for N1 disease[60,61,65], whereas similar levels of sensitivity and specificity were seen in N3 disease for both imaging modalities; however, this may have reflected the low prevalence of N3 disease in the study groups. Increased SUV of the primary tumor was correlated positively with lymph node metastases in two studies[57,61], possibly indicating increased glucose transport capacity which may in turn correlate with increased aggressiveness of the primary tumor[69].

PERITONEAL DISEASE

A common site of spread for gastric adenocarcinoma is the peritoneum. As many as 25% of patients with locally advanced tumors on EUS will have sub-radiographic occult peritoneal disease that may be identified only at laparoscopy[80]. PET is not a reliable indicator of peritoneal disease, with sensitivity for detection of peritoneal carcinomatosis of between 9% and 30% with normal resolution scans, and increased to 50% sensitivity with the use of a higher resolution 3.9 mm slice. This compares unfavorably with CT which demonstrates a sensitivity of 76%-80% for peritoneal cancer[57,75,81]. Peritoneal lesions are often small and diffuse in nature, which may go some way to explaining the low detection rate. Specificity remains high at 79%-98% in the same series, with less specificity with higher resolution imaging. Due to the need to confirm the absence of metastatic peritoneal spread prior to definitive surgery, staging laparoscopy may still be necessary, as this is the most sensitive modality to evaluate the peritoneum[82,83].

RESPONSE TO TREATMENT

With the introduction of neoadjuvant or perioperative

Table 4 Positron emission tomography computed tomography for the detection of gastric cancer recurrence

Author	Yr	*n*	Discriminating factor	Sensitivity (%) PET	Specificity (%) PET
De Potter *et al*[85]	2002	33		70	69
Jadvar *et al*[90]	2003	16		94	100
Yoshioka *et al*[75]	2003		Liver	78-85	82-74
			Lung	67	88
			Bone	30	82
			Pleural	4	100
			Ascites	24	76
Patriti *et al*[89]	2007	51		100	
Nakamoto *et al*[88]	2009	44	Previous suspicious imaging	80	100
		14	Tumor markers positive	73	83
		26	Routine	50	88
Park *et al*[117]	2009	105		75	77
Sim *et al*[86]	2009	52		68.40	71.40
Sohn *et al*[118]	2009	212	Post ablation	0	

PET: Positron emission tomography.

chemotherapy it is of interest to try to determine those who may respond to such chemotherapy, and those who are likely to fail to respond. This may be crucial in future in order to spare non-responders further potentially toxic chemotherapy, or to switch to another, non cross resistant regimen. The advantage of PET over CT in this regard is that the CT response by RECIST (Response Evaluation Criteria in Solid Tumors) as measured by the change in size may be a late manifestation of a response. PET may demonstrate a decrease in FDG uptake at an earlier stage than could be demonstrated by conventional imaging.

In one study of 44 pure gastric carcinoma patients treated with neoadjuvant cisplatin and 5-fluororuacil, 35 showed FDG uptake at baseline, before the initiation of chemotherapy. The PET response at 14 d post-chemotherapy was correlated with histopathological response at the time of surgery. The PET response was defined as > 35% reduction in the SUV value of the target lesion. A histopathological response was defined as < 10% viable tumor cells remaining in the operative surgical specimen. A metabolic response correctly predicted the histological response after completion of chemotherapy in 10/13 responding and 19/22 non-responding tumors, corresponding with a sensitivity of 77% (95% CI: 46%-95%) and a specificity of 86% (95% CI: 65%-97%)[41]. Metabolic response appeared to correlate significantly with survival. At 2-year follow-up, survival in the metabolic responder group was 90%, compared with 25% in the metabolic non responder group. A second smaller study in the setting of metastatic gastric cancer using chemotherapy and the biologic agent cetuximab demonstrated in this study, PET demonstrated a sensitivity of 83% and a specificity of 75% for the prediction of ultimate best response by RECIST. There was also a significant correlation between metabolic response and progression-free survival in this cohort[84].

FDG-PET AND PREDICTION OF PATIENT SURVIVAL: GASTRIC ADENOCARCINOMA

Data on survival with respect to PET-positive tumors may be confounded by the fact that PET-negative tumors in most studies may represent earlier stage disease. For example, in one study, The 2-year survival rate for patients with PET-positive cancers was 65.9%, and for those with PET-negative cancers was 94.4%, but a significant proportion of PET-negative tumors were T1/T2 *vs* T3/T4 for the tumors visible on PET[61]. One study on recurrent gastric carcinoma with 33 patients showed a higher median survival for those with PET negative recurrence *vs* PET positive recurrence of 18.5 mo *vs* 6.9 mo respectively, however, other studies have failed to corroborate this finding[63,85].

FDG-PET TO DETECT RECURRENCE OF RESECTED DISEASE: GASTRIC ADENOCARCINOMA

When compared to contrast CT, PET showed a non-significant trend towards decreased sensitivity and increased specificity in the detection of recurrent disease. Contrast-enhanced CT was significantly more sensitive for the diagnosis of peritoneal recurrence (87% *vs* 47%)[86]. This concurs with another series demonstrating a high sensitivity of 78% and 67% for liver and lung lesions, respectively, with a lower sensitivity of 30% for bone metastases. Sensitivity for pleural carcinomatosis and ascites were also similarly low[75]. As FDG also demonstrates uptake in acute inflammation and fractures in addition to physiological uptake in the abdomen, this may lead to false positives in the detection of boney disease[87]. Table 4 summarizes these data.

Notably, the utility of FGD-PET in the detection of recurrent gastric cancer is largely dependent on the prevalence of recurrent disease in the screened population. In a population undergoing routine screening examination following definitive primary therapy the sensitivity of screening may be as low as 50%-70%. In contrast, positive predictive value is high in a high prevalence population (i.e., those in whom disease is suspected). This is illustrated when comparing the positive predictive value of 100% in a population with a suspicion of disease based on previous radiological imaging *vs* 25% in a population with no clinical or radiological suspicion of recurrent disease[85,86,88]. If the population undergoing testing has an a priori suspicion of disease based on previous imaging or tumor markers, then sensitivity for detection may reach 94%-100%. Specificity is generally high at 70%-100% for PET in the detection of recurrent disease[89,90].

PANCREAS ADENOCARCINOMA

Pancreatic cancer ranks as one of the most lethal malignancies and only 20% are suitable for resection at presentation. Accurate delineation of tumoral extent and anatomy are crucial prior to surgery in order to avoid potentially futile laparotomy. Conventional work up includes abdominal ultrasound, CT, EUS and MRCP.

PET AND THE DIAGNOSIS AND MANAGEMENT OF PANCREATIC MALIGNANCY

As the normal pancreas exhibits low FDG uptake, and pancreatic tumors have been demonstrated to have high GLUT-1 expression, the expectation is that pancreatic tumors should not be difficult to differentiate from the normal parenchyma by FDG-PET[91]. In an initial study in 1997 by Zimny *et al*[92], 106 patients with pancreatic lesions were examined using FDG-PET; 85% of pancreatic carcinomas were correctly identified, and in 84% of cases of chronic pancreatitis it was possible to exclude malignancy. Ten of 11 false negatives were due to elevated plasma glucose. In patients with normal plasma glucose the sensitivity, specificity, positive and negative predictive values were 98%, 84%, 96% and 93%, respectively. The SUV of carcinoma was significantly higher than that of chronic pancreatitis (6.4 ± 3.6 for pancreatic carcinoma *vs* 3.6 ± 1.7 for chronic pancreatitis ($P < 0.001$). Inokuma *et al*[93] examined the utility of PET in the diagnosis of pancreas cancer in comparison to CT and EUS. In a study of 45 patients PET had a lower sensitivity than EUS, but a higher specificity than all other modalities, and highest positive predictive value and overall accuracy. In a larger study, comparing PET with CT and MRI, the sensitivity of PET was lower than that of CT but higher than that of MRI (91% CT *vs* 82% PET *vs* 78% MRI), and PET had the highest specificity and positive predictive value among the three modalities. There was no correlation between the SUV of the tumor and the degree of differentiation. The ability of PET to detect disease was improved by the correction of SUV for blood glucose[94]. The ability of PET to detect pancreatic cancer may be greater than CT at smaller lesion sizes[95]. In the differentiation of benign *vs* malignant cystic disease of the pancreas, Sperti *et al*[96] showed that PET was superior to CT with respect to sensitivity, specificity, positive and negative predictive value, and diagnostic accuracy at 94%, 94%, 89%, 97%, and 94%, respectively; these figures for CT were 65%, 88%, 73%, 83%, and 80%. A review by Gambhir *et al* suggested a sensitivity of 94% and a specificity of 90% for PET when compared with that of CT (84% and 75%, respectively)[97]

FDG-PET AND STAGING: PANCREAS ADENOCARCINOMA

FDG-PET is not the preferred modality to stage the depth of invasion or invasion of local-regional structures the primary tumor of the pancreas due to its poor spatial resolution. At this time, thin slice CT or EUS are better able to delineate the anatomical boundaries of the primary tumor and thus resectability. Similarly, PET is poorly sensitive for the detection of loco-regional lymph node metastases, which may be due to their proximity to the primary lesion. Sensitivity has ranged from as low as 49% to as high as 76% for the detection of local field lymph node involvement[98,99]. For pancreatic tumors, similar to gastric adenocarcinoma, FDG-PET is sensitive for the detection of metastatic disease to the liver and bone, but less so to the peritoneum. In a series of 168 patients Fröhlich *et al*[100] determined PET had a sensitivity of 97% for hepatic lesions > 1 cm, but only 43% for those < 1 cm, with 95% specificity. Three quarters of false positives were due to intrahepatic cholestasis. A study of 59 patients by Diederichs *et al*[99] confirmed these findings, with an overall sensitivity for the detection of hepatic metastases of 70%, again missing some metastases < 1 cm in diameter. The sensitivity for the detection of peritoneal disease was 25%.

IS SUV UPTAKE PROGNOSTIC IN PANCREATIC CANCER?

An SUV cut-off of ⩾ 4.0 was used by Sperti and colleagues to characterize patients with pancreatic cancer into two groups. Those with an SUV ⩾ 4.0 had an overall survival of only 7 mo, compared to 32 mo in the lower SUV group. This applied also to those who underwent resection. Tumor SUV was confirmed in multivariate analysis to be an independent predictor of survival[96]. This is in agreement with data published by Nakata *et al*[101] for patients with inoperable pancreatic tumors, in which those with a tumor SUV of > 3.0 were shown to have inferior survival to those with SUV uptake of < 3.0. In contrast to many other malignancies, proliferative activity as measured by the Ki67 index did not correlate with FDG uptake in pancreatic tumors[102].

PET AS A PREDICTOR OF RESPONSE TO CHEMOTHERAPY: PANCREAS ADENOCARCINOMA

PET has been used in an attempt to measure the response to neoadjuvant chemoradiotherapy in pancreatic cancer. In a study of 20 patients with locally advanced pancreas adenocarcinoma, of those who had > 50% reduction from the baseline SUV, 10% had a complete surgical resection, compared to 6% of those who had < 50% reduction. Those with a significant response also had a 23.2 mo survival compared to 11.3 mo in those who did not respond[103]. This is in agreement with a study by Bang *et al* which demonstrated the superiority of PET in the detection of a treatment response to chemoradiotherapy, detecting a response in one-third of patients, where conventional

CT failed to detect any response. Those who developed a response on PET also had significantly longer survival than those who did not. The PET and tumor marker response following palliative chemotherapy were also correlated positively with patient survival in a recent Japanese study[104] which contrasts with results of a study by Kobayashi *et al*[105] in which only a fall in tumor markers and not SUV was correlated with survival.

DETECTION OF RECURRENT DISEASE

Ruf *et al*[106], in a study of 31 patients with suspected recurrence after surgery, demonstrated that PET was superior to the combination of CT and MRI in the detection of recurrence (96% *vs* 39%). CT/MRI failed to detect any local recurrence, but did perform well in the detection of small hepatic metastases when compared to PET (92% *vs* 42%). Thus PET may be superior in the detection of recurrence within the tumor bed, but CT/MRI may have better discriminatory power within the hepatic parenchyma. PET may also complement the use of tumor markers or CT for the detection of recurrent disease when CT findings are equivocal, as demonstrated in a small study by Rose *et al*[95], where PET detected 100% of recurrences felt to be equivocal on CT. In a recent study of 45 patients with suspected recurrent disease, PET fused with contrast CT was shown to have a sensitivity of 94.7% for the detection histologically proven metastatic disease. Notably there was also a high sensitivity in this study for the detection of all sites of recurrence, with sensitivity for detection of local recurrence, abdominal lymph node metastasis, and peritoneal dissemination being 83.3%, 87.5%, and 83.3%, respectively[107].

METHODS OF IMPROVING THE ACCURACY OF PET IN PANCREAS CANCER

Although PET is superior to CT for the differentiation of benign *vs* malignant lesions, false positives may occur, most commonly due to pancreatitis, post instrumentation of the biliary tree, due to retroperitoneal fibrosis or hemorrhage or inflammation of a pancreatic pseudocyst. If C-reactive protein serum levels are elevated, the specificity of PET may fall to 50%[108]. Using delayed PET may aid in the differentiation of benign *vs* malignant lesions as evidenced in a prospective series of 47 patients where the diagnostic accuracy for malignant *vs* benign disease was 91.5% using this method[109]. Optimal glycemic control is also an important factor in the accuracy of PET scanning in pancreatic disease as noted in the study by Zimny where 91% of false negative results were due to hyperglycemia reducing the sensitivity of PET from 96% to 63% in those with an abnormally high serum glucose[92].

The fusion of PET-CT may show promise. A retrospective study by Lemke *et al*[110] showed that use of PET-CT improved the sensitivity of either individual imaging modality. Sensitivity was 76% for CT, 84% for PET and 89% for PET-CT but this came at a cost of a loss of specificity. Addition of CT imaging to fusion PET-CT may lead to further gains. In another study the sensitivity for the detection of metastatic disease by PET-CT, CT, and PET-CT plus CT was 61%, 57%, and 87%, respectively[111]. Enhanced PET-CT has also been shown to be superior to PET alone compared to unenhanced PET-CT imaging in two studies[107,112]. Use of the alternative radiotracer FLT has not been shown to be of benefit in pancreas cancer. In a small pilot study, FLT-PET demonstrated low levels of uptake in the primary tumor and detected only 40% of primary pancreatic tumors compared to 100% with FDG-PET[113].

CONCLUSION

FDG-PET imaging is now a standard practice in staging cancers of the esophagus. The role of FDG-PET/CT imaging in staging gastric carcinoma, however, is complicated by the higher rate of FDG-non-avid malignancies and by the false positive rate within the stomach due to inflammatory conditions. For each upper GI malignancy, depth of invasion and nodal status are not well evaluated by FDG-PET scans. However, for locally-advanced malignancies, an FDG-PET scan may be used to identify occult metastatic disease which may then significantly then change the treatment plan. A newer application of this imaging modality is the assessment of metabolic response, which correlates with chemotherapy sensitivity and survival. Preliminary prospective clinical studies suggest FDG-PET scans can predict response to therapy. With these data, the utility of FDG-PET scanning in upper GI malignancies is increasingly commonplace. With the identification of new FDG-PET tracers, we expect a further expansion of the application of PET imaging in upper GI malignancies.

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