PAPER

^{18}F-Fluoro-2-deoxyglucose positron emission tomography in the evaluation of gastrointestinal malignancies

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Positron emission tomography with ^{18}F-fluoro-2-deoxyglucose is an imaging technology that is demonstrating increasing utility in the evaluation of gastrointestinal malignancies.

Early studies of several gastrointestinal tumours have shown increased glycolysis and increased glucose transporter proteins associated with increased metabolism. ^{18}F-fluoro-2-deoxyglucose (FDG) is a positron emitting radiotracer that is transported intracellularly and phosphorylated by hexokinase to FDG-6-PO_4 through the same cellular membrane transport pathways as glucose. Unlike glucose, however, FDG-6-PO_4 is subsequently trapped intracellularly due to lack of further metabolism from insufficient amounts of glucose phosphatase. After intravenous administration, this substrate accumulates in tumours throughout an uptake phase, and whole body imaging can then be performed to identify regions of high glycolytic activity. Technical advances in positron emission tomography (PET) instrumentation and algorithm implementation have facilitated high quality clinical whole body imaging. The recently developed combination in-line PET and CT instrumentation provide co-registered metabolic and anatomical information. This is anticipated to significantly improve accuracy and reduce scanning time.

Conventional anatomical methods for tumour detection may not accurately distinguish benign and malignant processes based on size criteria alone, and interpretation may be difficult when prior surgery or radiation therapy results in distortion of the normal anatomy. FDG PET provides a rapid, non-invasive method to interrogate the glycolytic activity throughout the whole body in a single imaging session. The indications, accuracy, advantages, and limitations of FDG PET in colorectal and oesophageal carcinoma will be reviewed. Emerging indications in several other gastrointestinal malignancies will also be briefly discussed.

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COLORECTAL CARCINOMA

The primary indications for FDG PET in colorectal carcinoma are for staging, restaging, and detection of recurrence. The value of FDG PET in detection of recurrent colorectal carcinoma is well established.[1–17] A meta-analysis of the literature has demonstrated the high accuracy of FDG PET in the evaluation of recurrent colorectal carcinoma.[2] The overall sensitivity for detection of recurrent colorectal carcinoma is 97% (95% confidence levels 95% to 99%), and the overall specificity is slightly lower at 76% (95% confidence intervals 65% to 88%). Because of higher accuracy compared with conventional anatomical imaging, patient manangement is changed in 29% (95% confidence intervals 25% to 34%). Based on similar data[9 10 12 18 19] the European consensus conference has categorised FDG PET as an established technique to reliably detect relapsing colorectal carcinoma with significantly superior performance compared with conventional imaging.[17] A recent study confirmed the superior accuracy of FDG PET compared with conventional imaging modalities.[20]

Recent data in a prospective study of 102 patients have confirmed the impact of FDG PET on the management of patients with suspected recurrence.[1] Oncologists were first asked to assign a treatment plan for patients with resectable disease based on the available staging information including CT, and this was compared with the treatment plan after incremental information was provided from FDG PET. In six patients, the referring oncologist would not commit to a management plan without the results of FDG PET. In the remaining 96 patients, the treatment plan was changed in 54 (56%). Overall, this resulted in a change in patient management for 60 of 102 (59%). Validation of the PET findings was possible in 57 patients and was correct for the presence and extent of disease in 52 (91%). Relapse was confirmed for 49 of 50 (98%), and only one (2%) false positive was attributable to pelvic abscess. True negatives were confirmed in seven patients and in only 4 of 57 (7%) patients, the extent of metastatic disease was underestimated by PET. These were primarily in small lesions less than 1 cm. Planned surgery was abandoned because of positive PET findings in 26 of 43 (60%), and therefore, the most imortant benefit of PET was avoidance of inappropriate local therapy by documentation of widespread disease.[1] A retrospective study of 100 patients with suspected colorectal recurrence showed higher accuracy for FDG PET compared with both CT and serum carcinoembryonic antigen (CEA) concentrations.[13] For FDG PET, the sensitivity, specificity, and accuracy were 98%, 90%, and 95% compared with CT of 91%, 72%, and 82%, respectively. FDG PET was accurate in

Abbreviations: PET, positron emission tomography; FDG, ^{18}F-fluoro-2-deoxyglucose; CT, computed tomography; CEA, carcinoembryonic antigen

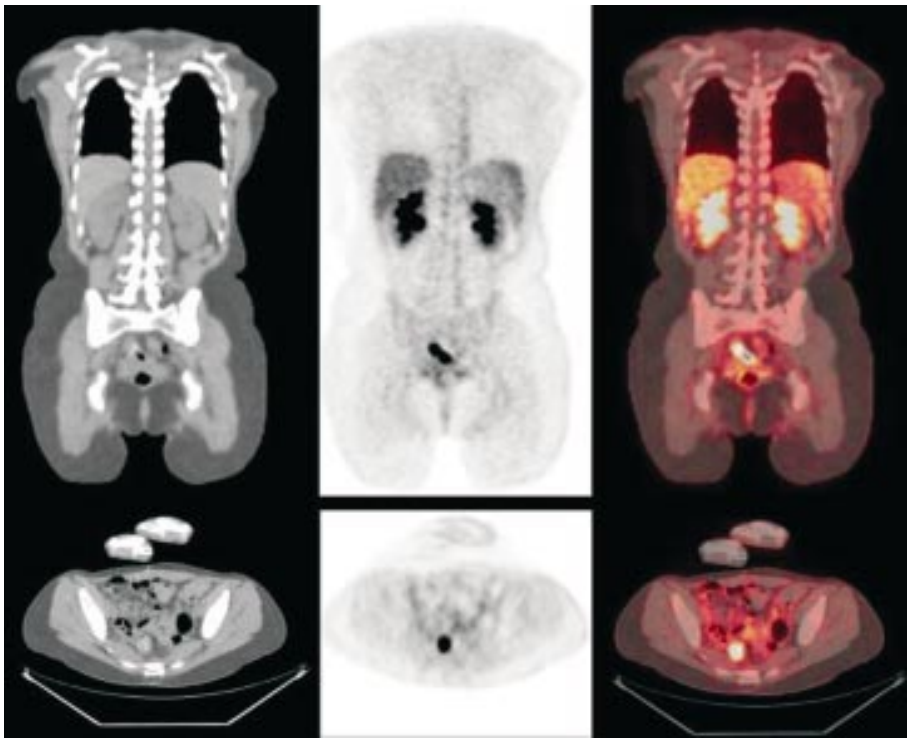

Figure 1 A 45 year old woman with stage III colorectal cancer presented with rising CEA after primary tumour resection. (Top row) Coronal and (bottom row) transaxial tomographic slices. (Left) CT was interpreted as negative for recurrence. (Centre) FDG PET shows intense activity at the anastamosis compatible with tumour recurrence. This was subsequently verified after surgery. (Right) Fusion of PET and CT localises the abnormality.

detecting local recurrence in 96%, provided additional information in 86%, and influenced surgical decisions in 61% of patients.[13] An early prospective study of 51 patients analysed for resection of colorectal metastases showed 20% change in clinical management after FDG PET results were known. When FDG PET was retrospectively considered decisive, the change in management increased to 29%. Other studies have shown similar results[2] even despite the use of less advanced techniques that did not use PET attenuation correction.[4]

A clinical presentation where FDG PET may be especially useful is in the evaluation of recurrent colorectal cancer when conventional diagnostic imaging is unrevealing and the serum CEA is increased.[21] In 22 patients with abnormal CEA and normal conventional imaging, FDG PET was positive in 17 patients. Of these, 15 of 17 patients were true positive and only two were false positive, yielding a positive predictive value of 89%. In all five patients with negative follow up, FDG PET was true negative, yielding a negative predictive value of 100%.[21] In a larger retrospective study of 50 patients with normal or equivocal anatomical imaging, FDG PET identified 34 of 43 true positives patients (sensitivity of 79%) with only four false positives (positive predictive value of 89%).[22] For analysis by recurrent lesions, PET detected 42 of 56 true positive lesions (sensitivity of 75%) and showed only 11 false positive lesions (42 true positives of 53 total positives; positive predictive value of 79%). Overall, 14 of 50 patients (28%) had a change in patient management to surgical resection with curative intent.[22] Another prospective study of 28 patients similarly showed the ability of FDG PET to detect recurrence and determine tumour resectability.[23] These studies clearly show that FDG PET had a beneficial impact on patient management. Figure 1 illustrates an example of combined PET-CT used in localising tumour recurrence.

Detection of primary colorectal carcinoma

The ability to detect a primary colorectal carcinoma has been demonstrated with high sensitivity, but it may suffer in specificity because of inflammatory bowel conditions and normal physiological bowel uptake.[18] A retrospective analysis of patients referred for both colonoscopy and FDG PET confirmed that primary tumours and large adenomatous polyps can be detected by FDG PET. These patients were referred for a wide variety of indications, and therefore, the specificity and positive predictive value were adversely affected by inflammatory conditions and physiological bowel activity. Additional studies have similarly demonstrated increased FDG uptake in large premalignant adenomas[24 25] but the ability to detect small lesions and the comparatively low specificity in an unselected population will probably limit its use for this indication.

Cost effectiveness

A recent decision tree analysis for patients with suspected colorectal recurrence and an increased CEA concentration showed that the addition of FDG PET to conventional CT would be associated with an increase in the mean life expectancy.[26] Because FDG PET can more accurately assess the presence of metastases, a more appropriate population can be referred for curative surgery. Although this resulted in an increase in the mean cost per patient, the overall cost effectiveness was well within the range of accepted medical practice.[26] With FDG PET, more accurate staging may obviate unnecessary surgeries in up to 32% of patients.[11 12] Other investigations have provided similar estimates in change of management.[10] A recent study showed that the addition of FDG PET to the diagnostic evaluation of liver resection candidates more appropriately identified the subset that was amenable to surgical resection. This more appropriate selection of surgical candidates demonstrated an overall three year survival rate of 77% compared with the previously established rate of only 40%.[15]

Evaluation of therapy

The role of FDG PET in evaluating response to therapy of the primary lesion is currently under investigation. Therapy for the primary lesion may include radiation or combination chemotherapy in addition to radiotherapy. In a study of the effect of radiation therapy on primary rectal carcinoma, tumour FDG uptake and cell kinetics were not strongly

correlated.[27] Although early studies have showed encouraging results in identifying response to therapy, these studies postulated increased FDG due to inflammatory may be confused with residual viable tumour.[28] A more recent pilot study in 15 patients comparing FDG PET before and after combined chemotherapy and radiation therapy showed better correlation with therapy response. All 15 patients responded to therapy and showed correlation with FDG PET, but the small sample size and lack of true negative responses limited the conclusions that could be made from this investigation.[29]

Therapy for liver metastases primarily entails chemotherapy without concomittant radiotherapy, and FDG has shown more encouraging initial results. A small study of 18 patients (27 lesions) showed the tumour to normal liver ratios had a significantly greater reduction in metabolism in responders compared with non-responders (67% *v* 99%; $p<0.001$).[30] In the four to five week T:L ratio, FDG PET was able to discriminate response from non-response both in a lesion by lesion and overall patient response assessment (sensitivity 100%; specificity 90% and 75%, respectively).[30] Small preliminary studies after hepatic artery chemoembolisation or chemotherapy have reported FDG uptake correlation with parameters of tumour response.[31 32] Larger prospective studies evaluating FDG uptake and the effects of radiation therapy and chemotherapy are necessary to better define the prognostic value.

Sensitivity and specificity limitations

The sensitivity and specificity for detection of disease may be affected by several factors. False positive results have been reported with a number of inflammatory conditions including liver abscesses, and post-radiation inflammation.[8] Physiological activity in the genitourinary system and normal bowel activity may also be difficult to distinguish from tumour recurrence.

Sources of false negative results include mucinous adenocarcinomas,[16] small lesions, micrometastatic disease, and decreased but viable tumour after chemotherapy.[33] In earlier studies, technical limitations such as lack of whole body attenuation correction, and use of filtered back projection may have also affected image quality and lesion detectability.[4] Anatomical correlation is likely to facilitate localisation of abnormalities and assist in distinguishing normal physiological activity from abnormal uptake. Recently developed combined in line PET and CT instrumentation with co-registered anatomical and metabolic information is currently being investigated to define the incremental benefit in accuracy.

OESOPHAGEAL CARCINOMA

The established indications of FDG PET in oesophageal carcinoma are for detection of metastatic disease and for restaging or evaluation of recurrence. For these indications, studies have demonstrated higher diagnostic accuracy than conventional anatomical imaging modalities. A more accurate evaluation of distant metastases also provides important prognostic information and the evaluation of tumour response to chemotherapy is showing promising initial results that require further validation.

Compared with conventional anatomical imaging, FDG PET has a demonstrated a higher sensitivity in the detection of distant metastatic disease. In a prospective study of 74 patients with oesophageal carcinoma, FDG PET detected the primary in 95% of patients, and had a significantly higher accuracy for diagnosing stage IV disease compared with the combination of CT and oesophageal ultrasound (82% versus 64%).[34] FDG PET also had a significantly higher specificity for lymph node metastases, however, the sensitivity for local

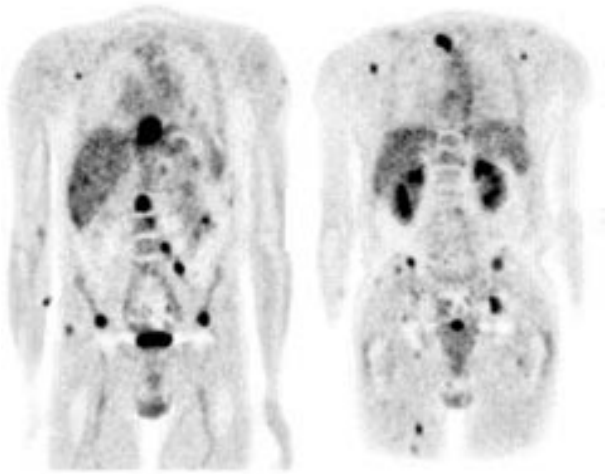

Figure 2 A 57 year old man with oesophageal cancer and clinical stage T3N1 presented for staging evaluation. (Left) Anterior coronal and (right) posterior coronal FDG PET show multiple foci of intense metabolic activity compatible with widespread metastases. CT scan confirmed many of these sites, but was unable to detect spread to lymph nodes and distant soft tissue site.

lymph node disease was significantly lower than for oesophageal ultrasound (33% versus 81%, respectively). FDG PET provided additional upstaging (15%) and downstaging (7%) for overall 22% change in patient management. This confirmed an earlier study that showed PET to be more sensitive than CT in detection of metastatic disease.[35] In 36 patients with newly diagnosed oesophageal carcinoma, FDG PET identified all primary oesophageal tumours and showed higher diagnostic accuracy in evaluation of metastatic disease (76% in 22 of 29 patients versus 45% 13 of 29 patients, respectively). Similarly, a study of 58 patients showed higher accuracy of FDG PET in determining resectability.[36] Of 17 patients with unresectable disease attributable to metastases, FDG PET identified all patients compared with CT that identified only five. In the remaining 35 patients that underwent surgical exploration, FDG PET was positive in 11 of 21 pathologically confirmed metastases compared with CT that was positive in only 6 of 21. Other similarly designed prospective studies have confirmed the utility of FDG PET in staging for distant metastases.[37] Figure 2 illustrates an example of distant metastases identified by FDG PET.

An important limitation of FDG PET in staging occurs in the lymphatic drainage adjacent to the site of the primary lesion. Intense uptake that is commonly present at the site of the primary may obscure interpretation of the adjacent regional lymph node basins. Oesophageal ultrasound has shown better sensitivity in assessment of regional lymph node metastases in these regions.[34 38]

Preliminary results of FDG PET to evaluate response to chemotherapy have been encouraging.[39] In a prospective study of 40 patients with oesophageal carcinoma, FDG PET was obtained at baseline and 14 days after completion of chemotherapy. The FDG uptake was significantly decreased in those pathologically deemed responders versus non-responders (−54% (17%) versus −15% (21%)). Using a change in FDG uptake of 35% as the threshold, PET showed a sensitivity 93% (14 of 15) and specificity 95% (21 of 22) in predicting responders. The non-responders were associated with a shorter time to progression or recurrence ($p=0.01$) and shorter overall survival ($p=0.04$).[39] In a similar study of 27 patients undergoing neoadjuvant chemotherapy and radiation therapy, responders showed decreased FDG uptake (72% (11%)) significantly different compared with non-responders (42% (22%)).[40] Sensitivity to detect response was 100% and

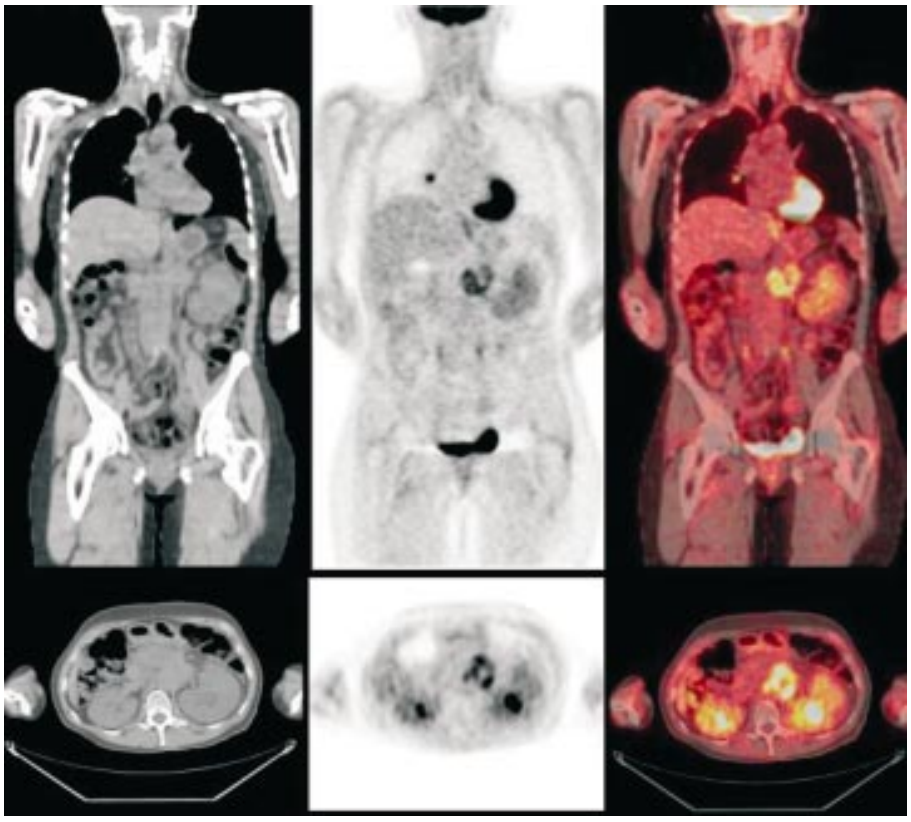

Figure 3 A 43 year old woman with pancreatic cancer presented for evaluation of lung nodules. (Top row) Coronal and (bottom row) transaxial tomographic slices. (Left) CT shows the mass in the abdomen, but is unable to characterise the hilar lymph node. (Centre) FDG PET shows intense activity in the abdominal mass and increased uptake in the hilar lymph node (additional lung abnormalities not shown) compatible with local recurrence and distant metastases. Clinical follow up of lung abnormalities was consistent with metastases. (Right) Fusion of PET and CT localises the abnormalities.

corresponding specificity was 55% with non-responders again showing shorter survival.[40]

For oesophageal carcinoma, FDG PET has confirmed higher diagnostic accuracy compared with conventional anatomical modalities such as CT in the detection of distant metastatic disease and is superior in evaluation of tumour recurrence. The data support FDG PET in the evaluation of neoadjuvant chemotherapy and this also provides prognostic information.

PANCREATIC CARCINOMA

FDG PET has shown utility in the differentiation of benign compared with malignant pancreatic masses. In several studies comparing this technique with CT, FDG PET has shown higher overall diagnostic accuracy and has resulted in a change in patient management. In a study of 106 patients with pancreatic masses (74 with pancreatic cancer and 32 with chronic pancreatitis), the overall sensitivity and specificity were 85% and 84%, respectively.[41] False positives occurred in inflammatory processes and false negatives occurred in patients with increased glucose levels. In the subgroup with normal glucose levels, the sensitivity improved to 98% and specificity was unchanged at 84%. Similarly, in a study of 65 patients evaluated for suspected pancreatic cancer, FDG PET showed a significantly higher sensitivity and specificity compared with CT (92% and 85% versus 65% and 61%, respectively).[42] Although FDG PET was false positive in several cases of chronic pancreatitis, CT was similarly false positive in these and several other cases. In a large study of 171 patients with suspected pancreatic cancer, FDG PET showed a good sensitivity (86%) and specificity (78%) in those with normal glucose levels (n=152), but lower sensitivity (42%) with similar specificity (86%) in those with increased glucose levels (n=19).[43] A smaller study of 56 patients with suspected pancreatic cancer showed FDG sensitivity and specificity that was superior to CT (94% and 97% versus 65% and 87%, respectively),[44] and an earlier study including 37 patients showed comparable results for FDG PET sensitivity (88%) and specificity (83%).[45] Based on these data, the European consensus conference designated FDG PET as an established indication for differentiation of benign and malignant pancreatic masses.[17] Earlier series have shown similarly good sensitivity and specificity.[46–52] A more recent prospective study of 42 patients, showed a lower sensitivity (71%) and lower specificity (64%).[53] False negatives were present in 9 of 42, but 3 of 9 had increased serum glucose levels and one was a predominantly mucinous adenocarcinoma that has been reported to have low FDG uptake. The aetiology of false positives was not clearly defined, but all had undergone a recent interventional study and inflammation was cited as a possible cause.[53]

The issue of false positives with inflammation may be problematic because of the comparatively high incidence and similar clinical, radiographic, and FDG PET uptake in chronic pancreatitis.[54] FDG PET studies using dual time point imaging[55 56] and dynamic imaging with kinetic analysis have shown higher specificity.[57] The issue of false negative results has primarily been reported in those with raised blood glucose levels or in diabetic patients. A lower test sensitivity has been demonstrated in association with high serum glucose levels.[41 43]

For staging, FDG PET has shown high sensitivity for liver metastases when serum blood glucose levels are normal and intrahepatic cholestasis is not present.[58] In lesions over 1 cm in size, the ability to detect liver metastases was excellent with a sensitivity of 97% (28 of 29) and excellent specificity of 95%. Marked intrahepatic cholestasis was associated with most of false positive results. Pancreatic tumours of neuroendocrine origin have shown lower accuracy with FDG, and thus, other PET radiotracers such as somatostatin receptor analogues are currently being developed and investigated.[59] Figure 3 illustrates the utility of FDG PET in identifying distant metastases.

The accuracy of FDG PET in the identification of primary pancreatic cancer and metastatic disease has resulted in

significant changes in patient management. FDG PET influenced the surgical management in up to 43% of cases by more accurate identification of tumour and by clarifying indeterminate lesions by CT or by detecting sites of unknown metastases or recurrence.[45] FDG PET may also identify tumour recurrence and metabolic response to therapy that may not be seen by CT.[60]

Preliminary data also suggest that tumour response assessed with FDG PET after chemotherapy shows correlation with prognosis.[61] In a prospective pilot study of 11 patients treated with chemotherapy, absence of FDG uptake one month after chemotherapy correlated with a significantly longer progression free survival and overall survival. The best CT criteria showed no correlation with either of these parameters. These encouraging preliminary data for FDG PET require further validation in a larger population.

Hepatocellular carcinoma

Several studies have shown the FDG PET has a comparatively low sensitivity for primary hepatocellular carcinoma. In a study of 20 patients with hepatocellular carcinoma, the diagnostic sensitivity was 55% compared with CT with a sensitivity of 90%.[62] A potential factor contributing to the lower sensitivity is the higher level of glucose-6-phosphatase in liver that is not found in normal tissue. This enzyme dephosphorylates FDG-6-PO_4 and decreases intracellular trapping, thus lowering radiotracer accumulation in tumours. In high grade hepatocellular carcinoma characterised by less cellular differentiation, this enzymatic activity may be present in lower concentrations. This is supported by the data showing increased FDG uptake is associated with higher tumour grades[62] that correlate with higher phosphorylation activity along with lower glucose-6-phosphatase dephosphorylation activity.[63] The FDG trapping as quantified by the SUV uptake ratio is inversely correlated with survival.[64] In a different clinical scenario, a decrease in the FDG uptake after transcatheter arterial chemoembolisation correlates with tumour necrosis, and therefore, these preliminary data are promising for use of FDG PET as an indicator of tumour viability after therapy.[65].

GASTRIC CARCINOMA

Limited data are available regarding the use of FDG PET for evaluation of gastric carcinoma.[66 67] In a retrospective study of 33 patients with gastric cancer evaluated for possible recurrence, FDG PET showed a comparatively low sensitivity (70%) and low specificity (69%).[66] The presence of signet cell type is comparatively high (62% prevalence) and has been postulated as a potential factor in low sensitivity.[68 69] The presence of glucose transporter-1 is rarely present in signet ring cell carcinoma and mucinous adenocarcinoma (2.0% and 6.3%, respectively)[68] and this has also been implicated as a potential cause of false negatives.[66] In glucose-1 transporter positive tumours, there is a significant association with indices of tumour aggressiveness including depth of invasion, lymphatic permeation, venous invasion, lymph node metastasis, hepatic metastasis, and carcinoma stage.[68] The survival of patients with glucose-1 transporter positive tumours is also significantly shorter,[68] and FDG positive tumours are associated with significantly shorter survival.[66] Thus, FDG uptake in these tumours is significantly related to poor prognosis.

CHOLANGIOCARCINOMA

There is limited reported experience using FDG PET for this rare tumour. The largest published study evaluated 34 patients with biliary disease (26 malignant and 8 benign) with eight normal controls.[70] The overall sensitivity and specificity were high (92% and 93%, respectively) in identifying the primary lesion. FDG PET also detected distant metastatic disease in 70% (7 of 10), however, the detection rate for regional or hepatoduodenal lymph node metastasis was only 13% (2 of 15). In an earlier preliminary study of 15 patients with biliary lesions (six malignant and nine benign) and five normal controls, the overall performance was excellent with all six of six true positives and all 14 of 14 true negatives.[71] A study of 15 consecutive patients with obstructive jaundice and a hilar mass showed less encouraging results.[72] FDG PET showed a sensitivity of 83%, and no specificity with all three false negative results in mucinous adenocarcinomas.[72] Overall, the data are encouraging, but the potential for false negatives in mucinous adenocarcinomas should be recognised.

SUMMARY

FDG PET has confirmed utility in the evaluation of colorectal and oesophageal carcinoma. The ability to detect metabolic abnormalities before structural anatomical abnormalities permits earlier detection of distant metastatic disease. Metabolic information is also especially advantageous in the detection of recurrent disease when tumour markers such as CEA are abnormal and anatomical imaging is unrevealing. By more accurately staging disease, FDG PET has shown both cost effectiveness and benefit in more appropriately influencing patient management. The cost savings are manifest through avoidance of unnecessary surgeries, and the benefits of more accurately staging metastatic disease are evident in data such as higher five year survival for patients selected for curative resection based on the findings of FDG PET. A currently evolving indication is evaluation of tumour response to therapy that may also provide prognostic information.

Further studies are in progress to evaluate diagnostic accuracy, cost effectiveness, and utility of FDG PET in the evaluation and management of several other gastrointestinal tumours. The initial results are encouraging and in many cases have shown higher accuracy than conventional anatomical imaging. Further developments in PET instrumentation such as co-registered PET and CT, algorithm development and implementation, and new radiotracer development may further improve the diagnostic evaluation and ultimately provide information for more appropriate medical management.

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