FDG PETCT in colorectal cancer

Introduction
Colorectal cancer represents the second most common malignancy worldwide, with approximately one million newly diagnosed cases each year, and is the fourth leading cause of cancer mortality.1,2 This article provides an overview of the role of FDG (fluorodeoxyglucose) PET (positron emission tomography) CT (computed tomography) for assessment in patients with colorectal cancer. A summary of key learning points is given in figure 1.

PETCT technique
PET is a nuclear medicine examination utilising FDG as a primary tracer. The FDG-PET component provides metabolic information by utilising the intensity of FDG uptake as a surrogate measure of a tumour’s metabolic activity, assessed both qualitatively via visual examination of the degree of uptake of a tumour relative to blood pool, and quantitatively via a standard uptake value (SUV). Not only is FDG taken up by tumours, but there is also some degree of physiological bowel uptake, and artefactual bowel uptake can be seen in response to administered medications. Careful evaluation of the spectrum of uptake pattern is mandatory to avoid false-positive interpretations. The routine use of bowel preparation and oral contrast for PETCT in colorectal cancer is debatable.

Indications of PETCT in colorectal cancer
The current evidence-based indications for the use of PETCT in the UK with regards to colorectal cancers is summarised below.3
1. Staging of patients with synchronous metastases at presentation suitable for resection or patients with equivocal findings on other imaging, for example, pulmonary or liver lesions.
2. Restaging of patients with recurrence being considered for radical surgery and/or metastatectomy.
3. Detection of recurrence in patients with rising tumour markers and/or clinical suspicion of recurrence with normal or equivocal findings on other imaging.

FDG PETCT for diagnosing and local staging of colorectal carcinoma
Based on the existing evidence, the use of PETCT in the initial diagnosis of colorectal cancer is not justified.4 Accurate T-staging is not possible with PETCT, as it does not provide the anatomic detail or the spatial resolution to accurately judge the degree to which a tumour extends through the rectal wall.5 The sensitivity for detection of locoregional nodal metastases is also low because lymph nodes are usually close to the primary tumour and cannot be differentiated from it as a result of ‘blooming’ (high intensity radiotracer uptake in the primary lesion which artifactually extends into the adjacent soft tissues and obscures uptake in small mesorectal nodes).6

FDG PETCT in management of colorectal cancer patients with metastatic disease
About 20% of patients with colorectal cancer are diagnosed with metastatic disease at presentation, the liver, lungs and peritoneum being the most common sites.7 Growing subsets of patients with metastatic colorectal cancer are being considered for treatment with curative intent. Accurate restaging of patients with potentially resectable metastases using PETCT is therefore crucial for optimal management.8

Several studies have shown the impact of PETCT on the management of this subgroup of patients. In a study of 157 patients with potentially resectable liver and/or pulmonary colorectal cancer metastases, PETCT upstaged disease in 33.1%, down staged disease in 24.9% and based on PETCT results surgery was averted in 33.8% patients.9 A survey of physicians who referred patients with colorectal cancer for PET found that the PET findings contributed to management change in 62% of patients.10 Nearly 35-55% patients with colorectal cancer develop liver metastases.11 For selected patients with metastases limited to the liver, hepatic resection may be curative with a five-year survival of greater than 30%, therefore accurate identification of the number, size, location and characterisation of hepatic lesions is essential.12 Despite its superior performance, PETCT cannot replace contrast enhanced MRI for detection of liver metastases, in particular smaller lesions, as PETCT is limited by its intrinsic resolution.13 Therefore if surgical resection is planned then dedicated contrast enhanced MRI should be performed in addition to PETCT for all patients with potentially resectable hepatic metastases (figure 2). Around 10-25% of patients with colorectal cancer develop pulmonary metastases but only a few of these have metastases confined to the lungs and it is currently impossible to identify those who may benefit the most from thoracotomy.14 For the detection of pulmonary metastases breath-hold diagnostic CT remains the mainstay for diagnosis, and suspicious pulmonary lesions on CT should be considered metastatic even if not FDG avid, particularly if new and with interval increase in size.

FDG PETCT for peritoneal metastases from colorectal cancer
Peritoneal metastases can occur in 10 to 30% of gastrointestinal cancers at presentation but is more frequent in recurrent disease. Peritoneal metastases have been historically regarded as a terminal development, however, if limited to the peritoneal cavity then in selected cases treatment with cytoreductive surgery and heated intraperitoneal chemotherapy can now improve prognosis, with survival reaching up to 60 months.15,16 Traditionally the gold standard for detection has been surgical exploration and an accurate non-invasive diagnosis of peritoneal metastasis is a major challenge. FDG PETCT has the potential to improve detection of peritoneal metastases as lesion conspicuity is high due to low background activity, fused PETCT offers the combined benefits of anatomic and functional imaging and has a role in preoperative patient selection (figure 3). Only limited data exist with regards to the role of PETCT in accurately detecting the true extent of disease and further studies would be needed comparing the preoperative peritoneal carcinomatosis index (PCI) score with the surgical PCI score to inform regarding the accuracy of FDG PETCT in this regard.

PETCT in management of colorectal cancer patients with recurrent disease
FDG PETCT is now considered the standard of care for suspected recurrence of colorectal carcinoma and has a direct impact on patient management in up to two-thirds of cases.17 Recurrent disease can be seen in up to one-third of patients, usually within three years of curative surgery.18,19 The dif-
ferentiation between local post-treatment change and recurrence can be extremely difficult on both CT and MR. A metaanalysis concluded that PETCT might be the modality of choice in evaluating patients with high suspicion of recurrence.

Characterisation of suspected local recurrence is based on a combination of findings including recognition of the pattern of uptake, intensity of uptake, time interval since previous surgery and other ancillary findings on PETCT. Local lesions are considered as positive for recurrence if they demonstrate focal, high intensity FDG uptake persisting several months after surgery. Local lesions without abnormal increased FDG uptake or with a diffuse peripheral low grade uptake occurring soon after surgery are considered benign and likely due to inflammation as opposed to recurrence (figure 4).

Carcinoembryonic antigen is widely used in the surveillance of post-operative colorectal carcinoma patients; however, the therapeutic decision-making is hampered by a false-negative rate of 30-40%. Data from several studies suggest that PETCT has a role in the detection of occult disease in patients with unexplained rising CEA levels with most studies showing high positive predictive values.

Limitations of PETCT

PET has a spatial resolution of 5-7mm and therefore has limited sensitivity for detecting small metastases. Certain tumours such as mucinous adenocarcinomas can be falsely negative due to limited FDG uptake because of their low cellular activity. The sensitivity of PETCT for detection of metastases is also lowered in patients treated by neoadjuvant chemotherapy. PETCT images are also susceptible to misregistration artefacts. Physiological FDG uptake in displaced pelvic organs can also account for erroneous interpretation.

In addition PETCT performed too soon after surgery (within six weeks) or radiotherapy (within eight weeks) may be false positive due to inflammatory uptake.

18F-FDG PETCT for response assessment in colorectal cancer

Pathological complete response (pCR) is noted in up to 30% of patients who undergo preoperative chemoradiotherapy (CRT). The key question raised is whether radical surgery should be necessary for patients with clinical complete response to CRT. Clinical assessment after CRT is known to be quite poor and conventional imaging modalities cannot distinguish fibrosis or scars from viable tumour cells in residual masses. The literature is mixed in regard to the ability of PETCT to predict response to neoadjuvant treatment in patients with rectal cancer. The majority of studies have reported post-treatment SUV to be lower than pretreatment scans, but post treatment SUV was not found to be quite poor and conventional imaging modalities cannot distinguish fibrosis or scars from viable tumour cells in residual masses.

References

28. Lannec Y, Mestet U, Gerbi G et al. The role of FDG PET imaging of 18-fluorodeoxyglucose positron emission tomography (PET-FDG) scan and computerized tomography (CT) in restaging patients with hepatic colorectal metastases following neoadjuvant chemotherapy: Comparison with operative and pathological findings. J Gastrointest Surg 2007;11(7):929-44.
1. Knowledge of the patterns of physiological FDG uptake in the large bowel and artefactual uptake secondary to drugs (metformin) is important to avoid false positive results.

2. Current guidelines do not recommend the routine use of FDG PETCT for initial diagnosis and staging of colorectal cancer.

3. The main role of FDG PETCT in restaging patients with potentially resectable metastatic disease is to avoid futile surgeries by identifying unexpected disease not seen on conventional imaging.

4. In patients with potentially resectable hepatic metastases, contrast enhanced MRI should be performed in addition to PETCT as a prerequisite, preoperative assessment tool.

5. FDG PETCT is the modality of choice for evaluating patients with a suspicion of local recurrence because of its high accuracy in lesion characterisation.

6. FDG PETCT is a useful problem solving test for evaluating patients with rising tumour markers and a negative conventional diagnostic work-up.

7. FDG PETCT post CRT can identify functional tumour response but fails to accurately predict the pathological complete responders.

8. False negative FDG PETCT results can be seen due to the small size of the lesion (<6mm), mucinous nature of the primary disease and assessment soon after neoadjuvant chemotherapy (<6 weeks).

**Figure 1**
Key learning points of FDG PETCT imaging in colorectal cancers.

**Figure 2**
Assessment of potentially resectable hepatic metastases. A 37-year-old woman with colorectal cancer treated with hemicolectomy followed by left hemihepatectomy for liver metastases. Follow-up PETCT showed a new FDG avid hepatic lesion adjacent to the staple line (arrows in B and D) which was not convincingly seen either on conventional contrast enhanced CT (A) or MR imaging (C) likely due to artefacts from surgical staples which can make assessment difficult. However, MR demonstrated two additional subtle focal lesions at the hepatic dome on T2W (arrows in E) that were not seen on the fused PETCT image at the same level (F). Small lesions (6mm or less) can be below the sensitivity of PET emphasising the complimentary role of the two modalities for complete assessment of the liver.

**Figure 3**
Depiction of unsuspected sites of disease. A 69-year-old female with rectosigmoid carcinoma. Conventional imaging revealed a rectosigmoid carcinoma with only a solitary left omental deposit (arrow in A). On FDG PETCT the omental deposit (long arrow in B, C) and the rectosigmoid primary (see in MIP image D) both demonstrated high intensity FDG uptake. However, in addition PETCT showed a left paraaortic node which, although sub-cm sized, showed high intensity uptake (red crosshairs) highly suspicious for metastatic retroperitoneal nodal disease making the patient unsuitable for curative surgery.

**Figure 4**
Assessment of suspected local recurrence. In the first case, conventional CT (A) demonstrated presacral soft tissue thickening seen following low anterior resection and radiotherapy for rectal cancer with no definite evidence to suggest recurrence. Fused PETCT, however, clearly depicted a focal area of eccentric uptake within this presacral soft tissue (arrow in B), suspicious for locally recurrent disease. The second case depicts typical appearances of a post-surgical collection seen as low density lesion subtended by hyperdense rim (C), with a smooth peripheral rim of FDG uptake along the walls of the collection (arrows in D).