# Management of recurrent colorectal cancer with positron emission tomography

*The use of positron emission tomography, on its own and in combination with computed tomography, has been integrated into the management algorithm of patients with suspected recurrence of colorectal cancer. This article looks at the biological basis of positron emission tomography, its clinical advantages and disadvantages.*

Colorectal cancer is the second most common malignancy in men and the third most common in women in the UK. Surgical resection remains the mainstay of treatment with good prognosis in tumours that are limited to the mucosa or confined within the muscularis propria. Even after apparently curative resection, recurrences occur usually within the first 2–3 years following surgery (Moertel et al, 1990; Barr et al, 1992; American Cancer Society, 1996; Sagar and Pemberton, 1996). Additional therapies such as chemotherapy and radiotherapy can reduce recurrence and improve long-term survival in selected groups of patients. However, the optimal management requires detailed assessment of the extent of the disease to identify those who are suitable for resection and those in whom radical surgery can be avoided enabling a palliative course of action. Advances in medical imaging have allowed these decisions to be made preoperatively.

In addition, early identification of loco-regional and distant recurrence following surgery is important in order to plan the ongoing management of such patients. Previous studies have shown that over 50% of patients with metastatic colorectal cancer brought to the operating room for attempted curative surgery were unable to undergo the planned operation because more extensive disease than anticipated was discovered at laparotomy (Charnsangavej and Whitley, 1993; Gupta et al, 1993; Babineau et al, 1994; John et al, 1994). Accurate detection of an increased tumour burden by non-invasive means would allow curative surgery to be offered to a better selected group of patients with metastatic colorectal cancer. Various modalities are used in the follow up of patients. Carcinoembryonic antigen (CEA) is only 59% sensitive and 84% specific and does not provide any information as to the site or sites of recurrence (Moertel et al, 1993). Cross-sectional imaging has been central to the assessment of these patients using computed tomography (CT), magnetic resonance imaging (MRI) and ultrasound. Although these imaging modalities can detect lesions, they cannot reliably distinguish between benign and malignant tumours or between pre- and post-therapeutic alterations such as scarring, inflammation or necrosis and neoplastic processes. Whole body positron emission tomography (PET) has been reported to be more sensitive and accurate than other imaging modalities.

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This review introduces PET, how it works, its relative strengths and limitations and the different clinical scenarios where it is increasingly contributing to the management of patients with recurrent colorectal cancer.

## Biological basis for PET

PET scanning was originally developed in the 1970s as a research tool (Ter-Pogossian et al, 1975) and was only introduced in the clinical set up in the 1990s. It uses short-lived radionuclides attached to biological molecules to allow the visualization of metabolic processes in the body by producing an image of the distribution. Positrons are positively charged subnuclear particles that collide in tissue close to the point of positron emission generating two high-energy photons at 180° to each other. These are detected by the PET scanner and used to determine their point of origin. The radionuclide most commonly used is fluorine-18 (18F), which is attached to a molecule that mimics glucose metabolism; 2-fluoro-2-deoxy-D-glucose (FDG) thereby producing 18F-FDG.

The biological basis of PET centres on the observations by German biochemist Otto Warburg in 1924 that cancer cells have enhanced glycolysis (Warburg, 1956). Tumour cells rely on adenosine triphosphate (ATP) generated from glycolysis to meet the energy requirements of rapidly replicating tissue. After intravenous injection, 18F-FDG is taken up by tumour cells and phosphorylated by hexokinase to FDG-6-phosphate in proportion to the glycolytic rates. Unlike glucose-6-phosphate, FDG-6-phosphate is not metabolized in the glycolytic pathway and remains trapped intracellularly because tumour cells do not contain sufficient amounts of glucose-6-phosphatase to reverse this reaction during the imaging procedure. Thus, the trapped FDG-6-phosphate provides a record of glycolysis in cells throughout the body that is imaged 45–60 minutes after the injection of FDG. The patients fast for 6 hours before the procedure to maximize the rate of uptake of 18F-FDG in tumours compared with normal tissue.

The data acquired can be reconstructed in sagittal, coronal or axial planes and this functional information can complement the high-resolution structural information provided by CT and MRI. The new generation scanners combine CT or MRI to produce co-registered images.

This technique does have some limitations (Barrington and O'Doherty, 2003). Non-malignant tissue that demonstrates either high glucose metabolism (myocardium, brain) or organs via which 18F-FDG is excreted (kidney, bladder) will also appear as high uptake on the PET scan. Normal physiological uptake also occurs in the small bowel and colon and experience is needed to differentiate this from pathology (Cook et al, 1999). The other major pitfall is that FDG uptake also occurs in inflammatory processes. Although the level of uptake is generally higher in tumours than in infection or inflammation there is overlap, which may result in diagnostic confusion. The timing of PET scanning in relation to treatment is an important consideration as uptake may be altered soon after treatment with increased uptake after radiotherapy (Tutt et al, 2004) and reduced uptake after chemotherapy as a result of stunning (Cremerius et al, 1998).

## Management and detection of recurrent colorectal disease

PET scanning has an increasing role in identifying patients who are suitable for surgical resection of recurrent disease. Two subgroups of patients have a particularly favourable outcome: those with isolated resectable local disease (Sagar and Pemberton, 1996) and those with resectable metastases confined to the liver (Ruers and Bleichrodt, 2002) and the lung (Rizk and Downey, 2002).

### Role of PET in evaluation of hepatic metastases

PET is a valuable tool in the preoperative assessment of patients with hepatic disease from colorectal carcinoma, primarily as a result of its ability to identify extrahepatic and distant sites of metastatic disease that would preclude curative surgery (Lai et al, 1996; Vitola et al, 1996; Fong et al, 1999). Many groups have now reported comparisons between conventional imaging and PET and confirm that PET has sensitivity and specificity approaching 100% for intrahepatic disease and 90% for extrahepatic disease (Beets et al, 1994; Lai et al, 1996; Delbeke et al, 1997; Flamen et al, 1999; Arulampalam et al, 2001; Johnson et al, 2001). Several studies have also shown that surgical management is changed substantially when PET is used as part of the preoperative staging protocol (Beets et al, 1994; Delbeke et al, 1997; Ogunbiyi et al, 1997; Flamen et al, 1999; Arulampalam et al, 2001; Johnson et al, 2001). In fact Strasberg et al (2001) suggested that incorporation of PET into the selection of patients with liver metastases for hepatic resection might improve the survival, possibly leading to a 3-year survival of 77%.

Various degrees of accuracy in the evaluation of hepatic metastases have been reported (Ogunbiyi et al, 1997; Boykin et al, 1999; Valk, 1999; Imadahl et al, 2000; Rohren et al, 2002), and this was addressed in a meta-analysis of the detection of recurrent colorectal cancer with FDG-PET (Huebner et al, 2000). The true accuracy has been hampered by the lack of well-designed controls. In these articles, no defined reference standard was used. PET findings were validated by the use of biopsy, clinical follow up, imaging follow up and even correlation with the imaging methods against which PET was being compared. In addition, small lesions in the liver were often excluded from the calculations of sensitivity and specificity, despite the importance of detecting these metastases.

Rohren et al (2002) used intraoperative ultrasonography and surgical exploration as the reference standard, which steered away from the problems seen in other articles. They confirmed that PET is highly accurate in determining the presence or absence of hepatic metastases in patients referred for potential resection of colorectal metastases to the liver, with sensitivity and specificity rates of 95% and 100% respectively. This indicates that PET is as accurate as other non-invasive cross-sectional techniques such as CT and MRI. However, they also noted that PET was less accurate in determining the number and precise distribution of hepatic metastases with smaller lesions being more difficult to visualize. This could be a result of insufficient tracer localization within a small tumour volume, high background uptake of FDG in the normal hepatic parenchyma, and respiratory motion of the liver during image acquisition. Even in retrospect small lesions, especially those less than 1 cm, could not be visualized. Nonetheless, despite these findings, several authors have consistently found that PET correctly upstages 6–32% of patients thus avoiding unnecessary surgery (Beets et al, 1994; Delbeke et al, 1997; Ogunbiyi et al, 1997; Boykin et al, 1999; Valk et al, 1999; Flamen et al, 1999; Imadahl et al, 2000; Arulampalam et al, 2001; Johnson et al, 2001) and improving the cost effectiveness of PET in comparison to CT (Huebner et al, 2000; Miles, 2001).

### Detection of recurrence in patients with raised CEA levels

CEA measurement is widely used in the surveillance of patients with resected colorectal cancer but its value in terms of patient outcome is controversial. Although it may detect recurrence it does not identify the site or size of recurrent disease and further imaging is required to provide this anatomical data. Although a second look laparotomy may detect recurrence in about 90% of patients, this subjects a significant number of unresectable patients to an unnecessary operation.

Flanagan et al (1998) looked at a small sample of 22 patients with rising CEA and normal CT imaging. PET correctly identified relapse in 17 out of 22 patients with sensitivity and specificity values of 100% and 71% respectively. In another study of 28 patients with raised CEA, normal CT and blind second look laparotomy, the results of PET and CEA scintigraphy were analysed as predictors of correct selection of patients for resection of recurrent disease (Libutti et al, 2001). Biopsy-proven recurrence was seen in 94% of patients and PET correctly predicted unresectable disease in 90% of patients whereas CEA scintigraphy failed to predict any. In addition, PET correctly predicted resectable disease in 81% and CEA scintigraphy in only 13% of patients. With patient by patient analysis, PET had a sensitivity of 89% and specificity of 50%. However, an accurate calculation of specificity was limited in the study as only two of the 28 patients who were explored were found to be free of disease. PET accurately predicted this in one patient and had a false positive reading in the other.

It would appear that PET is a useful adjunct to CEA surveillance and reduces unnecessary laparotomy in patients with unresectable disease. However, confirmation is required from larger series of asymtomatic patients with normal cross sectional imaging.

## Comparison of PET with CT imaging in patients with recurrent disease

Several studies have been performed comparing CT scan with PET scan in clinical decision making, but most use clinical decisions as an outcome (Schiepers et al, 1995; Ogunbiyi et al, 1997; Valk et al, 1999). Unfortunately, more therapeutic decisions are being made based on PET scan data without a clear understanding of how well the diagnostic findings correlate with the clinical findings.

Johnson et al (2001) reviewed 41 patients with recurrent colorectal cancer all of whom had CT imaging and PET scan before surgical exploration. PET scan was found to be more sensitive than CT when compared with actual operative findings in the liver (100% *vs* 69%), extrahepatic region (90% *vs* 52%), and abdomen as a whole (87% *vs* 67%). Sensitivities were not significantly different in the pelvic region (87% *vs* 61%). The advantage of this particular study is that every patient who was scanned underwent a surgical exploration; however, this does not mean that if the diagnostic test and the surgical findings were at variance, the surgical findings were always correct and the scan was always wrong.

Valk et al (1999) also compared PET with CT in a trial using histological diagnosis, serial CT imaging and clinical follow up as reference standards. In these patients PET sensitivity and specificity were 93% and 98% respectively, compared with 69% and 96% for CT. The authors also analysed cost-effectiveness based on discussions with the referring doctors and the assumption that patients with metastatic lesions in more than one anatomical location were no longer surgical candidates. The cost of surgical procedures that were avoided because of PET was then compared to the cost of PET imaging. The authors reported that unnecessary surgery would have been avoided in 32% of the patients with recurrent disease and concluded that $3000/patient could have been saved if PET had been included in the management algorithm. Delbeke et al (1997) and Meta et al (2001) provided similar estimates regarding the impact of PET.

## The clinical impact of PET in patients with suspected or confirmed colorectal cancer

The first study to address the impact of PET on managing patients with recurrent colorectal cancer from the referring physician's point of view was carried out in the form of a questionnaire (Meta et al, 2001). The aim was to determine the management changes which occurred as a result of the PET scan results. Of the 60 responses, changes in clinical stage were reported in 42%. As a result of the PET findings, major surgery was avoided in 41% of patients whereby treatment was changed from surgery to radiation, medical treatment or no treatment. On the other hand, surgery was the treatment of choice in 12% of patients because of the PET findings. These results are in keeping with previous studies, which reported that PET changed patient management or the clinical stage in 20–50% of patients with colorectal cancer (Beets et al, 1994; Lai et al, 1996; Vitola et al, 1996; Ogunbiyi et al, 1997). This survey-based study does, however, have its limitations; 50% of the surveys were not returned which likely introduced a responder bias. As a worst case scenario only supporters of PET might have responded, whereas those who believed that PET imaging was not useful might have refrained from the study.

Kalff et al (2002) carried out a prospective study to confirm the benefits of PET scanning suggested by earlier retrospective studies. The referring oncologists were asked to assign a treatment plan for 102 consecutive patients referred for a PET scan for suspected or confirmed recurrence with evidence of resectable disease on conventional imaging. Their plan was altered for 56% as a direct result of unexpected PET findings. The discrepant PET results were validated and were correct for both the presence and the extent of malignant disease in 91% of these patients, but gave a false positive in one patient because of a pelvic abscess and underestimated the extent of disease in four patients. Relapse was confirmed in 49 of 50 evaluable patients with positive PET findings. Planned surgery was abandoned in 26 (60%) of 43 patients because of incremental PET findings.

## Discussion

PET is no longer an emerging technology but has found a role in the management of patients with recurrent colorectal cancer. It provides functional information about tissue behaviour which complements the anatomical information gained from conventional imaging modalities such as CT and MRI. The limitations of PET that have been discussed in this review are increasingly being addressed with the introduction of modern PET-CT images combining both functional and anatomical detail.

These findings indicate that in a population of patients with recurrent colorectal disease PET is substantially more sensitive than conventional imaging. One must note, however, that underestimation of disease is not uncommon and negative results need ongoing surveillance as a minimum. Limited detection of low bulk disease and recurrent disease in the pelvis is a recognized limitation of PET (Boykin et al, 1999), but is also a failing of all imaging approaches. Respiratory movement and normal physiological uptake of 18F-FDG into the liver and the colon reduce the contrast resolution of PET thus liver lesions less than 1 cm are often not recognized.

Although PET scans are increasingly being used in the United States with numbers rising from 69 000 in 1998 to 155 000 in 2000, the scarcity of scanners in the UK may limit its speed of incorporation into the diagnostic and management pathway of recurrent colorectal cancer. More research is required to assess its role in other areas such as assessment of the tumour response to treatment, staging of disease at initial diagnosis and its use in follow up of patients after a curative surgical resection. **BJHM**

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American Cancer Society (1996) *Cancer facts and figures.* American Cancer Society, New York

Arulampalam T, Costa D, Visvikis D, Boulos P, Taylor I, Ell P (2001) The impact of FDG-PET on the management alogarithm for recurrent colorectal cancer. *Eur J Nucl Med* **28:** 1758–65

Babineau TJ, Lewis WD, Jemkins RL (1994) Role of staging laparoscopy in the treatment of hepatic malignancy. *Am J Surg* **167:** 151–5

Barr LC, Skene AI, Meirion J (1992) Metastasectomy. *Br J Surg* **79:** 1268–74

Barrington SF, O'Doherty MJ (2003) Limitations of PET for imaging lymphoma. *Eur J Nucl Med* **30**(suppl 1): s117–s127

Beets G, Penninckx F, Schiepers C (1994) Clinical value of whole body PET with 18F FDG in recurrent colorectal cancer. *Br J Surg* **81:** 1666–70

Boykin KN, Zibari GB, Lilien DL (1999) The use of FDG-PET for the evaluation of colorectal metastases to the liver. *Am Surg* **65:** 1183

Charnsangavej C, Whitley NO (1993) Metastases to the pancreas and peripancreatic lymph nodes from carcinoma of the right colon: CT findings in 12 patients. *Am J Roentgenol* **160:** 49–52

Cook GJ, Maisey MN, Fogelman I (1999) Normal variants artefacts and interpretative pitfalls in PET imaging with 18-FDG and carbon-11 methionine. *Eur J Nucl Med* **26:** 1363–78

Cremerius U, Effert PJ, Adam G (1998) FDG-PET for detection and therapy control of metastatic germ cell tumour. *J Nucl Med* **39:** 815–22

Delbeke D, Vitola JV, Sandler MP (1997) Staging recurrent metastatic colorectal carcinoma with PET. *J Nucl Med* **38:** 1196–201

Flamen P, Stroobants S, Van Cutsem E (1999) Additional value of whole body PET with fluorine-18-2-fluoro-2-deoxy-D-glucose in recurrent colorectal cancer. *J Clin Oncol* **17:** 894–901

Flanagan FL, Dehdasti F, Ogunbiyi OA, Rodner IJ Siegel BA (1998) Utility of FDG-PET for investigating unexplained plasma CEA elevation in patients for colorectal cancer. *Ann Surg* **227:** 319–23

Fong Y, Saldinger PF, Akhurst T (1999) Utility of 18-F FDG PET scanning on selection of patients for resection of hepatic colorectal metastases. *Am J Surg* **278:** 282

Gupta NC, Frank AR, Mailliard J (1993) Accurate detection of liver metastases in patients with primary malignancies using FDG-PET imaging. *J Nucl Med* **34:** 6P

Huebner RH, Park KC, Shepard JE (2000) A meta-analysis of the literature for whole body FDG-PET detection of recurrent colorectal cancer. *J Nucl Med* **41:** 1177

Imadahl A, Reinhardt MJ, Nitzsche EU (2000) Impact of 18F FDG-PET for decision making in colorectal cancer recurrences. *Lang Arch Surg* **385:** 129

John T, Greig JD, Crosbie JL (1994) Superior staging of liver tumours with laparoscopy and laparoscopic ultrasound. *Ann Surg* **220:** 711–19

Johnson K, Bakhsh A, Young D, Martin TE, Arnold M (2001) Correlating computed tomography and PET scan with operative findings in metastatic colorectal cancer. *Dis Colon Rectum* **44:** 354–7

Kalff V, Hicks RJ, Ware RE, Hogg A, Binns D, McKenzie AF (2002) The clinical impact of 18F-FDG PET in patients with suspected or confirmed recurrence of colorectal cancer: A prospective study. *J Nuc Med* **43**(4): 492–9

Lai DT, Fulham M, Steven MS (1996) The role of whole body positron emission tomography with 18-F FDG in identifying operable colorectal cancer metastases to the liver. *Arch Surg* **131:** 703

Libutti SK, Alexander HR, Choike P (2001) A prospective study of 2-18-F-FDG PET scan, 99m Tc-labelled arcitumonab (CEA-scan) and blind second look laparotomy for detecting colon cancer recurrence in patients with increasing CEA levels. *Ann Surg Oncol* **8:** 779–86

Meta J, Seltzer MA, Schiepers C (2001) Impact of IF-FDG-PET on managing patients with colorectal cancer: the referring physician's perspective. *J Nucl Med* **42**(4): 586–90

Miles KA (2001) An approach of demonstrating cost effectiveness of diagnostic imaging modalities in Australia illustrated by PET. *Aus Radiol* **45:** 9–18

Moertel CG, Fleming TR, Macdonald JS (1990) Levamisole and flurouracil for adjuvant therapy of resected colorectal cancer. *N Eng J Med* **322:** 352–8

Moertel CG, Fleming TR, Macdonald JS (1993) An evaluation of the carcinoembryonic antigen (CEA) test for monitoring patients with resected colon cancer. *JAMA* **270:** 943–7

Ogunbiyi OA, Flanagan FL, Dehdasti F (1997) Detection of recurrent and metastatic colorectal cancer. Comparison of PET and computed tomography. *Ann Surg Oncol* **4:** 613–20

Rizk NP, Downey RJ (2002) Resection of pulmonary metastases from colorectal cancer. *Semin Thorac Cardiovasc Surg* **14:** 29–34

Rohren EM, Paulson EK, Hagge R (2002) The role of 18-F FDG PET in preoperative assessment of the liver in patients being considered for curative resection of hepatic metastases from colorectal cancer. *Clin Nucl Med* **27**(8): 550–5

Ruers T, Bleichrodt RP (2002) Treatment of liver metastases. An update on the possibilities and results. *Eur J Cancer* **38:** 1023–33

Sagar PM, Pemberton JH (1996) Surgical Management of locally recurrent rectal cancer (review). *Br J Surg* **83:** 293–304

Schiepers C, Penninckx F, De Vadder N (1995) Contribution of PET in the diagnosis of recurrent colorectal cancer: comparison with conventional imaging. *Eur J Surg Oncol* **21:** 517–22

Strasberg SM, Dehdasti F, Siegal BA, Drebin JA, Linchan D (2001) Survival of patients evaluated by FDG-PET before hepatic resection for metastatic colorectal carcinoma. A prospective database study. *Ann Surg* **233:** 293–9

Ter-Pogossian MM, Phelps ME, Hoffman EJ (1975) A positron emission transaxial tomograph (PETT) for nuclear imaging. *Radiology* **114:** 89–98

Tutt J, Plunkett T, Barrington S, Leslie M (2004) The role of positron emission tomography in the management of colorectal cancer. *Colorectal Dis* **6(1)**: 2–9

Valk PE, Abella-Columna E, Haseman MK (1999) Whole body PET imaging with 18F FDG in management of recurrent colorectal cancer. *Arch Surg* **134:** 503–11

Vitola JV, Delbeke D, Sandler MP (1996) Positron emission tomography to stage suspected metastatic colorectal carcinoma to the liver. *Am J Surg* **171:** 21

Warburg O (1956) On the origin of cancer cells. *Science* **123:** 309–14


## KEY POINTS

- The biological basis for positron emission tomography (PET) scanning is that tumour cells readily uptake 18F-fluorodeoxyglucose when compared to normal tissue.
- PET has a sensitivity and specificity of greater than 95% in the detection of intrahepatic metastases but lesions less than 1 cm are often difficult to characterize.
- PET is superior to computed tomography in the detection of recurrent disease in hepatic and extra-hepatic sites but fails to provide anatomical detail.
- Recurrent disease is best assessed with a combination of PET and computed tomography images which provides both functional and anatomical detail.