

The expanding role of PET technology in the management of patients with colorectal cancer

R. A. Herbertson^{1,2*}, S. T. Lee^{1,3,4}, N. Tebbutt^{1,2} & A. M. Scott^{1,3,4}

¹Ludwig Institute for Cancer Research, Melbourne Centre for Clinical Sciences, ²Ludwig Institute Oncology Unit, ³Centre for Positron Emission Tomography,

⁴Department of Medicine, University of Melbourne, Austin Health, Heidelberg, Victoria, Australia

Received 21 January 2007; revised 20 February 2007; accepted 20 February 2007

The therapeutic options and subsequent survival of colorectal cancer (CRC) patients has increased substantially over recent years. While surgical excision of the primary cancer results in cure of ~50% of patients, recurrence and metastatic disease still remains a significant cause of death. Although resection of liver or lung metastases can result in cure, relapse rates remain high, indicating that patient selection needs improvement. Positron emission tomography (PET) technology has a great deal to offer with respect to CRC management, particularly in the setting of patient selection for metastasectomy and in the evaluation of possible recurrent disease, however it has not yet become a routine part of the management of all CRC patients. This review article aims to discuss the current and future implications of PET technology in the optimal management of CRC patients throughout their care pathway.

Key words: colorectal cancer, positron emission tomography

introduction

colorectal cancer

The last 5 years have brought significant improvements in the disease-free and overall survival of colorectal cancer (CRC) patients both in the primary and metastatic setting. This has largely been achieved by more accurate staging of disease, the improved and expanded role of surgery, and an increased number of available chemotherapeutic options. While the prognosis for untreated patients with metastatic disease is likely to be 6–12 months, the routine use of chemotherapeutics such as oxaliplatin and irinotecan and the future role of combinations with epidermal growth factor receptor and vascular endothelial growth factor targeted antibodies means patients have many more lines of potentially efficacious treatment. For those with unresectable disease, median survival is currently up to 20 months with combination chemotherapy [1, 2]. The increased role of surgery for metastatic disease is now well established, although the extent of resectability remains the topic of debate within the multi-disciplinary team. Liver-specific imaging in this situation often includes computed tomography (CT), magnetic resonance imaging (MRI), or 2-[fluorine-18]fluoro-2-deoxy-D-glucose (FDG)-PET, usually as directed by local surgical unit protocol. Less than 20% of patients who present with

hepatic metastases are potentially resectable, but it is clear that surgery is their only chance of potential cure. Five year overall survival following complete resection of isolated liver metastases has been reported as 30%–40% with a 10 year survival of 23%–26% [3, 4], indicating the proportion of patient who relapse following potentially curative resection remains high.

FDG-PET

Positron emission tomography (PET) technology uses radiotracers to detect and quantify cellular and biochemical processes non-invasively. ¹⁸F-2-fluoro-2-deoxy-D-glucose (FDG) is the most common radiotracer currently used in oncology. This is a glucose analogue attached to a positron emitting radionuclide ¹⁸F, which is taken up by cells overexpressing cell surface GLUT1 transporters, such as cancer cells. Once inside the cell, it is phosphorylated by hexokinase into glucose-6-phosphate and becomes trapped, as it is unable to enter the normal cellular glycolytic pathways. This intracellular trapping occurs preferentially in malignant cells as they are also known to have an increased metabolic rate and reduced glucose-6-phosphatase activity. The PET scanner is able to detect the positrons emitted by ¹⁸F as it decays intracellularly, and represent this visually. Semi-quantitative analysis of FDG-PET images can be carried out by calculating the standardised uptake value (SUV), which represents the metabolic activity for the tumour compared with that in surrounding tissue, corrected for injected dose and patient weight. PET imaging with radiotracers specific to other cellular processes such as membrane synthesis, cell proliferation,

*Correspondence to: Dr R. A. Herbertson, Ludwig Institute for Cancer Research, Melbourne Centre for Clinical Sciences, 1st Floor, Harold Stokes Building, Austin Hospital, 145 Studley Road, Heidelberg, Victoria 3084 Australia.
Tel: +61-394963098; Fax: +61-94965892; E-mail: rebecca.herbertson@ludwig.edu.au

cellular perfusion, and tumour hypoxia are also under investigation, and will also be discussed.

integrated FDG-PET/CT

Although FDG-PET allows the evaluation of the whole body, it is limited in the detection of small lesions (i.e. <1 cm) [5], not all tumour types are FDG avid, and it lacks specific anatomical detail. False positives in the presence of chronic inflammation and following surgery or radiotherapy may occur secondary to increased FDG uptake in neutrophils, granulation tissue, and macrophages. CT has long been established as the standard imaging modality for the assessment of malignancy, which is able to provide anatomical information and detect pathological change by identifying abnormal contrast enhancement. Depicting malignant change in normal sized structures such as lymph nodes or distinguishing residual scar tissue from active tumour are difficult with CT. Combining the functional information obtained from a FDG-PET scan with the anatomical detail of a CT scan has been shown to improve sensitivity, specificity, and accuracy of disease assessment [6–8]. Although much of the published evidence supporting the use of PET technology in CRC focuses on FDG-PET [6, 9, 10], it is increasingly well recognised that integrated FDG-PET/CT may provide superior information and is now the modality of choice where the resources are available. This article will review the evidence for FDG-PET and the more recent studies using FDG-PET/CT in CRC patients.

the role of PET technology in CRC

primary diagnosis and staging

The low sensitivity of FDG-PET for small lesions (<1 cm), and the chance of false positives in inflammatory bowel lesions, explains the current lack of evidence to indicate FDG-PET should be part of the routine screening or staging of patients. That is not to say it does not contribute to more accurate staging. While FDG-PET alone has a low sensitivity for lymph node involvement, small studies have shown FDG-PET/CT is more accurate in assessing tumour-node-metastasis stage compared with CT and FDG-PET alone [6, 9–13]. However, another study found it not superior to conventional staging with CT [12]. The primary staging of rectal cancers is one specific indication where FDG-PET/CT is likely to significantly impact on patient management, through more accurate staging. Although MRI already has an established role in rectal tumour staging by facilitating accurate assessment of the mesorectal fascia (and hence prospects for carrying out a total mesorectal excision) [14], the addition of FDG-PET/CT is likely to optimise accurate assessment of nodal [15] and metastatic disease. Combining accurate evaluation of tumour extent and local disease should aid the multi-disciplinary team in their decision making regarding the need for neo-adjuvant radiotherapy, however current published evidence is in a small cohort [15].

The detection of liver metastases is directly related to the size of the lesions. When detecting lesions <1.5 cm, spiral CT has been shown to be more sensitive than FDG-PET alone, but the addition of FDG-PET to standard staging CT is

complementary, and improves therapeutic management of patients with liver metastases [5]. FDG-PET can lead to changes in management in 2%–36% of CRC patients undergoing initial staging [11–13, 15, 16], but this small body of evidence (and lack of cost-benefit analysis) is yet to impact on general clinical practice, particularly when resources in many countries are currently limited.

patient selection for metastasectomy

One of the most compelling indications for the routine inclusion of FDG-PET/CT in CRC patient assessment is in those being considered for metastasectomy, as avoiding major surgery in patients with undetected nodal or distant metastatic disease is vital [17, 18]. Despite the now well-established role of liver metastasis resection in CRC patients, studies have indicated up to 75% of patients who undergo this potentially curative surgery still relapse [3, 19, 20], fuelling the debate as to what should be considered 'resectable'. This high relapse rate is at least partly a reflection of inaccurate staging, with occult extra-hepatic metastatic disease going undetected before surgery. Two meta-analyses demonstrate high sensitivity and specificity for FDG-PET in this setting [17, 18]. Wiering et al. [17] found that the pooled sensitivity and specificity of FDG-PET were 91.5% and 95.4% for extra-hepatic disease, compared to 60.9% and 91.1%, respectively, with CT. Bipat et al. [18] found a sensitivity of 94.6% on a per-patient basis with FDG-PET (64.7% with helical CT and 75.8% 1.5-T MRI) and 75.9% on a per-lesion basis (63.8% with helical CT and 64.4% 1.5-T MRI). On a per-lesion basis, Gadolinium and superparamagnetic iron oxide-enhanced MRI had significantly better sensitivity compared with non-enhanced MRI, but comparable sensitivity when compared with FDG-PET [18]. Currently, the need for liver-specific contrast-enhanced MRI in addition to CT is often reserved for the accurate characterisation of liver lesions in the presence of fatty infiltration (or after chemotherapy), but this is determined by local surgical unit policy. A change in therapeutic strategy on the basis of FDG-PET/CT in this setting in up to 30% of patients has been demonstrated [7, 17, 21], although it can also falsely upstage a small minority of patients [21]. Small studies have identified improved disease-free and overall survival in patients who were evaluated with FDG-PET before surgery [22, 23]. A considerable cost saving in terms of avoiding postoperative intensive care and potentially lengthy hospital stays is likely to be made by avoiding major surgery in patients with undetected extra-hepatic (or extra-pulmonary) disease. Figure 1 illustrates the use of FDG-PET/CT in the assessment of extra-hepatic disease before metastasectomy.

evaluation of recurrence

There is no evidence to support the use of FDG-PET in routine surveillance following curative primary surgery, however, FDG-PET and more recently integrated FDG-PET/CT now has an established role in the standard of care of patients with suspected recurrent disease (often presenting with a rising carcinoembryonic antigen) [24]. A meta-analysis of FDG-PET in the detection of recurrent CRC by Huebner et al found an overall sensitivity and specificity of 97% and 76% respectively,

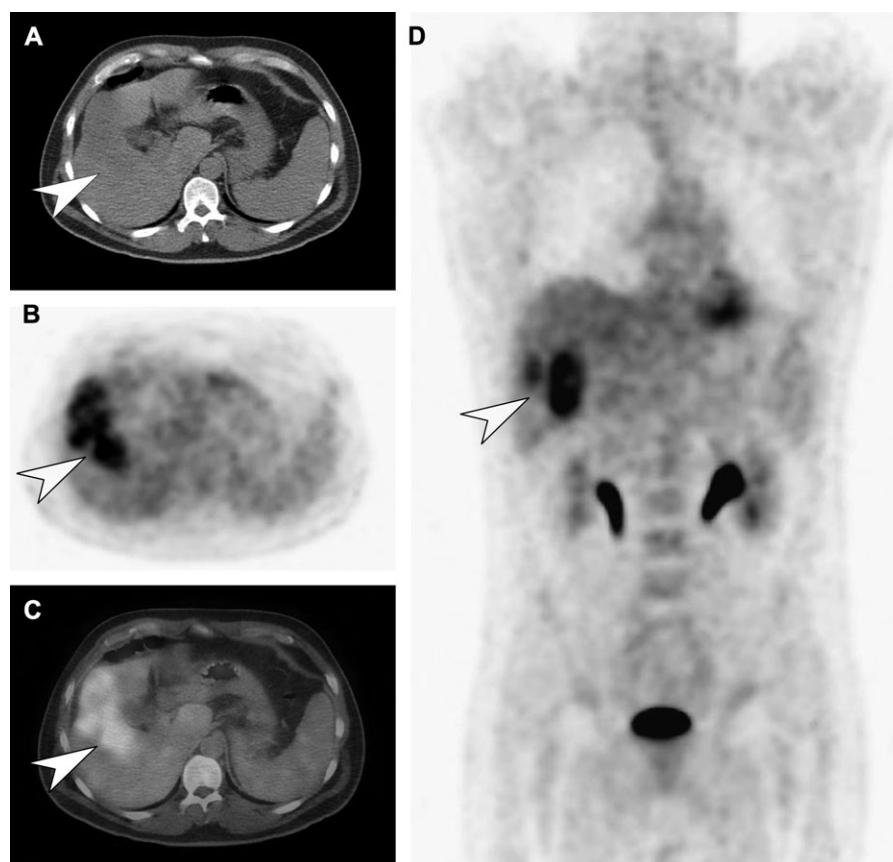


Figure 1. Pre-operative assessment prior to liver metastasectomy. Isolated liver metastasis (arrow) in the right lobe seen on CT (A), confirmed on transaxial FDG-PET (B) and integrated FDG-PET/CT (C) images. No extrahepatic disease was seen on whole body coronal FDG-PET (D), which demonstrated normal uptake in the myocardium, kidneys and urinary bladder.

which led to a change in management in 29%. This is similar to the 32% demonstrated in the summary of Gambhir et al. [16, 25]. The prospective, blinded comparison by Valk et al. [26] of FDG-PET and CT in CRC recurrence found that sensitivity and specificity were 93% and 98%, respectively, compared with 69% and 96% for CT. FDG-PET can be particularly helpful in the detection of omental or peritoneal disease, which is often difficult to detect on CT alone [27], but there are limitations to its sensitivity in the assessment of small pulmonary nodules (<1 cm) due to the resolution limitations of PET scanners. As well as being an important tool in the diagnosis of recurrence, FDG-PET also has a role in predicting resectability of recurrence, and hence improving the selection of patients suitable for further surgery [28]. Figure 2 demonstrates how FDG-PET/CT can aid in the detection of recurrent disease after liver surgery.

radiotherapy planning

Increasingly, it has been recognised that FDG-PET/CT can have a significant impact on radiotherapy planning in many tumour types. Although the data focusing specifically on rectal cancer are limited, it is likely that the results obtained in other tumour types translate to improved rectal tumour volume delineation in primary rectal carcinoma, but this requires further investigation. In a study by Ciernik et al. [29] of 39 cancer patients undergoing radiotherapy planning for lung, head and neck, and pelvic tumours, integrated FDG-PET/CT

led to an increase in the estimated gross tumour volume (GTV) in 17%–33%, and reduction in 19%–67% of cases. They concluded that in 56% of cases, GTV delineation was changed significantly if information from metabolic imaging was used in the planning process. The use of FDG-PET also reduced volume delineation variability between oncologists and revealed distant metastases in 16% leading to a change in treatment strategy from curative to palliative. Dizendorf et al. [30] found FDG-PET led to a change in management in 27% of 202 consecutive cancer patients as a result of the detection of distant or lymph node metastases, changing radiation volume or intention of treatment. Although small studies indicate that tumour target volume assessment may be improved with the addition of FDG-PET, further clarification of this specifically in rectal cancer patients is required.

response assessment

assessing early metabolic response to chemotherapy. Responding tumours undergo functional metabolic changes before any structural stabilisation or shrinkage can be visualised on CT scanning, and the development of FDG-PET means imaging the earliest of physiological changes in response to treatment is now becoming a reality. Neo-adjuvant chemotherapy (usually with an oxaliplatin-based regimen) is considered one of the standard options for multiple colorectal liver metastases to improve complete resection rate and overall survival [31], and is

known to downstage a proportion of those initially deemed unresectable [32]. This strategy can also help identify those with biologically aggressive disease as unsuitable for subsequent resection. FDG-PET can provide the opportunity to assess early metabolic response to neo-adjuvant chemotherapy, and may aid the decision regarding the most appropriate length of neo-adjuvant chemotherapy required to maximize response before surgery [33–36]. Findlay et al. [33] found tumour to liver ratio could discriminate responders from non-responders at 4–5 weeks, and review by Young et al. [37] stated that although reduction in SUV after one cycle of chemotherapy could predict response and correlate with subsequent tumour shrinkage, this measurement became more reliable after two or three cycles. Figure 3 demonstrates a complete metabolic response to chemotherapy on FDG-PET/CT.

The recent evidence indicating early metabolic response to chemotherapy correlates with later RECIST (Response Evaluation Criteria in Solid Tumours) response on CT [24, 33, 38, 39], has led to the proposed European Organisation for Research and Treatment of Cancer criteria for FDG-PET determined metabolic response [37]. The National Cancer Institute have also acknowledged the importance of FDG-PET

in assessing therapeutic efficacy, and have published protocols to standardise methods for obtaining and analysing FDG-PET across multicentre clinical trials [40]. FDG-PET in the assessment of metastatic gastrointestinal stromal tumours to imatinib mesylate is a good example of a clinical scenario where PET has proven benefit over CT in the assessment of early response to a molecular targeted therapy [41]. Using FDG-PET in the early assessment of new agents in early-phase clinical trials may also provide a way of assessing efficacy early and speeding up the drug development process.

assessing response to other treatment modalities. Including FDG-PET in response assessment at treatment completion may help in determining the presence of residual disease following radiotherapy, chemoradiotherapy or local ablative therapy [24, 42], and act as a baseline before ongoing follow-up. Although it can generally be carried out within 4 weeks of the completion of chemotherapy, there should be a longer interval left following radiation or surgery owing to the possibility of false positives with inflammation or regenerating tissue [24]. When carried out at an appropriate time point following treatment, it has the potential to offer information on residual



Figure 2. Evaluation of recurrent disease following left liver metastasectomy. No recurrent disease was identified on diagnostic CT (not shown). Subsequent FDG-PET scans showed a 3cm lesion (arrow) seen on transaxial PET image (A), localized to a soft tissue lesion on concurrent CT (B) and integrated FDG-PET/CT (C).

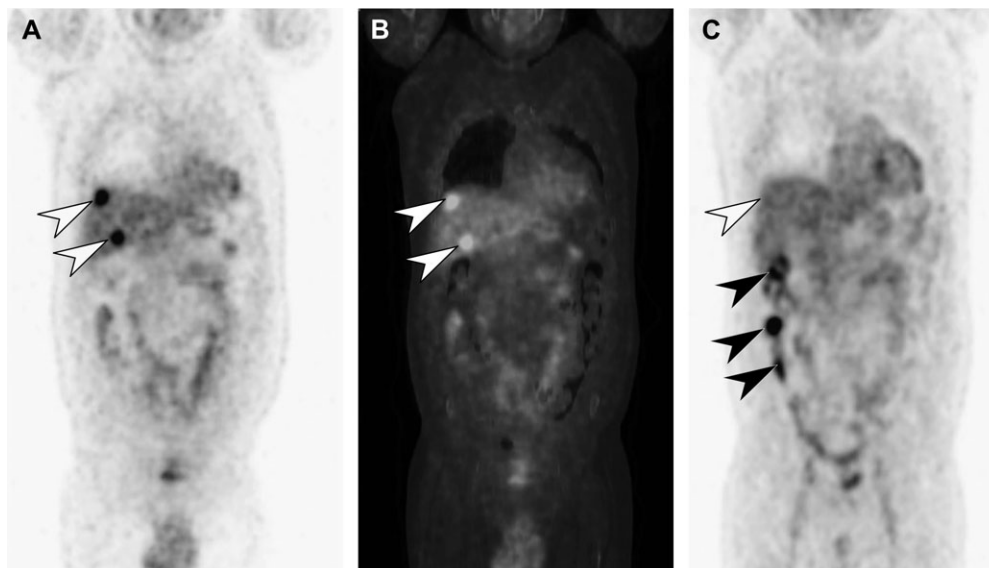


Figure 3. Assessment of response to chemotherapy. Pre-treatment coronal PET (A) and integrated coronal FDG-PET/CT (B), showing 2 metabolically active lesions in the liver (white arrows). Post-treatment coronal FDG-PET (C) shows complete metabolic response in these liver lesions (white arrow), with physiologic uptake in normal bowel (black arrows).

tumour cell viability, differentiate tumour from fibrosis or scarring, and help predict survival [43]. Two small studies looked at the ability of pre-operative FDG–PET to aid in assessing response to neo-adjuvant chemoradiation and subsequent outcome in rectal cancer. Guillem et al. [44] found a greater mean percentage decrease in SUVmax correlated with a better outcome in 15 rectal cancer patients, and Kalff et al. [45] found FDG–PET response following neo-adjuvant chemoradiation was associated with disease-free and overall survival.

molecular imaging using other PET radiotracers

With the development of novel molecular targeted therapies and biological agents, PET technology is the focus of much interest for its potential role in non-invasive molecular imaging, and the assessment of the molecular effects of new agents. PET is likely to have an increasingly important future role in translational research, having the ability to focus on underlying tumour cell biology and image malignant cellular processes. While the assessment of standard chemotherapeutics have focused on tumour shrinkage, novel therapies may have a cytostatic rather than cytotoxic effect, hence creating challenges especially in early-phase clinical trials using standard RECIST response criteria. Recognition that molecular imaging techniques must be developed alongside new therapies that specifically target molecular processes such as proliferation and angiogenesis has led to the investigation of newer radiotracers. ^{18}F -3'-deoxy-3- fluorothymidine (^{18}F -FLT), ^{11}C -choline, ^{15}O -water, and ^{18}F -fluoromisonidazole (^{18}F -FMISO) are all such investigational agents being evaluated in clinical trials.

markers of proliferation. Recent development of a biologically stable thymidine analogue ^{18}F -FLT can be used to detect cellular amino acid (and hence DNA) synthesis when it becomes trapped intracellularly following phosphorylation by thymidine kinase-1, which is elevated in malignant cells. These properties indicate that it may act as a potential marker of colorectal tumour cell proliferation, and hence provide a possible method for non-invasive grading of tumours. Although this remains an experimental indication, it has potential as a non-invasive method for predicting early response to adjuvant chemotherapy or assessing efficacy of cytostatic drugs [46].

Radiolabelled choline radiotracers such as ^{11}C -choline and ^{18}F -choline are also potential markers of cellular proliferation. Choline is needed for many cellular processes, but in tumour cells radiolabelled choline is thought to correlate with cell membrane phospholipid synthesis, and hence cellular proliferation rate [47]. ^{15}O -water is a freely diffusible radiotracer which is under investigation as a marker of perfusion [48]. It has the potential to be used in clinical trials to monitor changes in blood flow in response to chemotherapy or anti-angiogenic agents such as bevacizumab [49].

hypoxia imaging. Solid tumours become hypoxic when cellular proliferation exceeds the supply of oxygen from inadequate tumour vasculature, and it is thought to contribute to chemotherapy and radiotherapy resistance through a number of mechanisms in variety of tumour types [50]. Hypoxia is involved in initiating angiogenesis (via its influence on the 'angiogenic switch'), which is directly associated with metastatic

potential and cancer progression [50, 51]. ^{18}F -FMISO is a hypoxia selective agent that shows potential as a radiotracer for non-invasive imaging of tumour hypoxia and hence may have a future role in the evaluation of molecular response to agents such as bevacizumab. It is a nitromidazole derivative, which becomes trapped in hypoxic tissue as low partial pressure of Oxygen prevents re-oxidation of ^{18}F -FMISO metabolites. In glioma, it has been shown to provide a non-invasive assessment of hypoxia and be prognostic for treatment outcome [52], but studies in CRC patients are still in progress. Early resolution of ^{18}F -FMISO abnormality during treatment has been shown to be associated with improved locoregional control in head and neck cancer [53], and similar findings may be possible in CRC, but no published evidence is available. One limitation to hypoxia imaging is that it is often associated with reduced perfusion, meaning it maybe difficult for the radiotracer to be delivered to the area of interest [48], but Bruehlmeier et al. [54] found hypoxia was independent of perfusion in gliomas. Using ^{18}F -FMISO and ^{15}O -water for molecular response imaging in patients receiving agents like bevacizumab is under investigation. Selecting patients most likely to benefit from such targeted therapies and assessing early molecular response (e.g. reduced tumour hypoxia as a result of vasculature normalization), could improve cost-effectiveness, individualise treatment, and potentially improve outcome.

incidental colorectal lesions

FDG–PET has been shown to have an 84% specificity for detecting colonic adenomas, and the diagnostic test characteristics improve with the size and grade of adenoma [55]. Incidental FDG accumulations in the gastrointestinal tract have been reported in 1.3%–3% of patients having a FDG–PET/CT, and have been shown to be associated with a substantial risk of underlying cancer or pre-cancerous lesion [56, 57]. Further investigation of such lesions is essential, as early detection of an occult CRC is likely to have a significant impact on patient management and outcome.

summary

Although PET technology cannot replace CT or MRI for accurate anatomical imaging of CRC, there is sufficient evidence to indicate that FDG–PET can impact significantly on patient management. The strongest evidence currently supports its routine use in the assessment of suspected recurrence and in patient selection for metastasectomy. The Centers for Medicare and Medicaid Services (CMS) in the United States expanded its reimbursable coverage for FDG–PET to include 'all clinically appropriate uses of PET in CRC' in December 2000 [58]. For primary diagnosis coverage, 'PET must be used to potentially avoid or direct an invasive diagnostic procedure'. For use in staging or restaging of disease, PET is only covered if staging is uncertain following conventional imaging and if "the clinical management of the patient may differ according to the stage of the disease" [58]. Despite this, it is yet to become a routine component of the investigation of CRC patients for these indications in many other countries. While the CMS have accepted that accuracy data and evidence of impact on management are sufficient for

Table 1. Evidence for the use of FDG–PET in CRC with supporting references and recommendations

Indication	Summary of evidence	References	Recommendation
Primary diagnosis and staging	FDG–PET/CT improved TNM assessment and diagnostic interpretation of FDG–PET in cancer patients A few small studies in CRC assessing the additional benefit of FDG–PET indicate a potential impact on management in 2%–36% of patients	[6, 9, 10] [11–13, 15, 16]	There is limited evidence to support the routine use of FDG–PET in the initial staging of all CRC, but evidence is emerging that it may have a particular impact on the management of rectal cancer patients
Patient selection for metastasectomy	A number of prospective studies support the use of FDG–PET in the assessment of potentially resectable liver metastases on the basis of improved disease detection (especially extra-hepatic disease) and improved sensitivity (compared with CT) Meta-analysis reported FDG–PET in this situation led to management change in 31.6% of patients	[5, 7, 21–23] [17]	FDG–PET should be part of routine investigation of patients being considered for resection of liver metastases
Evaluation of recurrence	Small studies have shown FDG–PET to be more sensitive than CT in the detection of recurrence, and FDG–PET/CT more accurate, sensitive and specific than FDG–PET in this setting Meta-analysis of 11 studies reported a sensitivity of 97% and specificity of 76% for FDG–PET in detecting CRC recurrence. Leading to a management change in 29%	[8, 26, 28, 42, 62] [25]	FDG–PET should be part of the routine restaging of a patient with clinical or structural suspicion of recurrent CRC
Radiotherapy planning	No evidence could be found specifically in rectal cancer patients, but there is a small body of evidence to indicate FDG–PET/CT leads to changes in GTV, treatment intent, and hence management in cancer patients in general	[29, 30]	There is no current evidence to support this indication in rectal cancer. Clinical trials investigating the impact on management of FDG–PET/CT in radiotherapy planning of rectal cancer should be encouraged
Response assessment	Small studies have indicated FDG–PET following pre-operative chemoradiation may predict long-term outcome Small studies report that early FDG–PET response to chemotherapy can predict pathologically documented response, and discriminate response from non-response	[36, 44, 45] [33–35]	FDG–PET response following chemoradiation may help predict response, but this remains an experimental indication Although this is a promising future indication for FDG–PET, it should still currently be limited to clinical trials
Molecular imaging	There is evidence to indicate a number of radiotracers may have potential in the molecular imaging of tumours, including CRC.	[46–49, 53]	Molecular imaging of tumours is an increasingly important field but further research is required and should be encouraged

FDG–PET, 2-[fluorine-18]fluoro-2-deoxy-D-glucose positron emission tomography; CRC, colorectal cancer; CT, computed tomography; TNM, tumour–node–metastasis; GTV, gross tumour volume.

its inclusion in routine care in CRC patients, others have called for more prospective randomized trials to prove its ability impact on patient outcome. PET is a diagnostic test rather than an intervention; therefore, this type of outcome study is largely inappropriate. It would be very difficult to attribute an

improvement in outcome on the addition of a diagnostic test, as any result would be confounded by the effects of therapy [59]. Prospective studies are important, but guidelines for the funding of FDG–PET should be based on the evidence for impact on patient management, rather than outcome.

Cost–benefit analysis for the use of FDG–PET in CRC patients before metastasectomy is likely to fuel the support for public funding for this indication, as small studies have already indicated that it can reduce overall costs [60, 61]. Further similar studies for other CRC indications are warranted. The evidence presented (summarized in Table 1) clearly demonstrates FDG–PET impact on patient management, particularly in detection of metastatic or possible recurrent disease, and should therefore be utilized in patients with CRC in these clinical scenarios.

references

- Hurwitz H, Fehrenbacher L, Novotny W et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004; 350: 2335–2342.
- Grothey A, Sargent D, Goldberg RM, Schmoll H-J. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. *J Clin Oncol* 2004; 22: 1209–1214.
- Fong Y, Fortner J, Sun RL et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 1999; 230: 309–318; discussion 318–321.
- Choti MA, Sitzmann JV, Tiburi MF et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. *Ann Surg* 2002; 235: 759–766.
- Ruers TJ, Langenhoff BS, Neeleman N et al. Value of positron emission tomography with [F-18]fluorodeoxyglucose in patients with colorectal liver metastases: a prospective study. *J Clin Oncol* 2002; 20: 388–395.
- Antoch G, Saoudi N, Kuehl H et al. Accuracy of whole-body dual-modality Fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography and computed tomography (FDG-PET/CT) for tumor staging in solid tumors: comparison with CT and PET. *J Clin Oncol* 2004; 22: 4357–4368.
- Selzner M, Hany TF, Wildbrett P et al. Does the novel PET/CT imaging modality impact on the treatment of patients with metastatic colorectal cancer of the liver? *Ann Surg* 2004; 240: 1027–1034; discussion 1035–1026.
- Votrubova J, Belohlavek O, Jaruskova M et al. The role of FDG-PET/CT in the detection of recurrent colorectal cancer. *Eur J Nucl Med Mol Imaging* 2006; 33: 779–784.
- Bar-Shalom R, Yefremov N, Guralnik L et al. Clinical performance of PET/CT in evaluation of cancer: additional value for diagnostic imaging and patient management. *J Nucl Med* 2003; 44: 1200–1209.
- Hany TF, Steinert HC, Goerres GW et al. PET diagnostic accuracy: improvement with in-line PET-CT system: initial results. *Radiology* 2002; 225: 575–581.
- Park IJ, Kim HC, Yu CS et al. Efficacy of PET/CT in the accurate evaluation of primary colorectal carcinoma. *Eur J Surg Oncol* 2006; 32: 941–947.
- Furukawa H, Ikuma H, Seki A et al. Positron emission tomography scanning is not superior to whole body multidetector helical computed tomography in the preoperative staging of colorectal cancer. *Gut* 2006; 55: 1007–1011.
- Kantorova I, Lipska L, Belohlavek O et al. Routine (18)F-FDG PET preoperative staging of colorectal cancer: comparison with conventional staging and its impact on treatment decision making. *J Nucl Med* 2003; 44: 1784–1788.
- Klessen C, Rogalla P, Taupitz M. Local staging of rectal cancer: the current role of MRI. *Eur Radiol* 2007; 17: 379–389.
- Gearhart SL, Frassica D, Rosen R et al. Improved staging with pretreatment positron emission tomography/computed tomography in low rectal cancer. *Ann Surg Oncol* 2006; 13: 397–404.
- Gambhir SS, Czernin J, Schwimmer J et al. A tabulated summary of the FDG PET literature. *J Nucl Med* 2001; 42: 1S–93S.
- Wiering B, Krabbe PF, Jager GJ et al. The impact of fluor-18-deoxyglucose-positron emission tomography in the management of colorectal liver metastases. *Cancer* 2005; 104: 2658–2670.
- Bipat S, van Leeuwen MS, Comans EF et al. Colorectal liver metastases: CT, MR imaging, and PET for diagnosis—meta-analysis. *Radiology* 2005; 237: 123–131.
- Pessaux P, Lermite E, Brehant O et al. Repeat hepatectomy for recurrent colorectal liver metastases. *J Surg Oncol* 2006; 93: 1–7.
- Metcalfe MS, Mullin EJ, Maddern GJ. Choice of surveillance after hepatectomy for colorectal metastases. *Arch Surg* 2004; 139: 749–754.
- Truant S, Huglo D, Hebbar M et al. Prospective evaluation of the impact of [18F]fluoro-2-deoxy-D-glucose positron emission tomography of resectable colorectal liver metastases. *Br J Surg* 2005; 92: 362–369.
- Strasberg SM, Dehdashti F, Siegel BA et al. Survival of patients evaluated by FDG-PET before hepatic resection for metastatic colorectal carcinoma: a prospective database study. *Ann Surg* 2001; 233: 293–299.
- Fernandez FG, Drebin JA, Linehan DC et al. Five-year survival after resection of hepatic metastases from colorectal cancer in patients screened by positron emission tomography with F-18 fluorodeoxyglucose (FDG-PET). *Ann Surg* 2004; 240: 438–447; discussion 447–450.
- Juweid ME, Cheson BD. Positron-emission tomography and assessment of cancer therapy. *N Engl J Med* 2006; 354: 496–507.
- Huebner RH, Park KC, Shepherd JE et al. A meta-analysis of the literature for whole-body FDG PET detection of recurrent colorectal cancer. *J Nucl Med* 2000; 41: 1177–1189.
- Valk PE, Abella-Columna E, Haseman MK et al. Whole-body PET imaging with [18F]Fluorodeoxyglucose in management of recurrent colorectal cancer. *Arch Surg* 1999; 134: 503–511.
- Tanaka T, Kawai Y, Kanai M et al. Usefulness of FDG-positron emission tomography in diagnosing peritoneal recurrence of colorectal cancer. *Am J Surg* 2002; 184: 433–436.
- Lonneux M, Reffad AM, Detry R et al. FDG-PET improves the staging and selection of patients with recurrent colorectal cancer. *Eur J Nucl Med Mol Imaging* 2002; 29: 915–921.
- Ciernik IF, Dizendorf E, Baumert BG et al. Radiation treatment planning with an integrated positron emission and computer tomography (PET/CT): a feasibility study. *Int J Radiat Oncol Biol Phys* 2003; 57: 853–863.
- Dizendorf EV, Baumert BG, von Schulthess GK et al. Impact of whole-body 18F-FDG PET on staging and managing patients for radiation therapy. *J Nucl Med* 2003; 44: 24–29.
- Tanaka K, Adam R, Shimada H et al. Role of neoadjuvant chemotherapy in the treatment of multiple colorectal metastases to the liver. *Br J Surg* 2003; 90: 963–969.
- Leonard GD, Brenner B, Kemeny NE. Neoadjuvant chemotherapy before liver resection for patients with unresectable liver metastases from colorectal carcinoma. *J Clin Oncol* 2005; 23: 2038–2048.
- Findlay M, Young H, Cunningham D et al. Noninvasive monitoring of tumor metabolism using fluorodeoxyglucose and positron emission tomography in colorectal cancer liver metastases: correlation with tumor response to fluorouracil. *J Clin Oncol* 1996; 14: 700–708.
- Dimitrakopoulou-Strauss A, Strauss LG, Rudi J. PET-FDG as predictor of therapy response in patients with colorectal carcinoma. *Q J Nucl Med* 2003; 47: 8–13.
- Goshen E, Davidson T, Zwas ST, Aderka D. PET/CT in the evaluation of response to treatment of liver metastases from colorectal cancer with bevacizumab and irinotecan. *Technol Cancer Res Treat* 2006; 5: 37–43.
- Konski A, Hoffman J, Sigurdson E et al. Can molecular imaging predict response to preoperative chemoradiation in patients with rectal cancer? A Fox Chase Cancer Center prospective experience. *Semin Oncol* 2005; 32: S63–S67.
- Young H, Baum R, Cremerius U et al. Measurement of clinical and subclinical tumour response using [18F]-fluorodeoxyglucose and positron emission tomography: review and 1999 EORTC recommendations. *Eur J Cancer* 1999; 35: 1773–1782.
- Eli PJ. The contribution of PET/CT to improved patient management. *Br J Radiol* 2006; 79: 32–36.
- Weber W, Petersen V, Schmidt B et al. Positron emission tomography in non-small-cell lung cancer: prediction of response to chemotherapy by quantitative assessment of glucose use. *J Clin Oncol* 2003; 21: 2651–2657.

40. Shankar LK, Hoffman JM, Bacharach S et al. Consensus recommendations for the use of 18F-FDG PET as an indicator of therapeutic response in patients in National Cancer Institute Trials. *J Nucl Med* 2006; 47: 1059–1066.
41. Gayed I, Vu T, Iyer R et al. The role of 18F-FDG PET in staging and early prediction of response to therapy of recurrent gastrointestinal stromal tumors. *J Nucl Med* 2004; 45: 17–21.
42. Langenhoff BS, Oyen WJ, Jager GJ et al. Efficacy of fluorine-18-deoxyglucose positron emission tomography in detecting tumor recurrence after local ablative therapy for liver metastases: a prospective study. *J Clin Oncol* 2002; 20: 4453–4458.
43. de Geus-Oei LF, Wiering B, Krabbe PF et al. FDG-PET for prediction of survival of patients with metastatic colorectal carcinoma. *Ann Oncol* 2006; 17: 1650–1655.
44. Guillem JG, Moore HG, Akhurst T et al. Sequential preoperative fluorodeoxyglucose-positron emission tomography assessment of response to preoperative chemoradiation: a means for determining longterm outcomes of rectal cancer. *J Am Coll Surg* 2004; 199: 1–7.
45. Kalff V, Duong C, Drummond EG et al. Findings on 18F-FDG PET scans after neoadjuvant chemoradiation provides prognostic stratification in patients with locally advanced rectal carcinoma subsequently treated by radical surgery. *J Nucl Med* 2006; 47: 14–22.
46. Francis DL, Freeman A, Visvikis D et al. In vivo imaging of cellular proliferation in colorectal cancer using positron emission tomography. *Gut* 2003; 52: 1602–1606.
47. Cook GJ. Oncological molecular imaging: nuclear medicine techniques. *Br J Radiol* 2003; 76: S152–S158.
48. Weber WA. Positron emission tomography as an imaging biomarker. *J Clin Oncol* 2006; 24: 3282–3292.
49. Laking GR, West C, Buckley DL et al. Imaging vascular physiology to monitor cancer treatment. *Crit Rev Oncol Hematol* 2006; 58: 95–113.
50. Shannon AM, Bouchier-Hayes DJ, Condon CM, Toomey D. Tumour hypoxia, chemotherapeutic resistance and hypoxia-related therapies. *Cancer Treat Rev* 2003; 29: 297–307.
51. Yoshimura H, Dhar DK, Kohno H et al. Prognostic impact of hypoxia-inducible factors 1 α and 2 α in colorectal cancer patients: correlation with tumor angiogenesis and cyclooxygenase-2 expression. *Clin Cancer Res* 2004; 10: 8554–8560.
52. Cher LM, Murone C, Lawrentschuk N et al. Correlation of hypoxic cell fraction and angiogenesis with glucose metabolic rate in gliomas using 18F-fluoromisonidazole, 18F-FDG PET, and immunohistochemical studies. *J Nucl Med* 2006; 47: 410–418.
53. Hicks RJ, Rischin D, Fisher R et al. Utility of FMISO PET in advanced head and neck cancer treated with chemoradiation incorporating a hypoxia-targeting chemotherapy agent. *Eur J Nucl Med Mol Imaging* 2005; 32: 1384–1391.
54. Bruehlmeier M, Roelcke U, Schubiger PA, Ametamey SM. Assessment of hypoxia and perfusion in human brain tumors using PET with 18F-fluoromisonidazole and 15O-H₂O. *J Nucl Med* 2004; 45: 1851–1859.
55. van Kouwen MCA, Nagengast FM, Jansen JBMJ et al. 2-(18F)-Fluoro-2-Deoxy-D-Glucose Positron Emission Tomography Detects Clinically Relevant Adenomas of the Colon: a prospective study. *J Clin Oncol* 2005; 23: 3713–3717.
56. Kamel EM, Thumshirn M, Truninger K et al. Significance of incidental 18F-FDG accumulations in the gastrointestinal tract in PET/CT: correlation with endoscopic and histopathologic results. *J Nucl Med* 2004; 45: 1804–1810.
57. Israel O, Yefremov N, Bar-Shalom R et al. PET/CT detection of unexpected gastrointestinal foci of 18F-FDG uptake: incidence, localization patterns, and clinical significance. *J Nucl Med* 2005; 46: 758–762.
58. Services. CfMaM Medicare Expands Coverage of PET Scans. In Services UDoHaH (ed), edition 2000.
59. Bradbury I, Facey K, Laking G, Sharp P. Investing in new technology: the PET experience. *Br J Cancer* 2003; 89: 224–227.
60. Zubeldia JM, Bednarczyk EM, Baker JG, Nabi HA. The economic impact of 18FDG positron emission tomography in the surgical management of colorectal cancer with hepatic metastases. *Cancer Biother Radiopharm* 2005; 20: 450–456.
61. Lejeune C, Bismuth MJ, Conroy T et al. Use of a decision analysis model to assess the cost-effectiveness of 18F-FDG PET in the management of metachronous liver metastases of colorectal cancer. *J Nucl Med* 2005; 46: 2020–2028.
62. Arulampalam T, Costa D, Visvikis D et al. The impact of FDG-PET on the management algorithm for recurrent colorectal cancer. *Eur J Nucl Med* 2001; 28: 1758–1765.