PET/CT in Colorectal Cancer

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6.1 Introduction

Colorectal cancer, also called bowel cancer, is the third most common cancer in both males (14% of the male total) and females (11%) in the UK. In 2011, there were 41,581 new cases of bowel cancer in the UK. It is the second most common cause of cancer death in the UK, accounting for 10% of all deaths from cancer. The overall predicted 5-year survival rate is 59% for patients diagnosed with bowel cancer during 2010–2011 in England and Wales. Worldwide, it is also the third most common cancer, with more than 1,360,000 new cases diagnosed in 2012 (10% of the total).

Bowel cancer mortality rates have decreased overall in the UK and Europe since the 1970s, likely owing to the earlier detection and improved treatment. Over the last decade, European age-standardised mortality rates have decreased by 15% in males and 12% in females with colorectal cancer. Nonetheless, the burden of the

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Table 6.1 Clinical indications for ^{18}FDG-PET/CT in colorectal cancer

	^{18}FDG-PET/CT indications	Interpretation
Staging/diagnosis	Not routinely required Should be performed if CT detected synchronous liver metastases and patient is considered for radical treatment Should be performed if CT or MRI detected common iliac nodal metastases Should be considered if CT detected equivocal metastatic lesions	Lesions demonstrate increased metabolic activity
Restaging/ response assessment	Not routinely required Should be considered if avoidance of surgery is considered or indeterminate on conventional imaging such as CT or MRI	Reassessment ^{18}FDG-PET/CT should be interpreted with consideration of patients' clinical history including prior chemoradiation, local targeted therapy such as RFA or surgical history
Detection of recurrence	Should be performed in patients with recurrent disease being considered for radical treatment Should be performed in patients with rising tumour markers and/or being clinically suspicious of recurrence but with negative or equivocal findings on other imaging Assessment of indeterminate presacral mass	^{18}FDG-PET/CT study should be interpreted with consideration of patients' clinical history including chemoradiation, local targeted therapy such as RFA or surgical history

disease and mortality is still high, and further improvement in diagnostic accuracy including tumour-node-metastasis (TNM) staging and tumour biology characterisation remains essential for a better selection of treatment approaches by an experienced multidisciplinary expert team [1–3]. In addition to conventional morphological imaging modalities such as CT, ultrasound and MRI, ^{18}FDG-PET/CT plays instrumental roles in several areas critical for the optimal management of colorectal cancer, as summarised in Table 6.1 and discussed in detail below.

6.2 Primary Diagnosis/Staging

For routine staging of colon or rectal cancer, complete colonoscopy and CT of the chest and abdomen are required. In addition, pelvic MRI should be performed for all rectal cancer patients for better local disease delineation [2].

^{18}FDG-PET/CT is not required unless CT detects synchronous liver metastases, and the patient could be considered for curative liver surgery as ^{18}FDG-PET/CT is more sensitive than CT to rule out extrahepatic metastases. ^{18}FDG-PET/CT should

also be performed if staging CT or MRI scan detects nodal metastases in the common iliac region or equivocal findings such as indeterminate pulmonary, liver or bony lesions.

^{18}FDG-PET/CT is not required if other imaging modality, for example, CT, has already demonstrated widespread metastatic disease and the patient would not be eligible for radical treatment [2].

6.3 Response Assessment

As discussed in the previous chapter, Management of Colorectal Cancer, surgery is the mainstay of treatment of localised colorectal cancer. However, the treatment of low and mid rectal cancer (up to 10 cm distance of the anal verge) differs greatly from that of colon or sigmoid cancers. Whilst surgery for local control of disease in colonic cancer is more feasible, resection of mid and low rectal cancer is much more challenging as the surgery would be restricted by several factors due to the anatomical location of the rectum. In particular, from a surgical as well as post-surgery quality of life point of view, it is always of importance to preserve the sphincter function, if possible, and to maintain the genitourinary function. As a result, for colonic cancer, adjuvant chemotherapy is usually recommended only for locally advanced colon cancer patients after surgery, but neoadjuvant chemoradiation would be given to all patients with mid- or low rectal cancer to downstage the tumour so as to reduce the risk of local relapse, improve the chance of R0 resection, preserve sphincter function, avoid stoma or even avoid surgery in selected patients especially if a pathological complete response could be confirmed.

To assess response to treatment, currently, none of the imaging modalities (ERUS, MRI, CT) can reliably predict a complete remission. Although downsizing can be assessed with those imaging technologies, accuracy for pathological T staging and regression rate/histopathological response is low owing to multiple factors, fundamentally due to the inability of any of these imaging techniques to detect microscopic disease [2].

Recent studies suggested diffusion-weighted MRI might be more sensitive than MRI only in predicting a pathological complete response but still with limited accuracy. Similarly, the role of ^{18}FDG-PET/CT in this setting is also under investigation. Several ongoing studies are testing if ^{18}FDG-PET/CT is any better than MRI and/or if the combination of ^{18}FDG-PET/CT and MRI could be more reliable than each modality alone (Fig. 6.1) [4–11].

In line with the advancement of radiotherapy techniques, another area of clinical interest is if advanced imaging technologies such as functional MRI or PET/CT with either ^{18}FDG or other tracers such as ^{18}FLT or ^{18}FMISO could help identify relatively radioresistant tumour components so as to local intensification of radiotherapy could be deployed to achieve higher rates of disease control without unacceptable toxicity.

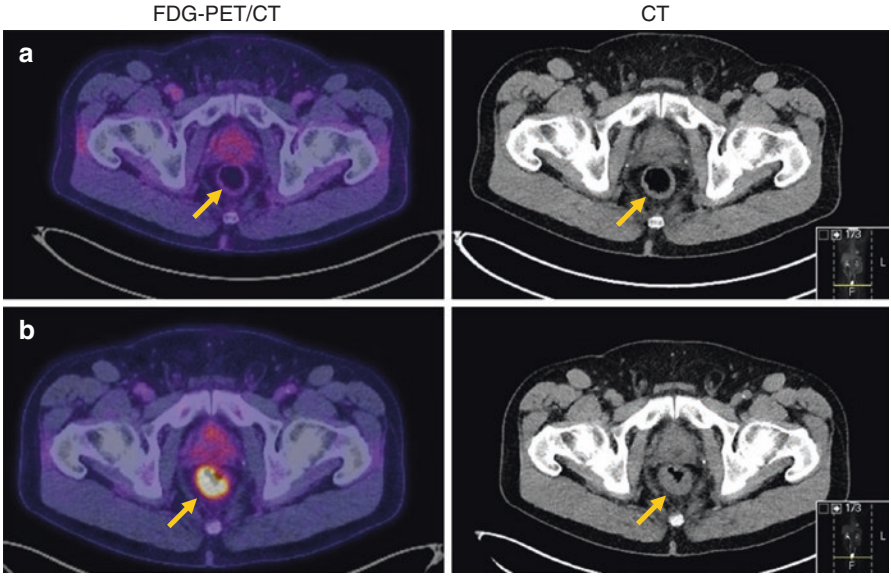

Fig. 6.1 ^{18}FDG-PET/CT performed 4 weeks after neoadjuvant chemoradiation demonstrates a true complete pathological response in a low rectal cancer patient

6.4 Detection of Recurrent Disease

^{18}FDG-PET/CT has demonstrated higher sensitivity than conventional imaging (CT or MRI) in detecting systemic metastatic disease. It therefore should be performed in patients with recurrent disease being considered for radical treatment and/or metastasectomy to avoid futile invasive interventions.

Likewise, ^{18}FDG-PET/CT should also be performed in patients with rising tumour markers (e.g. CEA) and/or being clinically suspicious of recurrence but with negative or equivocal findings on other imaging.

Another indication for ^{18}FDG-PET/CT is to evaluate the nature of post-surgery presacral masses. It is a common feature for patients to present with persistent presacral soft tissue mass after radical resection of rectal cancer. On conventional morphological imaging, such masses could be variable in size and morphological appearances and therefore difficult to tell on CT if active tumour grows within the mass until it has grown significantly.

6.5 Normal Variants and Artefacts

Compared to the old days when ^{18}FDG-PET studies were performed on stand-alone PET scanners, the advent of modern hybrid PET/CT technology at the beginning of the twenty-first century has made the recognition of non-cancerous variants much easier. However, several usual artefacts as summarised in Table 6.2 should always be born in mind when interpreting a routine ^{18}FDG-PET/CT study.

Table 6.2 Normal variants and artefacts on ^{18}FDG-PET/CT in colorectal cancer

Normal variants and artefacts	^{18}FDG-PET/CT imaging features
Non-specific bowel uptake	Variable, usually low-grade, diffuse uptake along the large bowel; can be high-grade uptake on metformin in diabetic patients but with no corresponding mural thickening on CT images of the PET/CT study
Diverticulitis	Variable but always associated with diverticular disease on CT images of the PET/CT study
Mucinous cancer	^{18}FDG uptake could be variable but usually relatively low grade in mucinous cancer and therefore low sensitivity in detecting such cancers
Urinary activity	Usually can be readily recognised with the aid of corresponding CT images of the modern PET/CT study but can be difficult in lean patients or in post-surgery patients due to the disturbed anatomy
Presacral mass	Non-cancerous presacral mass usually has very low-grade ^{18}FDG avidity, but if it contains active inflammatory component which are usually very ^{18}FDG avid, it could be very difficult to differentiate inflammation from tumour involvement. Interval re-scan or biopsy could be required

Non-specific Bowel Uptake: Another physiological variant is non-specific smooth muscle uptake of ^{18}FDG by the bowel wall. Although the appearances of such non-specific uptake could be highly variable but differing from bowel cancer, they are usually diffuse, and the uptake is usually relatively low grade. With the aid of the CT component of the modern hybrid ^{18}FDG-PET/CT, it is usually not difficult to recognise such physiological uptake as it would present with no corresponding bowel wall mural thickening, a typical feature for a bowel cancer.

Diabetic Patients: Particular attention should be made to diabetic patients as antidiabetic medication such as metformin usually leads to significantly increased ^{18}FDG uptake by the large bowel. This variant can be readily recognised in correlation with patients' medication history, and in addition, such uptake is usually also diffuse, along much of the large bowel, with no mural thickening.

Diverticulitis: Sometimes, active large bowel diverticulitis also leads to focal or diffuse increased ^{18}FDG uptake. This variant can be better identified with the aid of the CT component of the PET/CT study.

Mucinous Cancer: ^{18}FDG is known to have low avidity in mucinous or signet ring cancers which consist of approximately 10–15% of colorectal cancers, largely due to the low tumour cellularity and abundant mucin within such tumours. In a retrospective observation reported by Berger et al., ^{18}FDG-PET detected only 59% (13 out of 22) mucinous cancer.

Urinary Activity: ^{18}FDG is physiologically excreted by the urinary system. Aided by the corresponding CT images of the modern PET/CT study, it is usually not difficult to identify the urinary tract, but sometimes, it can be difficult to differentiate small-volume retroperitoneal nodal uptake from nearby ureteric activity; sometimes, it could also be difficult to identify the boundary of the rectal primary from the adjacent bladder especially when there is locally advanced rectal primary invading into adjacent structures. In such cases, corresponding with contrast-enhanced CT or pelvic MRI scans might be beneficial.

Presacral Mass: As discussed above, in rectal cancer patients, it is a usual feature to develop non-specific post-surgical presacral soft tissue masses. In most

cases, the mass is consisted of fibrotic tissue secondary to post-surgical inflammatory process. Such soft tissue is usually ill-defined and fairly small volume and could gradually reduce in size with time. However, local recurrence is unfortunately a common problem in rectal cancer usually involving the presacral region. ^{18}FDG-PET/CT has distinctive advantage in the early differentiation of active tumour from a chronic fibrotic process as the later would be either ^{18}FDG negative or showing very low-grade diffuse uptake, whilst the former usually demonstrates focal or irregular high-grade ^{18}FDG uptake. The only pitfall is, however, when the presacral mass contains active inflammatory elements, sometimes but not always, associated with fistulation.

Timing of 18FDG-PET/CT Scanning: ^{18}FDG-PET/CT should be performed routinely at least 4 weeks after surgery or completion of chemoradiation to avoid the contamination from active post-surgical inflammatory changes as well as local inflammation following radiotherapy which could mimic active residual disease. On the same note, even if the scan was performed long after surgical or other therapeutic intervention, there is always low-grade non-specific physiological ^{18}FDG uptake along the bowel wall. This would inevitably render it extremely difficult to rule out any small-volume residual disease on a ^{18}FDG-PET/CT study. Although in experienced eyes, non-specific low-grade uptake can be readily recognised, it is currently the limitations of any clinical imaging technology, including ^{18}FDG-PET/CT, to detect or rule out microscopic disease.

Key Points

- In addition to conventional morphological imaging modalities such as CT, ultrasound and MRI, ^{18}FDG-PET/CT plays instrumental roles in several areas critical for the optimal management of colorectal cancer.

Primary Diagnosis/Staging

- ^{18}FDG-PET/CT is not required unless CT detects synchronous liver metastases and the patient could be considered for curative liver surgery.
- ^{18}FDG-PET/CT should also be performed if staging CT or MRI scan detects nodal metastases or equivocal findings such as indeterminate pulmonary, liver or bony lesions.

Response Assessment

- Recent studies suggested diffusion-weighted MRI might be more sensitive than MRI only in predicting a pathological complete response but still with limited accuracy. Similarly, the role of ^{18}FDG-PET/CT in this setting is also under investigation.

Detection of Recurrent Disease

- ^{18}FDG-PET/CT has demonstrated higher sensitivity than conventional imaging (CT or MRI) in detecting systemic metastatic disease.
- ^{18}FDG-PET/CT should also be performed in patients with rising tumour markers and/or being clinically suspicious of recurrence but with negative or equivocal findings on other imaging.
- ^{18}FDG-PET/CT is used to evaluate the nature of post-surgery presacral masses.

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