The Role of Positron Emission Tomography

In the Management of Colorectal Cancer

A thesis submitted to the University of London for the Degree of Doctor of Medicine

by

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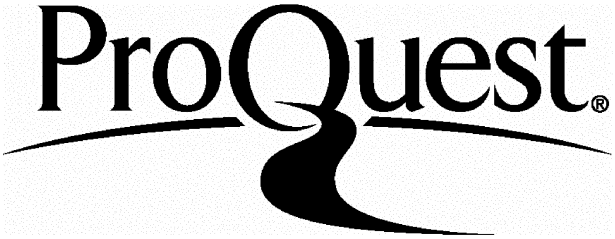

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Abstract

Colorectal cancer (CRC) is the second commonest cancer in the Western World. Successful treatment relies on accurate detection and staging of primary disease as well as the early identification of the presence and extent of recurrence. Morphological imaging techniques, particularly computed tomography, although established and widely available to carry out these tasks, have weaknesses. Positron emission tomography (PET) is a functional imaging technique that is able to detect cancer foci based on the uptake of positron labelled tracer in malignant tissue. PET can be considered both an alternative and complimentary method of imaging in CRC, which at present is not widely available or established in the UK.

The aims of this thesis were: firstly, to study the role of fluorodeoxyglucose (FDG) PET in the diagnosis and staging of both primary and recurrent/metastatic CRC. Secondly, having assessed the benefits and weaknesses of FDG-PET in these applications, to study a novel tracer, fluorothymidine (FLT).

Current modalities appear better suited than FDG-PET for diagnosing symptomatic primary CRC. There is evidence of increased accuracy for FDG-PET in staging primary disease, but the data is equivocal and larger studies are needed. However, FDG-PET imaging for suspected recurrent/metastatic disease is more accurate than conventional techniques and this leads to alteration in patient management. Experience with FLT-PET in CRC was established and tracer dynamics characterised. FLT shows promise, but the nature of the clinical benefits are not clear in this pilot study. The evidence suggests that PET has the potential to become routinely incorporated into patient management algorithms for recurrent/metastatic disease. Technological advances coupled with novel tracer research will facilitate this, making PET a formidable imaging tool for the oncologist, both medical and surgical.

Statement of Originality

The studies described and presented in this thesis are the original work of the author. All PET, CT scans and PET image/data reconstruction were performed by qualified radiographers in accordance with local protocol and clinical guidelines. Radioactive tracers were synthesised at the MRC Cyclotron Unit, Hammersmith Hospital, London and Wolfson Brain Injuries Unit, Addenbrookes Hospital, Cambridge. These were then transported to the Institute of Nuclear Medicine on the day of PET scanning. Radiochemical analysis was performed by a radiochemist at the Institute of Nuclear Medicine.

No part of this work has been submitted to any other university for consideration for an higher degree.

All clinical studies in this thesis were performed in accordance with protocols approved by the Ethics Committees of University College London and University College London Hospitals NHS Trust and after obtaining informed patient consent. Ethics Committee approval was given under the references 99/0308, 99/0309, 00/0295. All patients recruited to the studies described herein were interviewed by the author who was responsible for adherence to study protocols.

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List of abbreviations

CRC	Colorectal cancer
CT	Computed tomography
USS	Ultrasound
MR	Magnetic resonance imaging
SPECT	Single photon emission computed tomography
PET	Positron emission tomography
WHO	World Health Organisation
HNPCC	Hereditary non-polyposis colorectal cancer
FAP	Familial adenomatous polyposis
APC	Adenomatous polyposis coli
DNA	Deoxyribose nucleic acid
MS	Microsatellites
TGFβ	Transforming growth factor β
FJP	Familial juvenile polyposis
CS	Cowden syndrome
BBR	Bannayan-Ruvalcaba-Riley syndrome
NSAID	Non-steroidal anti-inflammatory drug
COX	Cyclo-oxygenase
Ba enema	Barium enema
CTC	CT colonography
UICC	Union Internationale Contre le Cancer
TNM	Tumour, Node, Metastasis
TME	Total mesorectal excision of the rectum
APR	Abdominoperineal resection
5-FU	5-fluorouracil
TS	Thymidylate synthase
MRC	Medical Research Council
FUTP	5-Fluorouridine triphosphate
RNA	Ribose nucleic acid
EORTC	European Organisation for Research and Treatment of Cancer
HAI	Hepatic arterial infusional chemotherapy
RT	Radiotherapy
CEA	Carcinoembryonic antigen
CLM	Colorectal liver metastases
ITU	Intensive Care Unit
HDU	High Dependency Unit
HU	Hounsfield Unit
CTAP	CT arterial portography
^{11}C	Carbon-11
^{15}O	Oxygen-15
^{18}F	Fluorine-18
^{14}N	Nitrogen-14
mm	Millimetre
FDG	2-[^{18}F]-fluoro-2-deoxy-D-glucose
NaI (T1)	Sodium iodide (Thallium activated)
BGO	Bismuth germanate oxide
PMT	Photomultiplier tube
^{99m}Tc	Technetium 99
FBP	Filtered backprojection

OSEM	Ordered Subsets Expectation Maximisation
cm	Centimetre
SUV	Standardised uptake value
[^{18}F]FU	[^{18}F]Fluorouracil
LSO	Lutetium orthosilicate
mg	Milligram
GLUT	Glucose transporter protein
UCLH	University College London Hospitals
PPV	Positive predictive value
NPV	Negative predictive value
CXR	Chest radiograph
ICP	Institute of Clinical PET
UCL	University College London
ARSAC	Administration of Radioactive Substances Advisory Committee
MDT	Multidisciplinary team
INM	Institute of Nuclear Medicine
µg/l	Micrograms per litre
ROI	Regions of interest
TP	True positive
FN	False negative
TN	True negative
FP	False positive
FLT	3'-Deoxy-3'-fluorothymidine
HIV	Human immunodeficiency virus
FLT-P	FLT monophosphate
NSCLC	Non-small cell lung cancer
TAC's	Time activity curves

CHAPTER 1

Introduction

1. Introduction

Overview

The effective management of patients with colorectal cancer (CRC) remains a diagnostic and therapeutic challenge at the beginning of the new Millennium. It is notable that despite advances in surgical technique, anaesthetic and post-operative care and oncological therapy, the outcome of treatment for patients with CRC in England and Wales falls short of our European colleagues in terms of survival [Berrino et al., 1995]. The reasons for this are inevitably complex, but do in part relate to the accuracy and timing of diagnosis both of primary tumour and recurrent or metastatic disease.

Since the discovery of X-rays by Roentgen in 1895, medical imaging has developed into a complex speciality. Imaging modalities can be divided into two distinct categories. In the first instance there are the techniques that give detailed morphological information that relates to the physical properties of the tissue under investigation. These include planar X-ray, computed tomography (CT), ultrasound (USS) and magnetic resonance imaging (MR). The second category of techniques are those that produce functional images using dynamic scintigraphy. These radioisotope imaging techniques include single photon emission computed tomography (SPECT) and positron emission tomography (PET). In addition to these, MR spectroscopy and functional MR are becoming available.

This thesis investigates the role of PET in the management of CRC patients. This introductory chapter gives an overview of CRC and the problems faced by clinicians, the current methods of cross-sectional imaging and introduces PET and the concepts behind it. In section 1.1, I describe the epidemiological background, aetiology and treatment of CRC. The next section analyses CT, the most frequently used anatomical imaging modality used to study CRC. Section 1.3 discusses the physics and biological basis for the use of PET imaging in oncology. Section 1.4 reviews the current status of CRC imaging as well as the experience documented with clinical PET to date. Section 1.5 summarises the chapter and states the general aims of this thesis, which are set out in more specific detail in section 1.6.

1.1 Colorectal cancer

CRC is a broad term used to define a malignant tumour arising from the epithelium of the large bowel mucosa. Ninety-five per cent of these tumours are adenocarcinomas with other histological types, such as squamous cell carcinoma, found at the anorectal junction. The World Health Organisation (WHO) classification of type and grade of CRC [Jass et al., 1989] is shown on table 1.1.

Histological type	Description	Grading system
Adenocarcinoma	Epithelium – glandular, tubular or villous	1-3
Mucinous adenocarcinoma	More than 50% extracellular mucin	1-3
Signet ring cell carcinoma	More than 50% signet ring cells (intracytoplasmic mucin)	3
Squamous cell carcinoma	Exclusive squamous differentiation	1-3
Adenosquamous carcinoma	Adenocarcinoma and squamous cell carcinoma (mixed)	1-3
Small cell carcinoma	Similar to small cell carcinoma of the lung (neuroendocrine)	4
Undifferentiated carcinoma	No indication of definitive differentiation. May be uniform or pleomorphic	4

Table 1.1

Histological type and grade of colorectal carcinoma according to WHO classification

1.1.1 Epidemiology

Understanding the magnitude of the clinical problem that CRC presents requires analysis of its epidemiology. It is estimated by WHO that, per annum, there are 800,000 new cases of CRC and approximately 500,000 deaths worldwide. CRC is the second commonest cancer in Europe [Jensen et al., 1990] and the USA [Landis et al., 1999]. The most recent statistics for England and Wales show that the total number of cases of CRC per annum has risen from 20,396 in 1971 to 29,500 in 1996 [Hayne D et al., 2001]. This represents an increase of approximately 45% over 25 years. Over the same period the direct age-standardised incidence rates have increased by 23% in men from 43.1 to 52.8 cases per 100,000. A smaller increase in direct age-standardised incidence of 10% was reported in women rising from 33 to 36.2 cases

per 100,000 between 1971 and 1996. The anatomical distribution of tumours in the large bowel follows a pattern of two-thirds colonic and one-third rectal, which represents approximately 20,000 new colon cancers and 10,000 new rectal cancers per year in England and Wales. There appears to be a marginal difference in distribution between the sexes for colonic carcinomas with females having a lower incidence than males. This sex difference has widened over the last 50 years and the current hypothesis for this difference is the introduction of exogenous steroid hormones in the 1950's. There appears to be an association between hormone replacement therapy and reduced risk of CRC [Boyle and Langman, 2000]. There is a definite preponderance for rectal carcinoma to occur in men.

1.1.2 Aetiology of colorectal cancer

The development of CRC has been the subject of intense study as both genetic and environmental factors have been implicated. Seventy-five to eighty per cent of CRC are termed "sporadic", usually occurring in the seventh decade. However, it is now clear that 5-10% of CRC's, arising predominantly in younger patients, are due to hereditary factors and certain syndromes such as hereditary non-polyposis colorectal carcinoma (HNPCC), familial adenomatous polyposis (FAP) and Peutz-Jeghers syndrome, are now well documented [Lynch and Smyrk, 1999]. It is particularly interesting that genetic mutations seen in sporadic CRC are similar to those present in the inherited syndromes (60-80% similar to FAP and 15% similar to HNPCC). Vogelstein and Fearon's [Fearon and Vogelstein, 1990] model for the progression from normal mucosa to adenoma then to carcinoma forms the basis for the genetic model of CRC oncogenesis and this is illustrated in figure 1.1. This figure demonstrates the step-wise genetic mutations that lead to phenotypic change in the epithelium of the large bowel. Other than the sporadic and genetic CRC's a further 15% or so are associated with a family history, but no conclusive genetic pattern is seen. In these cases it is likely that low risk inherited susceptibility, shared environmental factors or a combination of the two play a part in oncogenesis.

Against this background I will now describe the genetic basis for CRC oncogenesis before discussing environmental factors, which play a role in CRC initiation.

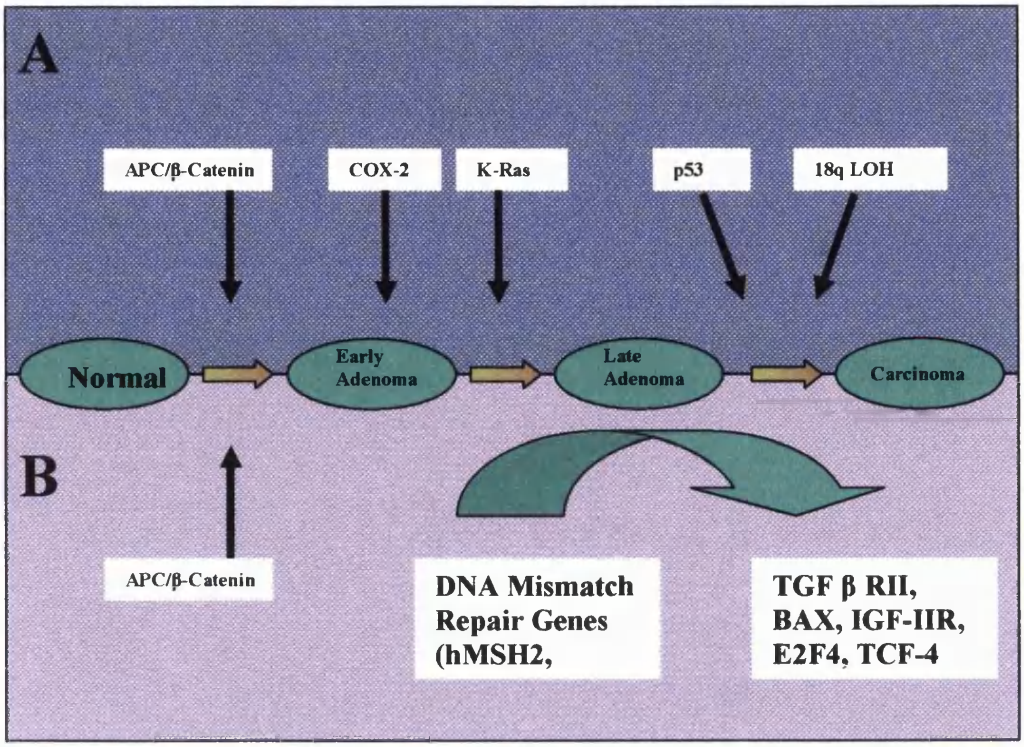


Figure 1.1 Overall scheme of key genetic events in CRC tumourigenesis. Two major pathways exist: eighty-five per cent of tumours follow genetic events illustrated in A (modified Vogelgram), which results in the classical adenoma-carcinoma progression. The remaining 15% of tumours are characterised by microsatellite instability and conform to path B. COX-2= Cyclo-oxygenase-2; LOH= loss of heterozygosity; BAX= apoptosis regulator molecule; IGF-IIR= Insulin like growth factor receptor class II; E2F= cell cycle regulated transcription factor; TCF-4= T-cell factor 4, transcription factor.

Our knowledge of CRC oncogenesis stems mainly from two types of inherited conditions which predispose to CRC: those inherited syndromes characterised by polyp formation and those that are not (table 1.2). This descriptive categorisation is likely to be superseded in due course by molecular classifications as knowledge increases. The most important syndrome characterised by polyposis is FAP.

FAP results from a germ-line mutation in the adenomatous polyposis coli (APC) gene which is found on chromosome 5q 21-22. APC is a tumour suppressor gene whose protein product is responsible for complexing with β-catenin and targeting it for degradation. The mutated gene product cannot perform this function and leads to accumulation of β-catenin, which in turn up-regulates genes responsible for proliferation and transformation of colonic epithelial cells. Clinically, the disease

manifests itself by the formation of hundreds of adenomas in the large bowel during the second to third decades. There may, in addition, be extracolonic manifestations, for example desmoid tumours and osteomas of the skull. The adenomatous colonic polyps undergo malignant change by the age of forty unless prophylactic colectomy is performed. Attenuated variants of the disease may also occur, making diagnosis problematic. The defective APC gene results in the tendency of the colonic epithelium to become hyperproliferative and subsequent mutations detailed in the cascade (figure 1.1) proceed.

Of the non-polyposis hereditary syndromes, HNPCC is the most well investigated example. This genetic disorder is characterised by defects in the deoxyribose nucleic acid (DNA) repair system. The specific abnormality is found in the 5 mismatch repair genes which comprise a precise DNA proof–reading system that is capable of correcting base pair mismatches during DNA replication [Moore J et al., 1999]. If the mismatch repair genes are defective, errors may accumulate in other genes. Genes that are most susceptible are those with short repetitive sequences known as microsatellites (MS). In the context of CRC, one such MS is the coding exon for the class II receptor for transforming growth factor β (TGFβ). Inactivation of this receptor removes the potent inhibitory effect of TGFβ on the colonic epithelium [Markowitz et al, 1995]. This group of patients tend to develop early onset CRC with a proximal colonic preponderance. The penetrance appears to be approximately 85% [Dunlop et al., 1997]. These patients also tend to develop an excess of synchronous and metachronous CRC, a variety of extracolonic malignancies as well as certain distinctive pathological features (an excess of mucoid, signet ring, poorly differentiated carcinomas with a Crohn's like reaction). Interestingly, even after taking into account the stage of tumour, patients with HNPCC tend to have a better survival compared to the general population who develop CRC [Watson et al., 1998].

In addition to these syndromes, evidence exists for an increased risk of CRC in patients with familial juvenile polyposis (FJP), Cowden syndrome (CS) and Bannayan-Ruvalcaba-Riley syndrome (BRR) [Lynch and Smyrk, 1999]. The group of patients with a family history of CRC in whom inherited factors probably contribute to the risk of CRC, but in whom elucidation of the genetics is incomplete may eventually be reclassified as knowledge increases. It is apparent that the mutation in the APC gene is an initiating factor in CRC oncogenesis. Description has been

confined to the initial genetic changes that occur during CRC oncogenesis. Other epigenetic events and details of k-ras and p53 mutation, DCC loss and abnormal methylation have not been described here.

Syndrome	Gene responsible	Chromosome location
Polyposis		
Familial adenomatous polyposis	APC	5q
Gardener's	APC	5q
Non-polyposis		
HNPCC	HMSH2, GTBP, hMLH1, hPMS1, hPMS2	2p,3p,2q,7p
Hereditary flat adenoma	APC/?mismatch repair genes	5q (?2p, 3p,3p, 7p)
Attenuated adenomatous polyposis coli	APC	5q
Muir-Torre	mismatch repair genes	2p, 3p, (?2q, 7p)
Miscellaneous		
Cowden's	PTEN	10q
Peutz-Jehgers	?	?
Hereditary mixed polyposis		6q
Turcott's	APC, hMLH1, hPMS2	5q,3p,7p

Table 1.2 Hereditary syndromes and genes thought to be responsible for initiating colorectal cancer (from Genetics of colorectal cancer [Brown and Bishop, 2000])

Although the multistep genetic model for CRC tumourigenesis is substantiated by robust evidence, there appear to be environmental factors that have an important impact [Potter et al., 1993], in the pathogenesis of colon cancer. The observational evidence suggests that the low incidence of CRC in rural communities in Africa and the Far East, who have a high fibre, low animal fat intake, contrast markedly with industrialised societies (with the notable exception of Japan). Furthermore, migrants from underdeveloped countries to more industrialised areas progressively increase their risk of developing CRC [Doll, 1980]. The hypothesis that environmental factors play a significant role in CRC oncogenesis is not without its critics.

The environmental factors can be considered as being dietary and non-dietary and deserve mention now. The former group include a high intake of animal fat, an increase in anaerobic microbes in the colon, tumour initiating effects of secondary

bile acids, a lack of dietary fibre and reduced intake of protective nutrients described below. The complex interaction between various dietary constituents is relatively poorly understood, but one proposed model is described as follows: intake of animal fats promotes the growth of anaerobic colonic flora, notably clostridia and bacteroides species. These micro-organisms act on fat and bile acids to form fatty acids and secondary bile acids, which in turn damage the mucosal lining and initiate cell replication. These compounds are also thought to be promoters for potential carcinogens [Weisberger et al, 1982] and this process is given further impetus by the production of nitrosamide from amines and amides released from dietary meat [Tannenbaum et al., 1978]. Simultaneously, the lack of dietary fibre reduces stool bulk and increases transit time, which in turn leads to increased exposure of carcinogens with reduced binding and dilution [Reddy, 1980]. On a molecular level these dietary agents may induce cellular damage due to a lack of detoxification by a variety of enzyme systems including cytochrome *p*450, the xenobiotic metabolising enzymes, glutathione-S-transferase and N-acetyl-transferase. Damage in turn leads is a stimulus for replication, which may initiate genetic mutations.

There are dietary compounds that may confer protection from CRC. It is speculated that certain anti-oxidant compounds such as vitamins A, C and E have an anti-cancer effect, but evidence is equivocal [Roncucci et al., 1993; Willett and Hunter, 1994]. These vitamins are thought to be deficient in a low fibre diet. Similarly vitamin D has been implicated as being protective, but data is scarce [Martinez and Willett, 1998]. Other compounds, which may have a protective role against colorectal carcinogenesis, include selenium, carotenoids, retinoids and oltipraz.

Of the non dietary agents that promote CRC a weak association has been demonstrated with cigarette smoking [Heineman et al., 1995]. More recently, attention has turned to the potential non-dietary chemoprotective agents particularly non-steroidal anti-inflammatory drugs (NSAID), such as aspirin and indomethacin. Animal models of CRC involving exposure to known carcinogens causing CRC demonstrate a lower incidence of cancers in animals given NSAIDs [Reddy et al., 1993]. This evidence along with human studies showing polyp regression associated with NSAID intake in FAP patients suggests a causal effect of NSAID ingestion [Labayle et al., 1991;Giardiello et al., 1993]. The proposed mechanism is one of increased apoptotic cell death [Piazza et al., 1995] mediated through inhibition of the

enzyme cyclo-oxygenase (COX). Specific inhibition of the COX-2 isoform, which is associated with the inflammatory response, appears to carry most benefit as this is induced by tumour promoting agents and mitogens [Eberhart et al., 1994]. Perhaps this is best demonstrated in APC deficient mice with a phenotype of numerous tumours crossed with COX-2 null mice. In these crossed mice there is an 80% reduction in tumours [Williams and Mann, 1999].Over-expression of COX-2 is described in human CRC tissue and appears to change ability to invade adjacent tissues as well as decreasing sensitivity to apoptotic signals [Sano et al., 1995]. Two selective COX-2 inhibitors are commercially available; celecoxib and rofecoxib, so attention must now be focused on firstly defining correct dosage and secondly, further robust clinical trials to demonstrate an actual effect. Selective COX-2 inhibitors have the added advantage of having fewer side-effects.

1.1.3 Treatment for colorectal cancer

Screening

Before I can discuss treatment of symptomatic CRC I must briefly present the current state of knowledge regarding screening for asymptomatic disease. Any attempt to reduce the incidence of CRC must focus on screening for the disease in asymptomatic individuals and specifically on detecting those with adenomatous polyps. There is strong supporting data to suggest that removal of adenomatous polyps reduces the incidence of CRC and this is probably best demonstrated by the US National Polyp Study [Winawer et al., 1993]. Patients are categorised into high, average and low risk groups according to the presence of specified risk factors (table 1.3). The screening tests that are available each have benefits and disadvantages, but the clear message that is now emerging is that there are significant benefits associated with screening average and high risk groups. In the average risk group faecal occult blood testing has been shown to reduce the mortality from CRC both in England [Hardcastle et al., 1996] and the United States [Mandel et al., 1999]. Current research is being driven by the need to further improve specificity and this may be achieved by the analysis of faecal DNA. Flexible sigmoidoscopy has been shown to reduce the incidence of rectosigmoid cancers [Selby et al., 1992] and indirect evidence exists for the benefits of colonoscopy [Rex et al., 1991]. Both these tests are more invasive than faecal occult blood testing, but they have the advantage of being able to detect as well as

treat mucosal lesions. These benefits are amplified when applied to the high-risk groups.

Risk factor
Age (over 50)
High fat / low-fibre
Excess calorie intake
Family history of colorectal cancer or adenomatous polyps
Chronic inflammatory bowel disease
Hereditary polyposis and non-polyposis syndromes

Table 1.3 Risk factors for CRC

Currently in the average risk group, it would be entirely acceptable to firstly perform a meticulous risk assessment and follow one of several available options [Winawer et al., 1997;Byers et al., 1997] such as an annual faecal occult blood test combined with a flexible sigmoidoscopy every five years both commencing at the age of 50. A rectal digital examination may also be offered annually. If any of these tests are positive, then the patient proceeds to a full colonoscopy. A less desirable alternative would be a double contrast barium enema (Ba enema). Alternative options include 10 yearly colonoscopy or 5 to 10 yearly double contrast Ba enema and flexible sigmoidoscopy [Winawer et al., 2000]. The options, which I mention here, are not widely accepted and since the optimal protocol remains unclear they continue to be evaluated. In the high-risk group, colonoscopy remains the preferred method of surveillance [Winawer et al., 1990].

I have included this discussion on screening for completeness, but I am not going to analyse screening intervals as this topic is not central to the main theme of the work that I will be presenting. I must, however, mention the existing potential of screening for CRC using CT colonography (CTC) [Johnson and Dachman, 2000], a technique that I discuss fully in section 1.2. Resolution for mucosal lesions is reportedly in the order of 5mm and the technique holds much promise. Powerful software is required to give sufficient image processing capability. If CTC proves to be as sensitive and specific as colonoscopy, the opportunity will be there for a reduction in diagnostic

sigmoidoscopies and colonoscopies, which carry a morbidity and cost. This may help to offset the initial capital costs involved in setting up CTC.

Although implementing a screening programme for CRC using current technology would take many years to reduce the overall incidence of CRC, the cost benefits are clearly demonstrated in analytical models [Wagner et al., 1996]. Although not specifically addressed in this thesis, metabolic imaging with PET may be possible and needs to be investigated.

Treatment of symptomatic colorectal cancer

Patients with CRC usually present to their family doctor with symptoms and signs of the primary tumour or with incidental findings by another hospital specialist. In England and Wales this accounts for approximately 75% of all CRC referrals. The remaining 25% present as acute emergencies (perforation, haemorrhage and obstruction). The presenting features may be one or a combination of the following: change in bowel habit, rectal bleeding, abdominal mass, weight loss, poor appetite or lethargy and shortness of breath. In April 2001, the Department of Health (England and Wales) introduced guidelines designed to facilitate the urgent referral of patients with symptoms of CRC from primary to secondary healthcare [Department of Health (England and Wales), 2001]. These guidelines are detailed in appendix A1 and are designed to detect upto 90% of CRC with the added benefit of requiring patients to be seen by a colorectal surgeon within two weeks (hence these guidelines are termed the "two week rule").

Prior to any treatment for CRC patients must undergo a systematic clinical and radiological assessment in order to determine the following:

i) The presence of co-morbidity
ii) A relevant family history
iii) Site, size and local infiltration of the tumour
iv) The presence of metastatic lymph nodes
v) The presence of distant metastases

The anatomical extent of tumour described in points (iii) to (v) comprise the stage of the tumour and was originally classified according to the Dukes classification for rectal tumours [Dukes CE, 1932]. This system was modified and applied to colonic adenocarcinomas and remains in use today. The more standardised system that is used throughout the world is the Union Internationale Contre le Cancer (UICC) Tumour, Node, Metastasis (TNM) classification [Sobin and Wittekind, 1997]. Both modified Dukes and the UICC TNM classifications are shown on table 1.4. The second system allows for a standardised means of comparing tumours both clinically and pathologically based on extent of local infiltration, lymph node involvement and distant metastases. This ultimately allows a clinicopathological stage to be assigned to an individual tumour. This is a useful and accurate means of selecting appropriate treatment and comparing data between patients in the same and different institutions. In contrast there is more scope for stage variation between reporting pathologists and institutions using the Dukes system.

Patients are clinically evaluated and then undergo a series of investigations, of which imaging is a cornerstone. The mainstay of the evaluation in the outpatient department rests on digital rectal examination combined with rigid and/or flexible sigmoidoscopy. These investigations are followed by radiological evaluation of the whole colon (discussed later in section 1.4) or a full colonoscopy. Colonoscopy is highly accurate for detecting abnormalities within the colon and in the case of polyps it may be used as a therapeutic modality also. In addition, if a malignant looking lesion is detected, a biopsy can be obtained for an accurate histological diagnosis.

T - Primary tumour
TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
Tis Carcinoma in situ: intraepithelial or invasion of the lamina propria
T1 Tumour invades submucosa
T2 Tumour invades muscularis propria
T3 Tumour invades through muscularis propria into subserosa or into non-peritonealized pericolic or perirectal tissues
T4 Tumour directly invades other organs or structures and or perforates visceral peritoneum
N - Regional lymph nodes
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastases
N1 Metastasis in 1-3 regional lymph nodes
N2 Metastasis in 4 or more regional lymph nodes
M - Distant metastases
MX Distant metastases cannot be assessed
M0 No distant metastases
M1 Distant metastases
Dukes classification
A Tumour confined to the bowel wall
B Tumour spread directly through the bowel wall into adjacent tissues but not lymph nodes
C C_1 Spread to nodes in proximity to the primary tumour C_2 Spread to regional nodes upto proximal limit of resection
D Distant metastases

Table 1.4 Staging systems for CRC

I will discuss those recent advances in therapy that justify and warrant an imaging modality, which may detect CRC both early and with more certainty. In patients with primary CRC the optimal chance of cure is achieved by the judicious use of surgical resection, systemic chemotherapy and radiotherapy. Approximately 80% of patients with primary CRC undergo elective resection of their tumours with the remainder undergoing emergency procedures. The study of PET being examined in this thesis pertains primarily to the elective evaluation of patients and it is the treatment of this group of patients that I will now concentrate.

Surgery for colorectal cancer

Cancer of the colon

Curative surgery for cancer of the colon comprises of a segmental resection of the primary lesion based on its arterial blood supply. This procedure should include dissection of regional lymph nodes, which acts as an accurate staging procedure for determining whether adjuvant chemotherapy will be of benefit [IMPACT, 1995]. Extended lymphadenectomy to the para-aortic nodes and initial ligation of the vascular pedicle were previously thought to confer survival advantages, but this does not appear to be the case [Sugarbaker and Corlew, 1982;Wiggers et al., 1988]. In every case the operating surgeon will ensure that they perform a thorough visual inspection and palpation of the abdomen and pelvis looking for synchronous tumours and metastatic disease. It is estimated that synchronous cancers occur in 1.5-7.5% of cases (probably 6% would be a fair estimate) [Davison AJ and Stern HS, 1995] and completion colectomy should then be carried out. Based on the evidence for progression of polyps into invasive cancers a case can also be made for completion colectomy once any existing polyps are removed and histopathologically evaluated. Usually this information is available pre-operatively, but in certain cases such as a stenosing primary CRC that does not permit passage of a colonoscope, the finding may be intra- or post-operative. It is essential to obtain histological diagnosis before converting a segmental resection to a radical colectomy. Henry Lynch suggests that these principles should also apply to patients with HNPCC, who have a 45% risk of developing a metachronous cancer within 10 years [Lynch, 1996].

Surgical treatment should result in tumour free resection margins, both longitudinal and circumferential as well as maintenance of intestinal continuity. It is possible to perform "curative" *en bloc* resections if the tumour is invading adjacent organs. However, if infiltration is extensive, it is likely that palliative control is the only option. It is conventional in such cases for the operating surgeon to mark the site of any residual tumour with metallic clips, with a view to possible palliative post-operative RT.

The principles of palliative surgery are designed to alleviate symptoms. Decision-making in this difficult situation is complex and must take into consideration the patients' ability to undergo surgery, their age and life expectancy as well as co-

morbidity. It cannot be stressed too highly that decisions on patient management need to be made on an individual case basis and this applies to all the following discussions on palliative surgery (colon, rectum and liver disease). The main symptoms may be the sequelae of intestinal obstruction, which may necessitate incomplete resection of the lesion or faecal diversion by means of a stoma or by-pass. In a proportion of colon cancers the primary tumour is operable, but distant metastases are present, usually in the liver. Approximately 25% of patients with a primary CRC already have metastatic disease in the liver [Ballantyne and Quin, 1993]. This presents further dilemmas for the surgeon. It is accepted that if the patient is fit and otherwise well, then palliative resection of the primary should be carried out if there are symptoms (obstruction, pain or bleeding) in the context of low volume hepatic replacement. If one of these factors is equivocal then the issue becomes more complex and as stated earlier individual circumstances should be considered.

Cancer of the rectum

The surgical techniques applied to resection of rectal cancers are different to those described above for primary colon cancers. The main reason for this is that there appears to be substantial evidence that primary rectal tumours spread laterally into the mesorectal tissues and total mesorectal excision (TME) is consequently associated with low rates of local recurrence [Heald and Ryall, 1986]. The principles of treatment in patients with T_2 stage tumours and above is for segmental resection of the rectum, again following the regional arterial supply and removing lymph nodes draining along this route. The current practice in Europe is not to carry out extended lymphadenectomy along the lateral pelvic walls, which would include the internal iliac artery. Japanese surgeons, who report local recurrence rates of 5%, do carry out this procedure, but there is a significant cost involved to the patient in terms of post-operative sexual and urinary dysfunction [Moriya et al., 1989].

Achieving cure and reducing local recurrence, therefore, involves TME along with neoadjuvant and/or adjuvant therapies, which will be described in due course. These procedures should aim to minimise damage to the autonomic nerve supply to the pelvis, specifically the hypogastric nerves. It is difficult to give an accurate incidence for these complications, as there are few validated studies. There may be an element

of underreporting of the problem by patients, but impotence may occur in upto 40% of men after pelvic dissection.

Along with the specific aims described above, surgery should be planned so as to maintain intestinal continuity without compromising cure. This should be achieved hand in hand with the preservation of sphincters and retaining satisfactory bowel function after surgery. A "safe" distance of 6cm from the anal verge to the lower extent of the tumour is probably sufficient to allow sphincter reconstruction with a colo-anal anastomosis. If tumours are lower than this or a technically difficult pelvis is encountered such as a deep and narrow male pelvis, the safe course of action to take is to perform an abdominoperineal resection (APR). An increasingly popular alternative to the APR is the "ultralow" Hartmann's procedure, which avoids perineal dissection. The objective of preserving intestinal continuity and anorectal function is very much dependent on sphincter reconstruction, but another important component of the procedure is the configuration of the proximal limb of the anastomosis. It is reported that J-colopouch-anal anastomoses preserve function far better than a straight colo-anal anastomosis [Seow-Choen, 1996] with long-term preservation of this function [Ho et al., 1996]. These pouches should be constructed ideally of descending colon with limbs being no more than 8cm in length.

This discussion has concentrated on radical rectal surgery, but a very important aspect of the treatment of rectal cancer is the possibility of performing local resections. It has been demonstrated that very early stage rectal tumours may not metastasise to lymph nodes with the logical conclusion that these tumours may be excised locally with no detrimental effect on local recurrence or survival [Dukes CE and Lockhart-Mummery, 1952]. There are certain criteria that must be met for such a procedure to be undertaken without compromising oncological principles. It is generally accepted in the UK that these tumours should be no more than 3cm in diameter, within the reach of the palpating finger per rectum and histological and radiological staging should confirm that it is well or possibly moderately differentiated with no lymph nodes involved in the pelvis (USS stage T_1) [Banerjee et al., 1995]. This requires meticulous pre-operative assessment, which must include multiple biopsies and endoanal USS and if possible endoanal MR. The techniques available for local resection fall into two categories. Firstly, there are the dorsal approaches (trans-sacral and trans-sphincteric). Both these techniques have fallen out of favour due to problems with wound healing

and sepsis. The second group of procedures are the transanal approaches. The standard transanal approach does require expertise and experience in order to be performed to an adequate oncological standard. The transanal endoscopic microsurgical approach is even more demanding and is practised in specialist centres. This technique was developed by Buess and colleagues [Buess et al,.1992; Banerjee et al., 1995] in 1983 and allows the surgeon to perform full thickness excisions with good visualisation of the tumour.

The results of local excision for rectal cancer are good for T_1 and T_2 tumours (in 400 patients assessed survival was 94% and local recurrence rate was 19%) [Graham et al., 1990]. The proponents of this approach to rectal cancer treatment counter claims of high local recurrence rates by stating that these figures are comparable with historical series, and if necessary salvage surgery is possible.

It cannot be stressed highly enough that this approach requires expertise and adequate histopathological and radiological support. Radical surgery may carry a higher morbidity, but remains the gold standard for the majority of rectal cancers, which are advanced and show adverse histopathological features.

Chemotherapy

The treatment of advanced primary, recurrent and metastatic CRC is based on the administration of cytotoxic chemotherapy. Chemotherapy for CRC has been used for 40 years and is based on the administration of 5-fluorouracil (5-FU). This compound is a prodrug, which when converted to its active form within the cell, acts as an inhibitor of thymidylate synthase (TS). TS is an enzyme required for the thymidine incorporation in the synthesis of DNA. 5-FU also damages replication by being metabolised within the cell to compounds that are directly incorporated into DNA and RNA. Toxicity of 5-FU is not insubstantial and includes vomiting, diarrhoea, potentially life-threatening immunosuppression, and mucositis.

5-FU used alone acts on cells that are actively replicating and initial trials employed a daily intravenous bolus for 5 days on a four weekly cycle. Other investigators used a weekly bolus injection for six months. The reported response rates were approximately 10-15%, which translated into survival of a median of 8-10 months.

Variations on the administration of 5-FU did improve response rates, but this was only associated with marginal improvements in survival [Seifert et al., 1975; Barbounis et al,. 1989]. These results were somewhat disappointing, so attempts were made either to modulate the delivery of 5-FU or to develop novel agents.

Attempts to combine 5-FU with levamisole, an anti-helminthic drug did not show any improvements in response or survival compared to single agent 5-FU. The next agent to be tried in combination with 5-FU was folinic acid. This proved more successful with improved response rates [Kohner-Wompner et al., 1992] and evidence for improved survival [Poon et al., 1989]. This last study demonstrated an increase in median survival from 7.5 months for 5-FU alone to 12.3 and 13.8 months when this was combined with high and low dose folinic acid respectively. A meta-analysis of 10 studies comparing 5-FU with 5-FU and folinic acid conducted by the advanced colorectal cancer research project demonstrated an improved response rate (11% vs. 23%) for the combined therapy and a non-significant trend towards improved survival [Advanced Colorectal Cancer Meta-analysis Project, 1992]. The combination of 5-FU and folinic acid has also been studied for the treatment of patients with CLM associated with extrahepatic disease within the Medical Research Council (MRC) CR06 trial.

The mechanism by which folinic acid enhances 5-FU cytotoxicity is through the formation of a stable tertiary complex between the folinic acid and 5-fluorodeoxyuridine monophosphate (a 5-FU metabolite) and TS. This complex depletes thymidine to a greater extent than 5-FU alone and thus increases cytotoxicity.

The combination of 5-FU with methotrexate shows many similarities in that response rates (10% vs. 19.5%) are improved with a non statistically significant improvement in median survival (9.1 vs. 10.7 months) [The Advanced Colorectal Cancer Meta-analysis Project, 1994]. Methotrexate is an inhibitor of dihydrofolate reductase, an enzyme that is central to folate metabolism, and which leads to an increase in 5-fluorouridine triphosphate (FUTP). RNA incorporates with FUTP resulting in increased cytotoxicity. 5-FU has been combined with a variety of other agents, but no improvements in survival have been shown. These agents include: methylnitrosurea + vincristine, carmustine, methylcarmustine, methylcarmustine + vincristine and cisplatinum.

The alternative to biomodulation of 5-FU is altering the delivery of the compound. Since 5-FU is only toxic to actively cycling cells, those in G0 are not susceptible. By increasing the time of exposure to the drugs by continuous infusion (24 hours a day for 6 months or more) resting cells may be killed when they enter the S phase at some time during treatment. The overall number of susceptible cells is increased, therefore, improving response rates and/or survival. A recent meta-analysis demonstrated an increase in response (22% vs. 14%), but only a marginal improvement in median survival (12.1 vs. 11.3 months) [Meta-analysis Group In Cancer, 1998]. Furthermore, the major side-effects of 5-FU are decreased, but the hand foot syndrome is more frequent.

The next logical step was to combine the biomodulation of 5-FU with folinic acid and administer the 5-FU as an infusion. This is done using the de Gramont regime (bolus 5-FU and folinic acid followed by a 48 hour infusion of 5-FU) and a multicentre trial in metastatic disease comparing this regime to the Mayo regime demonstrated an increased response rate (33% vs. 14%), increased time to progression (27.6 vs. 22 weeks) and a non statistically significant improvement in survival (62 vs. 56.8 weeks) [de Gramont et al., 1997]. There was also a significantly lower incidence of side effects in patients treated with the de Gramont regime. Similar trends are seen in the EORTC study of infusional 5-FU and biomodulation with methotrexate [Blijham et al., 1996].

5-FU has been discussed in detail, but this must be given intravenously. Oral agents have been investigated, but the main stumbling block appeared to be bioavailability of these compounds. More recent work with the 5-FU prodrug, Capecitabine appear encouraging with equivalence achieved when compared to the Mayo regime [Pazdur R et al., 1999;Cox JV et al., 1999]. Comparisons with infusional regimes are required, but the oral agents promise a change in direction with an associated reduction in morbidity and side-effects.

Finally, regional delivery of chemotherapy to the liver must be addressed as this is a logical way of delivering 5-FU to an organ that both has a high first pass metabolism of the drug and which is the commonest site for metastatic CRC. There is also a significant extraction of 5-FU by the liver, which makes it an ideal candidate for

hepatic arterial delivery. Trials to measure the differences in best supportive care, systemic chemotherapy and hepatic arterial infusional (HAI) chemotherapy have been difficult to design because of crossover between arms of the study, but the evidence from 6 studies suggests improved response rates (41% - 3% complete and 38% partial) compared with systemic therapy (14% - 2% complete and 12% partial) [Meta-Analysis Group in Cancer, 1996]. These studies were in patients with disseminated disease, which meant measuring time to relapse as an endpoint. The results are less conclusive for this (38 weeks for HAI vs. 32 with systemic therapy). Comparison with the de Gramont regime has been undertaken under the auspices of the MRC CR05 trial. There appears to be little evidence of a survival benefit.

Regional chemotherapy is also being used immediately after resection of CLM in to assess if this reduces the recurrence rate of CLM. Data from 156 patients treated at Memorial Sloan-Kettering Hospital, USA suggests that 2 year survival (85% vs. 69%) and hepatic disease free interval (89% vs, 59%) are improved when adjuvant HAI is administered [Kemeny N et al., 1999].

New agents that are showing great promise are Raltitrexed (binds to TS, so acts as a competitor to 5-FU), Irinotecan (topoisomerase I inhibitor) and Oxaliplatin (a third generation platinum compound). Irinotecan has been shown to improve response rates and survival in two studies [Cunningham et al., 1998;Rougier et al., 1998]. Oxaliplatin induces apoptotic cell death by causing DNA cross-linking and appears to have synergy with 5-FU. It has been used as a first line agent in metastatic CRC showing improved response rates and progression free survival without overall survival being increased [Seymour M et al., 1999]. The importance of modern chemotherapy is that as well as possible survival benefits, there is increasing evidence of an improved quality of life for CRC patients. This makes accurate staging vitally important.

So far I have dealt with the treatment of advanced metastatic CRC in this section, but the use of adjuvant chemotherapy is a critical part of therapy that offers the patient the best chance of cure. Based on the assumption that recurrence of disease is due the presence of micrometastases, which are undetected by conventional imaging and clinical evaluation, administration of adjuvant chemotherapy seems likely to reduce the chances of this phenomenon. This has been clearly demonstrated for patients with

Dukes stage C CRC given a combination of 5-FU and folinic acid for 6 months [Midgley and Kerr, 1997]. Overall survival is increased by 5-6% compared to controls. This benefit is not so clearly demonstrated in patients with Dukes B CRC. The uncertain arm of the QUASAR trial addresses this issue, but current evidence does not support the routine use of adjuvant chemotherapy in this broad group of patients. It may, however, be that there are potentially identifiable subpopulations within this group (Dukes B CRC), who will benefit from adjuvant chemotherapy. As in the case of advanced CRC, the use of infusional chemotherapy may improve the results mentioned previously. Initial reports did, in fact, point to a modest improvement (absolute survival of 4.7%) when using portal vein infusion [Liver Infusion Meta-analysis Group, 1997], but early results from the AXIS trial do not show a statistically significant difference [James RD and Axis Collaborators, 1999]. The main advantages are for curatively resected colon cancer. As with advanced disease, the focus of attention is shifting to the newer agents such as Irinotecan, Oxaliplatin and Capecitabine, but it is too early to comment on these as yet. Irinotecan has been clinically evaluated in the PETACC 3 study and Oxaliplatin in the MOISAIC study.

Radiotherapy

Current evidence does not suggest a role for radiotherapy (RT) in the routine treatment of colon cancers other than in the context of a clinical trial [Minsky, 1995]. The main reasons for the contrasting approaches to RT for colonic and rectal cancers stem form the fact that rectal tumours are contained within a finite volume in the pelvis. This means it is easier to target RT to a specific volume and the impact on surrounding structures is not as great as in the case of colonic tumours within the peritoneal cavity. Here, several organs such as the kidneys and small bowel are at significant risk of RT damage. Also, it is more difficult to achieve adequate clearance for rectal tumours, so the probability of residual disease is much higher. As local clearance is much better with colonic tumours the added benfit of RT is much smaller and not demonstrable in clinical trials.

Rectal cancer has a local recurrence rate of 20-45% and the introduction of TME has been shown to reduce this to approximately 7-10% [McFarlane et al., 1993; Enker, 1995; Aitken et al,. 1996]. The aim of RT is to reduce local recurrence further and it is

well established that surgery with adjuvant RT has a lower recurrence rate when compared to surgery only [Stockholm Rectal Cancer Study Group, 1990]. The question of when to give the RT is a subject of controversy, but in Europe and specifically in the UK guidelines recommend patients should receive preoperative RT for operable rectal cancer [Royal College of Surgeons, 1996]. In the United States guidelines issued by the National Cancer Institute recommend the use of combined post-operative RT and chemotherapy [National Cancer Institute, 1989]. The only randomised controlled trial to compare pre- and post-operative RT for rectal cancer showed pre-operative RT conferred superior local control [Frykholm et al, 1993]. Furthermore, the Swedish Rectal Cancer Trial demonstrated an improved survival at 5 years in the RT group [Swedish Rectal Cancer Trial, 1997]. It now appears that there is strong evidence to suggest that combining TME and surgery are better than TME alone and overall, there is an approximately 10-fold reduction in local recurrence using this combined approach [Kapiteijn et al., 2001]. Although not common practice, RT alone has been shown to have a cure rate of at least 80% in patients with small tumours (less than 5cm) [Basrur and Knight, 1983;Kovalic, 1988;Sischy et al., 1988], but it must be stressed that this treatment should probably be reserved for tumours less than 3cm that are well differentiated.

Certain uncontrollable factors exist that limit the effectiveness of RT. These include size of tumour [Gerard et al., 1996], clinical stage and the degree of fixity [MRC Working Party.Second report, 1984], for example local control can be achieved in 97% tumours of less than 3cm, but this falls to 60% for tethered tumours that are 3-5cm in size [Roth et al., 1989]. Controllable factors include the dose of RT, the size of the RT field, the timing of surgery and the use of chemotherapy.

The higher the dose of RT, the sooner the patient can complete treatment and undergo surgery. Certainly, evidence from a recent EORTC study [EORTC Study 22921, 1996] suggests that a pre-operative dose of 5 fractions of 5Gy are equivalent to 28 fractions of 1.8Gy. It must be noted that short course RT allows surgery to be completed sooner, but the total dose is 25Gy rather than 50Gy. In the post-operative setting there is evidence for the benefits of higher doses [Aleman et al., 1992] with respect to improved local control in patients with Dukes' B carcinomas. There is widespread acceptance that RT field size is important. Smaller fields are less toxic than larger RT fields that caused diarrhoea [Letschert et al., 1994], small bowel

obstruction due to late enteritis [Mak et al., 1994] and an increase in non-cancer deaths [Stockholm Rectal Cancer Study Group, 1990;Frykholm et al., 1996]. This latter finding has been explained specifically as a result of RT technique because mortality using a four field technique is identical (4% vs. 3%) in RT and non-RT control arms [Swedish Rectal Cancer Trial, 1993]. The reason appears to be that there is less small bowel irradiation as the volume of small bowel using a three or four field technique is half that using a two field technique [Frykholm et al., 1996]. Also the use of high energy linear accelerators to deliver RT give much better dose distribution than older linear accelerators and Cobalt-60 machines. Finally, as already pointed out, there may be a survival advantage when using pre-operative RT, but interim results from the Dutch pre-operative radiotherapy study [Kapiteijn et al., 2001] have so far only demonstrated a significant reduction in local recurrence (2.4% vs. 8.2%) with equivalent 2-year survival (82% with RT and 81.8% in the control group). The disadvantage of this policy is that a proportion of patients who do not need RT are unnecessarily irradiated. There is the added disadvantage of a delay in surgery if RT is prolonged as well as the fact that lymph node staging tends to be less reliable [Horn et al., 1990]. These factors must be taken into account and weighed up against the lower toxicity of pre-operative regimes, shorter course and better adherence to the intended treatment protocol [Pahlman and Glimelius, 1990].

More recent developments in the search for improving efficacy have concentrated on the combination of chemotherapy and RT for the treatment of rectal cancer and these will be briefly discussed now. Chemotherapy agents are used primarily as radiosensitizers, which enhance RT by impairing DNA repair once damaged by RT. The concomitant use of RT and chemotherapy has been shown to be more effective than RT alone [Gastrintestinal Tumour Study Group, 1992;Krook et al., 1991]. When this combination is given post-operatively, there is an increased toxicity compared to post-operative RT alone [Rominger et al., 1985] which may result in necrosis, fistula formation and bowel stenosis. The maximum tolerated dose of 5-FU is lower for concomitant compared to sequential delivery [Minsky et al., 1992a]. The scheduling of concomitant treatment is also more toxic post-operatively compared to pre-operative administration [Cooper et al., 1993;Minsky et al., 1992b] although there are others who question this [Hyams et al., 1997]. Pre-operative concomitant therapy is associated with greater toxicity than pre-operative RT alone [Boulis-Wassif et al., 1984]. The delivery of chemotherapy appears to be more favourable as an infusion

rather than a bolus [Rich et al., 1995] with regard to local control, but the survival benefits if they exist appear marginal at best [Boulis-Wassif et al., 1984] or associated with severe side effects [O'Connell et al., 1994].

In summary, therefore, current practice in the UK would recommend short course pre-operative RT followed by surgery for operable rectal cancers (currently being evaluated within the MRC CR07 trial), which may or may not be followed by adjuvant chemotherapy. Equally, a policy of best surgery, usually TME, can be followed by accurate histopathological staging and selective post-operative RT with or without concomitant chemotherapy. Features that would indicate the need for RT include lymph node or lateral circumferential margin positive tumours. Inoperable tumours may be downstaged with a longer 4-6 week course of pre-operative RT with concomitant infusional 5-FU chemotherapy. The MRC CR07 and Dutch CKVO-95-04 trials are currently recruiting in order to assess the relative benefits of pre- and post-operative chemotherapy. Unlike CR07, all patients in the Dutch trial are expected to undergo TME.

In advanced CRC, RT may be an effective palliative strategy for recurrence in the pelvis or in the rare instances of bone or cerebral metastases. There does not appear to be any survival benefit. RT should therefore be always considered as part of the armamentarium for treating advanced disease.

It is evident from the preceding discussion that many questions remain unanswered and this therapeutic strategy will inevitably be in a state of flux until results of ongoing clinical trials report. This applies to both chemotherapy and RT. It is also inevitable that the use of newer agents such as Irinotecan and Oxaliplatin will be incorporated into the changing chemotherapeutic arsenal in the not too distant future. For the purposes of this thesis, it is acknowledged that I have analysed the equivalent of a single frame in the middle of an ongoing motion picture.

Recurrent CRC and extrahepatic metastases

In upto 30% of cases recurrence following treatment of primary CRC is localised and therefore suitable for curative resection [Turk, 1993]. If detected early it is reported that survival may be improved, especially if radical surgery is performed [Shirouzu et

al., 1996]. In order to avoid unnecessary morbidity and mortality careful selection of patients is essential as only 20-30% of these particular cancers are curable [Barr et al., 1992;Wanebo et al., 1987].

There is debate as to the clinical benefit and cost-effectiveness of intensive follow-up for patients with CRC [Tornqvist et al., 1982; Renehan et al., 2002]. Once a diagnosis of recurrent or metastatic CRC is made it is imperative to assess the true extent of disease. Patients can then avoid morbidity of inappropriate surgery and the healthcare system can benefit from significant cost savings. It is also accepted that in asymptomatic patients who are diagnosed with recurrent disease, palliative chemotherapy is of benefit in reducing the rate of disease progression as previously discussed.

The management of recurrent and/or extra-hepatic metastatic CRC requires careful selection of treatment if the patient is to benefit in terms of survival or palliation. It is evident that effective treatment of recurrent and/or extra-hepatic metastatic CRC requires prudent use of surgical resection or intervention, chemotherapy and radiotherapy. These may be used alone or in combination and importantly, alternative palliative strategies may be required. These alternative strategies may include colonic stenting, laser treatment or the use of novel chemotherapeutic agents.
Detecting subclinical recurrent and metastatic CRC appears to be of value, therefore. Underpinning all therapeutic decisions for the clinician and patient is the need to have precise information on the exact extent of recurrent or metastatic disease. Surgical resection of localised rectal recurrence and isolated, stable hepatic or pulmonary disease is known to be effective [Steele et al., 1993; McCall et al., 1995; Benotti and Steele, 1992; Zavadsky and Lee, 1994]. Failure of surgery in these patients is almost always due to the presence of synchronous, but undetected disease. Patients with disseminated disease may benefit from systemic chemotherapy or RT, but again knowledge of the location of disease is essential.

Current practice for the follow-up of CRC patients in the UK consists of regular clinical examination, serial measurement of serum carcinoembryonic antigen (CEA) concentration, luminal mucosal surveillance (either with colonoscopy or Ba enema) and CT. Although frequently used [Vernava, III et al., 1994] CEA measurement is not sufficiently sensitive (59%) or specific (84%) [Moertel et al., 1993]. Reports of

luminal recurrence from CRC vary, but this may only occur in 6% of cases [Galandiuk et al., 1992]. The arguments for invasive investigations of the colon and rectum are equivocal. The routine use of CT for post-operative surveillance is conventional. This modality may be more sensitive than CEA measurement, especially for pelvic and intra-abdominal abnormalities, but specificity is a significant problem [Moss, 1989; Balthazar, 1991; Freeny et al., 1986]. This is illustrated by the difficulty in differentiating recurrence from benign fibrosis, which may result after surgery and/or radiotherapy. MR may augment CT in differentiating local recurrence from scar tissue in the pelvis [Makoto, 1990;Kimura et al., 1988], but there remain limitations in terms of specificity and size of tumour detected [Ito et al., 1992]. A major discussion point of this thesis is how best to follow up CRC patients and what role PET may have in this setting.

Colorectal liver metastases

By far the most common site of metastasis for CRC is the liver and this is a special case, which requires close attention. Colorectal liver metastases (CLM) are a significant clinical burden with upto 50% of patients with CRC developing hepatic metastases. These metastases are slow growing and may take upto 3 years to reach a size of 2cm [Allen-Mersh, 1991] and 4 years to cause death [Finlay and McArdle, 1986]. In approximately 25% of patients the metastasis is present at the time of diagnosing the primary CRC, having spread to the liver via the portal circulation. Upto 90% of CLM will eventually be diagnosed within 3 years of initial resection [Launois et al., 1994]. Upto 5-10% of patients with CLM can be cured by resection [Bengmark and Hafstrom, 1969;Scheele, 1993]. Extrapolating this using statistics presented in the introduction to this thesis (section 1.1), there would potentially be between 750 and 1500 patients per annum in England and Wales suitable for curative resection of CLM.

The only hope of cure in patients with CRC liver metastases is surgical resection, which has a five-year survival of upto 40%. However, surgery for CLM has significant morbidity and mortality associated with it [Doci et al., 1995]. It is, therefore, essential that patients are appropriately selected from those with truly isolated lesions. These patients stand the highest probability that the procedure will achieve cure. Unfortunately, only 20-25% of patients fall into this category and are

deemed suitable for liver resection. The other 75-80% of patients may benefit from palliative chemotherapy, which can in certain cases also lead to a small survival benefit.

In addition to conventional palliative chemotherapy a variety of strategies do exist to treat this poor prognosis group (table 1.5). Avoiding inappropriate surgery means decreased morbidity for this group of patients and there is still the opportunity to offer non-surgical treatment modalities.

Interstitial laser therapy
Radiofrequency thermoablation
Cryotherapy
Immunotherapy
Percutaneous alcohol injection

Table 1.5 Palliative strategies used to deal with CLM

When one analyses surgical resection more closely, the benefits of accurate pre - operative evaluation of the extent of disease are apparent. There are methodological problems with published data on liver resection as there are no studies comparing surgery with no treatment, usually historical controls are used. The main reason for this is that patients who have undergone surgery for four or more CLM have survived upto 10 years, therefore, on ethical grounds it is hard to justify no treatment [Fong et al., 1997]. In addition, there appears to be inclusion of patients with liver metastases other than from a CRC primary. Another determinant of survival is the percentage of hepatic replacement. If left untreated, the median survival is 10.6 months (range 3-24 months and a 5 year survival of 1%) [Taylor, 1996; Launois et al., 1994; Doci et al., 1995; Ballantyne and Quin, 1993].

The reported 5-year survival for this procedure is 25-38% [Selzner M and Clavien PA, 1999], but if patients are highly selected then the 5-year survival may be higher than 40% [Scheele et al., 1990;Scheele et al., 1991]. The cure rate may also be enhanced with the use of pre- and/or post-operative adjuvant therapies, but the central issue for the surgeon remains the accurate evaluation of the patient for the presence of synchronous hepatic and extrahepatic lesions. Both these factors indicate a poor outcome from surgery. However, the presence of multiple metastases in itself is not a

contraindication to resection as was previously thought to be the case. Fong and colleagues [Fong et al., 1997] reported a disease free survival of 38% at 10 years in patients who underwent resection of four or more lesions. Despite this evidence, pooled data from America, France and Germany suggests that the rate of "surgical failure" or relapse after resection is between 59% and 81% with a median time to recurrence being 9 to 19 months [Hughes et al., 1986;Lorenz et al., 1998;Nordlinger et al., 1994]. A majority of recurrences (50-60%) are confined to the liver alone.

The major cause for relapse is the presence of undetected synchronous disease [Taylor, 1996], although there are other complex factors at play. These factors include the presence of local infiltration and lymphatic spread in the original primary tumour, a time period of less than two years between diagnosis of the primary and hepatic lesion, greater than four hepatic lesions, and an elevated CEA level [Nordlinger et al., 1996]. A proportion of patients are thought to have occult hepatic metastases that remain dormant, but a proportion of these eventually do grow into overt disease [Zavadsky and Lee, 1994]. The presence of extrahepatic spread is a very poor prognostic sign and contraindicates curative resection. In 20% of patients metastatic disease is confined to the liver [Fong et al., 1997].

The importance of selecting patients who are likely to do well after surgery is emphasized by the mortality (0-8%) and morbidity (10-39%) rates [Doci et al., 1995; Jatzko et al., 1995]. If a patient undergoes unnecessary surgery, they are exposed to both mortality and morbidity. Recent improvements in anaesthetic care, surgical technique and understanding of hepatic anatomy, post operative intensive care and the use of devices to reduce blood loss have contributed to a reduction in both mortality and mortality. Also, these factors must be taken in the context of five-year survival ranging between 25-38% [Selzner M and Clavien PA, 1999]. Debate now centres on the use of pre and post operative adjuvant chemotherapy and whether these therapies improve survival.

Summary of treatments for colorectal cancer

The outlook for patients with CRC has improved over the last 25 years. There have been advances on several fronts in the battle to cure CRC, but this is reflected by only a small improvement in survival over the last 25 years in the UK [Hayne et al., 2001].

So the improvement does not reflect the advances in treatment and changes in practice over the same period.

I have described the current state of treatment options available to patients with CRC whether they have limited curable disease, advanced incurable metastatic disease or fall somewhere in the middle of this wide spectrum. It is also important to acknowledge the changes in peri-operative care, for example, the prevention of other surgical complications such as sepsis and deep vein thrombosis. The contribution that modern anaesthetic techniques and post-operative care have made is an additional significant factor. Even though the provision of intensive care unit (ITU) and high dependency unit (HDU) beds in the UK is inadequate, the availability of these services currently has played a major role in immediate reduction of morbidity and mortality.

Surgical techniques such as laparoscopic assisted resections may have many short-term benefits, for example improving the speed of recovery and reducing pain. Reports suggest that even though there are specific complications of this approach (small bowel injury and port-site recurrence) the procedure can be performed with acceptable morbidity and mortality [Milsom and Kim, 1997]. This operative technique is currently subject to evaluation in the context of randomised controlled trials in the UK. Interestingly, recent reports by Lacy and colleagues tested this technique within the setting of a randomised controlled trial and the conclusions that they draw are that this technique is more effective than open resection for treatment of colon cancer in terms of morbidity, hospital stay, tumour recurrence, and cancer-related survival [Lacy et al., 2002].

Other advances have either not been mentioned in detail or have been omitted from a full discussion due to the limitations of this section. These include discussion on combination chemotherapy, chronomodulation of chemotherapy, brachytherapy, immunotherapy and gene therapy. This is not to underestimate their importance, more that they are not mainstream treatments as yet.

Having examined the nature of the problem that CRC presents in terms of epidemiology I have analysed the aetiology in order to put the approaches to treatment into context. I have discussed the mainstay of treatments under various

surgical and non-surgical headings. The range of therapeutic options presented and the potential for effective novel therapies is clear. How can better imaging of CRC help improve current management? This question has been answered in very general terms if one considers the treatments for primary, recurrent and metastatic CRC presented so far and the need for accurate imaging in order to adequately diagnose and stage disease. The result will be that appropriate treatments can be given based on the early detection as well as the the true extent of disease.

1.2 Computed tomography

Imaging contributes significantly to clinical decision making algorithms in patients with CRC. Conventionally, anatomical imaging modalities have played a central role in imaging cancer and this also applies to CRC. The various different modalities that are used for specific applications in CRC are discussed in depth later in this chapter (section 1.4). These modalities include USS, MR, Ba enema as well as nuclear medicine techniques such as immunoscintigraphy and PET. This section, however, focuses on CT, the anatomical imaging modality most readily available and frequently used in oncology throughout the UK. CT can and is applied to every aspect of CRC imaging. Furthermore, subsequent chapters of this thesis investigate the differences between PET and CT in terms of accuracy of diagnosis and impact on clinical decision-making.

1.2.1 Basic principles of computed tomography

CT is an anatomical sectional imaging technique that was developed in the early 1970's [Hounsfield, 1973]. Initially, CT scanners were used to image the brain and with technological progress applications were found for CT imaging of the thorax, abdomen, pelvis and the extremities. These are the only parallels that CT has with PET. The basic principle of CT is that the tube produces an x-ray beam, which is directed through the patient. The x-rays are either absorbed or transmitted through individual body structures depending on the density of that structure. A detector placed at 180^0 picks up the resultant beam. In a CT scanner, the patient lies on a couch that is incrementally moved through a gantry that houses an x-ray source (tube) and a detector situated at 180^0 on the other side of the circular assembly. The tube and detector rotate around the patient as they are moved through the scanner and this

produces a series of thin "slices", each a cross-sectional image at a particular level through the patient's body (figure 1.2).

The physical linkages between the power cables and the x-ray tube mean that the tube is unable the rotate in continuous motion. This limitation has major consequences as after each image "slice" the system must stop, rotate back before proceeding to the next slice of tissue. Typically the time taken is 1 second per slice, which makes imaging of a region relatively slow with the risk of motion artefact being significant [Conall and Hanlon, 2002]. Depending on the resolution required, each slice can be between 1 and 10mm in thickness. The relationship between the amount of the x-ray beam that passes through a particular tissue is inversely proportional to the density of that tissue. The detected incident x-ray beam is converted into an electron stream, which is digitised and assigned a number, known as Hounsfield Units (HU). This represents the amount of energy absorbed by the body tissue it traverses and data is acquired for each angle of rotation. This data set can be reconstructed into various shades of black, grey and white using appropriate computer software. Water is assigned an HU of zero with air appearing black and bone white. This data can be stored on magnetic or digital tapes or be printed out like a plain radiograph. Images can also be viewed on a monitor. Unlike a plain radiograph the resultant image is not a "shadow" image of the structure under investigation in one plane, but a map of x-ray absorbtion in two dimensions.

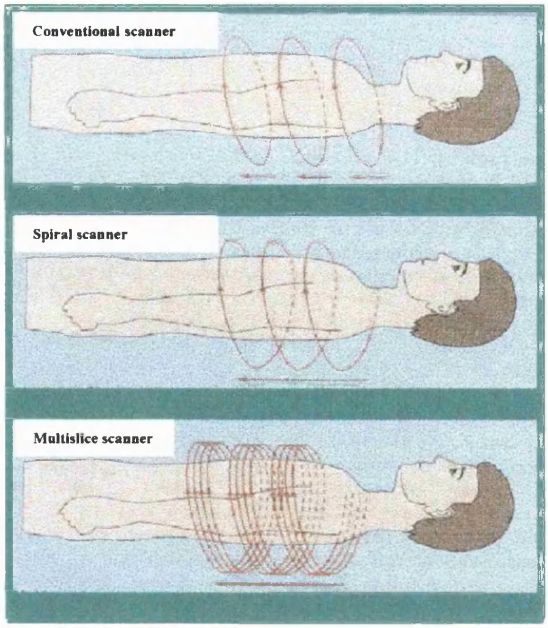


Figure 1.2 Diagram showing the different modes of data acquisition for conventional 2D CT (top), spiral CT (middle) and multislice CT (bottom)

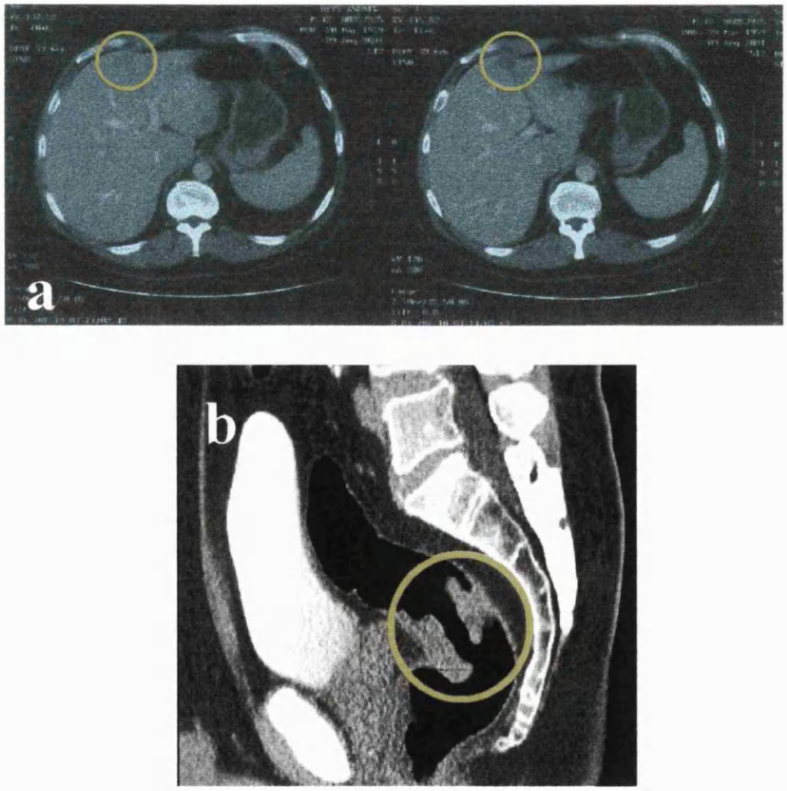


Figure 1.3 Sequential transaxial spiral CT "slices" (a) at the level of the liver. This patient had previously been treated for CRC. There is a suggestion that a CLM is present on these images (circled). It is possible to reconstruct images in the sagittal and coronal planes. This is demonstrated in image (b), a sagittal reconstruction through the pelvis in a different patient who had a symptomatic rectal carcinoma (circled).

CT is extremely well suited to displaying and delineating anatomical information primarily because of the method of producing the image. Contrast media can be injected intravenously or administered orally if certain gastrointestinal tract structures are being studied (for example the liver or intestinal lumen from mouth to anus). The principal function of contrast media (usually iodine based) is to enhance images of vessels, soft tissue structures and tumours.

A more recent advance to conventional CT has been the development of spiral or helical CT. Whereas conventional CT imaged each section or slice and then moved to the next; spiral CT obtains data in a different fashion. The patient moves continuously through the gantry as the x-ray source and detector circle the patient (also continuously) so that a volume of tissue is imaged. The advance was only possible due to the development of "slip ring" technology which allowed the tube and detector to rotate continuously without physical constraint. Data acquisition is substantially faster than conventional CT and contrast studies and resolution are much improved. This hardware has been augmented with the development of software that is capable of processing helical data and reconstructing images in coronal and sagittal as well as the transaxial plane (figure 1.3).

Spiral CT has revolutionised the throughput of patients in departments of radiology. With significantly reduced scan times, more patients can be imaged and the actual scan for individual patients is improved in terms of obtaining whole abdominal images in one breath hold. The ability to study differential arterial and venous phases of liver perfusion after the administration of intravenous contrast is just one more benefit of the technique. The capability of spiral CT in CRC imaging is, therefore, significant (e.g. CTC) with sensitivity for lesions and pathology being higher than with traditional CT methodology. However, this improved sensitivity is not matched by an equal improvement in specificity and it is in this area that PET and other functional modalities may complement CT.

The natural progression has been to join several detectors (4 to 8) together and these can detect x-ray data across a larger volume of tissue making scaning even faster with an improved resolution [Rubin et al., 1999]. This is known as multislice CT. The thorax, abdomen and pelvis can be imaged in a single breath hold, approximately 20

seconds). In terms of cost, a spiral CT scanner is about one third to one half the cost of a multislice CT machine.

CTC was possible with spiral CT scanners, but the advent of multislice CT has heralded the possibility of accurate "virtual colonoscopy", more correctly termed three-dimensional CTC [Hara et al., 2001]. This is a further extension of multislice CT technology that uses computer software to reconstruct data sets obtained from spiral CT of the abdomen into a "virtual" image of the mucosal lining of the colon and rectum [Vining, 1997; Amin et al., 1996]. Images can be reconstructed in two and three dimensions. In the three-dimensional mode and using a computer mouse to navigate it is possible to "fly through" the virtual colon and inspect the mucosa for lesions. This technique is in its' infancy, but provides the tantalising prospect of avoiding the hazards of an invasive colonoscopy in order to diagnose pathology in the colon and rectum [Harvey et al., 1998; Fenlon et al., 1999; Morra et al., 1999]. The technique is expensive mainly because of the costs of software and the need to renew CT hardware, but this situation is likely to change if it proves to be a sensitive and specific clinical investigation, which can be used to replace diagnostic colonoscopy (figure 1.4). The second obvious disadvantage of the technique is that tissue specimens cannot be retrieved as in conventional colonoscopy, but this has to be weighed up against the potential of avoiding conventional colonoscopy for diagnosis.

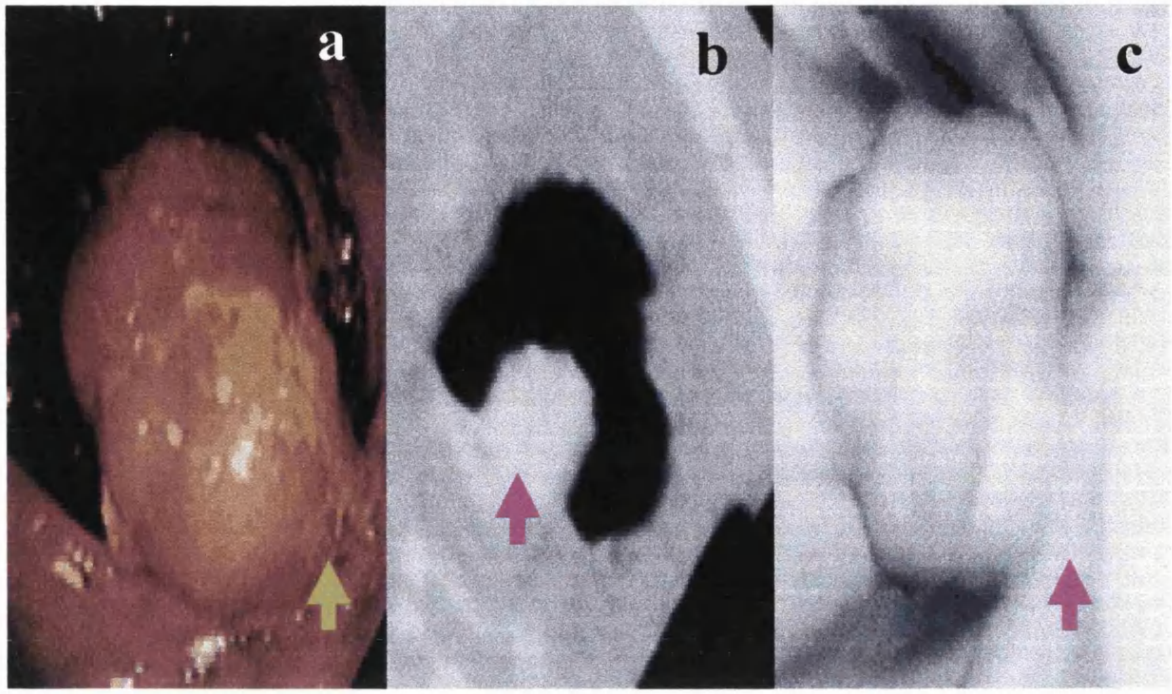


Figure 1.4 Photograph (a) shows a pedunculated adenomatous colonic polyp which has been marked with an arrow at its' base. Image (b) is a two dimensional multislice CT reconstruction of the same lesion, again arrowed at its' base. The black area is the colonic lumen. Image (c) is a three dimensional reconstruction of the multislice CT data. This is the equivalent of a single frame in a video clip of a virtual colonoscopy.

In addition, it is important to note that CT accounts for 40% of medical radiation, but represents only 4% of radiological examinations [Shrimpton and Edyvean, 1998]. Any expansion in the use of CT in CRC imaging has to be balanced against the risks of radiation. The National Radiological Protection Board has made specific reference to the likelihood of inappropriate examinations by CT [National Radiological Protection Board, 1990] and it is noteworthy that multislice CT tends to expose patients to a slightly higher dose of radiation compared to spiral CT. This debate must also be bourne in mind when considering PET as an imaging modality in CRC, both when used as an alternative or complimentary investigation.

1.2.2 Application of CT to colorectal cancer

CT methodology has been successfully adapted to CRC imaging and is used for diagnosis, staging and evaluation of therapy both in primary and recurrent disease. These applications will be discussed in this section, however, detailed description of the advantages and disadvantages are described in section 1.4.

Detecting primary CRC

CT has not been applied in a systematic way to screening for asymptomatic CRC. This is mainly due to concerns over radiation exposure of patients; furthermore, cost and clinical evidence for significant benefits do not exist. However, recent advances in technology described above have made the diagnosis of CRC in asymptomatic individuals a reality. This is primarily through the use of CTC with two- or three-dimensional reconstruction [Fletcher and Johnson, 2000]. Small cancers and polyps can be identified and this area is the subject of ongoing research. A few definitive reports exist, but the availability of the hardware, expertise and software of sufficient capability mean that research findings are yet to be translated to everyday clinical use.

A standard spiral CT is capable of detecting primary CRC with a high degree of accuracy, but the development of CTC promises to increase this [Chauoi et al., 2000]. Most reports are focused on the use of CTC for detecting polyps and I have tabulated the current data for this in table 1.6. In the few reports for the detection of CRC, CTC

appears to have a sensitivity and specificity of over 95% and Harvey and co-workers were able to detect all 38 CRC's in 52 patients assessed [Harvey et al., 1998].

Author	Patients	Sensitivity (%) Per polyp/patient	Specificity (%)
Fletcher [Fletcher et al., 2000]	180	75/85	93
Fenlon [Fenlon et al., 1999]	100	91/96	96
Yee [Yee et al., 1999]	155	94/100	-
Morrin [Morrin et al., 1999]	49	92/-	100
Pineau [Pineau & Vining 1999]	88	-/100	87
Dachman [Dachman et al., 1998]	44	83/-	100
Laghi [Laghi et al., 1999]	34	100/100	-
Macari [Macari et al., 1999]	37	100/100	-
Hopper [Hopper et al., 1998]	100	100/100	-

Table 1.6 Accuracy of CTC in detecting colorectal masses ≥10mm per polyp and per patient from Fletcher and Johnson [Fletcher & Johnson, 2000]

CTC involves bowel preparation for the patient prior to the examination. At the examination, the patient lies on a couch in a CT scanner while quantities of air are insufflated into the colon as in a double contrast Ba enema. The patient then undergoes a CT scan. The patient will have a distended colon so that mucosal pathology can visualised as demonstrated in figure 1.4. This technique is minimally invasive, highly accurate, avoids the problems of barium retention in a Ba enema. Information regarding tumour infiltration, especially in high stage tumours is accurate. This technique is now gaining acceptance in the UK. Of great promise is three-dimensional reconstruction CTC (virtual colonoscopy). As described previously, this investigation seems to have most the benefits of conventional colonoscopy without the invasiveness. However, the inability to take biopsies and exposure to radiation are important disadvantages. For the clinician, one other

important benefit is the ability to manoeuvre images on the workstation screen, so as to look at certain areas in great detail. In addition to this, a proportion of patients undergoing colonoscopy have incomplete examinations for a variety of reasons, including malrotation, redundant colon, adhesions and ventral hernias. CTC is possible in these patients as demonstrated by Fenlon and colleagues [Fenlon HM et al., 1999].This procedure is usually performed on a cleansed colon, however, it is possible to image the unprepared colon using faecal tagging techniques.

Staging primary CRC:

The three areas to be addressed are: 1) assessment of local infiltration; 2) assessment of local lymph node involvement; 3) detection of distant metastases particularly CLM.

As described above and in section 1.4.2 CT is capable of accurately delineating tumour infiltration especially in advanced tumours. There may be inaccuracies with lower stage tumours, but the advent of high-resolution spiral CT appears to have remedied this situation [Harvey et al., 1998].

One of the drawbacks of CT is well demonstrated by its capability to detect malignant lymphadenopathy. Anatomical imaging modalities rely on size criteria for diagnosing lymph nodes as malignant. In the case of CT the arbitrary figure used is 1cm. This gives the modality an inherent inaccuracy as malignant cells are present in lymph nodes smaller than 1cm and conversely a proportion of nodes greater than 3cm in diameter are benign [Rodriguez-Bigas et al., 1996]. This point is illustrated in section 1.4.2 with specific examples.

Although CT is widely used to detect liver metastases, there is evidence that it may not be as accurate as generally perceived with a proportion of lesions being missed on CT. Significantly, even if a liver metastasis is detected CT may be inaccurate in evaluating the number of lesions present and this has significant implications for surgical management [Steele et al., 1991].

Detecting recurrent CRC:

Early reports suggested that CT would prove to be a sensitive, non-invasive means by which to detect recurrent CRC [Lee et al., 1981; Reznek et al., 1983; McCarthy et al., 1985]. Sugarbaker and colleagues [Sugarbaker et al., 1987], therefore, studied CT in the context of a surveillance investigation and found that in 66 patients assessed CT failed to detect a recurrence in 31 out of 33 patients with confirmed recurrence. Although other reports seem to corroborate this evidence [Mendez et al., 1993] modern spiral CT is substantially more accurate than non-spiral CT, but increasingly it appears that MRI is more accurate for detecting recurrence especially in the pelvis. Very few recurrences are intraluminal [Galandiuk et al., 1992] and CTC may be used to detect these and metachronous tumours.

When one looks at the reasons for this poor performance by CT, it is apparent that the main reason for "failure" is the inability to differentiate benign, fibrotic tissue, which results from surgery and/or RT, from malignant tumour recurrence. The use of intravenous contrast agents does not significantly improve this situation. Technology for morphological imaging can be at its most advanced, but the fact is that there are no tissue characteristics that permit an accurate diagnosis. Observations of changes that occur over time are the surrogate means by which we are currently able to deal with patients who are found to have an indeterminate soft tissue mass in the abdomen or pelvis. This, however, may lead to missing the opportunity of resecting a localised recurrence, for example, of a rectal carcinoma in the pelvis.

The accuracy of CT for detecting hepatic metastases is crucial to successful management and ultimate outcome. As described earlier in this section, CT is inaccurate for detecting CLM, but the reasons for this can now be examined in more detail. The blood supply of CLM is almost exclusively from the hepatic artery, whereas that of the normal liver parenchyma is derived from the portal venous circulation as well as the hepatic artery. CT can image the liver using the differential blood supply as a means of demonstrating CLM. The principal is that an intravenous bolus of contrast is given followed by a sequence of scanning timed to coincide with the portal venous phase. The latter is usually 40-60 seconds following administration of contrast. The resultant image demonstrates CLM with lower attenuation values than normal parenchyma and of the order of 50-80 HU. However, the attenuation of

metastases increases with time and that of normal liver tissue decreases. The timing of scanning is vital as if delayed, the imaging may be at a point in time when there is little attenuation difference leading to lesions being missed. Spiral CT, with its rapid image acquisition times, has partially addressed this problem and reported sensitivity ranging from 68-79% [Zerhouni et al., 1996; Paul et al., 1994].

Arterial portography combined with CT (CTAP) is a strategy, which greatly improves the accuracy of CT for detecting CLM. After deploying an angiographic catheter, usually in the superior mesenteric vein, contrast is injected and CT image acquisition is commenced. The imaging demonstrates high normal liver parenchymal enhancement with little in the CLM. The difference in enhancement is in the order of 150 HU and resolution is between 5-10 mm. The specificity of the technique, however, is generally low due to the fact that lesions, which interrupt the portal venous circulation, result in an area of diminished attenuation. Currently, therefore, because of this and its invasive nature CTAP is not the first choice imaging investigation for patients suspected of having CLM.

In addition to these complexities of data acquisition, CT has a resolution that is in the order of 1 cm for liver lesions. Lesions less than this size may not be confidently diagnosed. This last statement also applies to the detection of extrahepatic metastases and local recurrences.

Evaluating the extent of recurrent CRC:

CT can be used to investigate the presence of widespread dissemination. The preceding discussion on detection of recurrent and/or metastatic lesions applies very much to detection of additional metastatic lesions. This is the case whether the "index" recurrent/metastatic lesion is locoregional, hepatic or at a distant site such as the lung. The current situation is that although CT may be able to detect recurrence or a metastatic deposit, the ability to evaluate the true extent of disease is poor. The impact of knowing about disseminated disease on the decision to proceed with surgery in patients with a local recurrence of rectal cancer, CLM or even an isolated pulmonary metastasis is significant and CT alone is inadequate.

Evaluating therapy response in CRC:

Evaluating the response to therapy is a major part of the workload for CT in patients with CRC. Morphological characteristics of the lesion(s) being treated are used as predictors of response to RT and chemotherapy, but are also used to monitor these treatments.

Currently, CT is not only used to judge response in terms of reduction in tumour volume, but also the presence of additional lesions. From the preceding discussion it is evident that CT may not be a sufficiently accurate tool to do this, however its use is common. The primary reason for inaccuracies stems from the fact that both RT and chemotherapy may render whole or part of a lesion seen on CT non-viable. The lesion is still seen on CT, but it may not be metabolically active in terms of cellular replication, growth and metastatic potential.

1.2.3 Failings of CT in colorectal cancer imaging

CT has played a significant role in improving tumour imaging over the last two decades. The modality is widely available and there are sufficiently experienced clinicians to perform and interpret the investigation. However, CT involves exposure to radiation (not the case for USS and MRI) and currently demand outstrips supply for the investigation.

In addition to this there are some important pitfalls when applying CT to CRC management and it is these that must be addressed if the current "gold standard" is to be raised. First amongst these is the inability to diagnose malignancy in normal sized lymph nodes. Secondly, the poor detection rate for intrahepatic lesions and thirdly, the inability to accurately diagnose scar tissue, which may harbour malignancy. In each of these scenarios it is evident that the principle of anatomical imaging may be the shortcoming. An ideal imaging solution is one that is able to detect all foci of malignant tissue at an early stage with a high degree of sensitivity and specificity. It should also be relatively cost effective to implement clinically, widely available and have minimum of side effects. In order to address these issues I am now going to discuss PET as an alternative approach to these clinical problems.

1.3 Positron Emission tomography

1.3.1 Physical properties and biological basis for PET in oncology

Background:

PET is a minimally-invasive metabolic imaging modality that uses radio-labelled ligands to deliver high-resolution data of metabolism and function, highly relevant to pathological disease processes, such as cancer. This technique utilises the capability of individual radiotracers (referred to as "tracers" in this thesis) to target specific metabolic processes with picomolar sensitivity. Wong and colleagues [Wong WH et al., 1999] have extensively reviewed the basis for the use of PET in oncology and in this section I will present an overview of this subject. The capability of PET in oncological imaging is derived from a unique set of circumstances. Firstly, malignancy leads to alterations in cellular biochemical reactions. Secondly, it is possible to synthesise analogues of native compounds that take part in these deranged reactions. The synthesised analogues may be composed of the elements carbon, oxygen, fluorine and nitrogen all of which exist as positron-labelled isotopes (^{11}C, ^{15}O, ^{18}F and ^{13}N). It is, therefore, possible to use these positron-emitting analogues of natural compounds, to target specific biochemical processes or organ function. A tracer can be used as an in vivo marker of the particular pathological process being studied because it decays by positron emission.

Positron decay ultimately results in the emission of two 511 KeV photons that can be detected by external assemblies. This form of radioactive decay can be quantitated and an image of the biodistribution of tracer can be tomographically reconstructed in the transaxial, sagittal and coronal planes. Furthermore, dynamic modelling of tracer kinetics allows data to be made available for other functional parameters such as tissue perfusion, metabolic rate and the density of targeted receptors. Conceptually, this is far removed from conventional anatomical imaging of disease. Cell structure, hence tissue and organ morphology, is dependent on cellular biochemical function. The deranged biochemical processes resulting from malignant change that are detected by PET are thought to precede the morphological changes detected by conventional imaging. These factors may confer advantages when imaging malignant disease.

1.3.1.1 Mechanism of positron decay

The atomic nucleus is composed of positively charged protons and non-charged neutrons. When in close proximity, protons have a natural repulsive force due to their like-charge, therefore, they tend towards break up of the nucleus. The electrostatic stability of an atomic nucleus is maintained because neutrons are able to bind the like-charged protons together with a strong attractive force. When an unstable nucleus, which is deficient of neutrons, is artificially created, there is a natural tendency for break up of the nucleus due to the repulsive forces between the protons (figure 1.5).

Positron decay takes place in order to convert the nucleus into a more stable state by transmutation of a proton into a neutron and a positron (an antiparticle to an electron). Because of the repulsive electrostatic forces the positron is expelled from the nucleus with some kinetic energy and almost immediately (within 0.2-2mm) collides with an orbiting electron. Both particles form a quasi-stable positronium before they annihilate. Due to momentum and energy conservation laws, the resultant energy is discharged as two high-energy, 511 KeV photons that travel at 180^0 to each other. The two external detectors of the PET camera system, which are in electronic time coincidence, are able to detect the emitted annihilation quanta and the point of origin can be calculated using appropriate computational software and reconstruction methodology. The annihilation coincidence detection, as this process is known, approximates very closely to, but is not identical to the anatomical location of tracer accumulation. This error in PET scanning is very small, but increases with the energy of the positron. Along with the detection limitations of the PET camera, the positron range error determines the practical resolution of the system.

Following the detection of two annihilation photons, a line can be projected through the point where the annihilation took place between the detectors (figure 1.6). This is a true coincidence event; however, two further events may be registered by the PET detector system. The first of these is a random coincidence event where within the

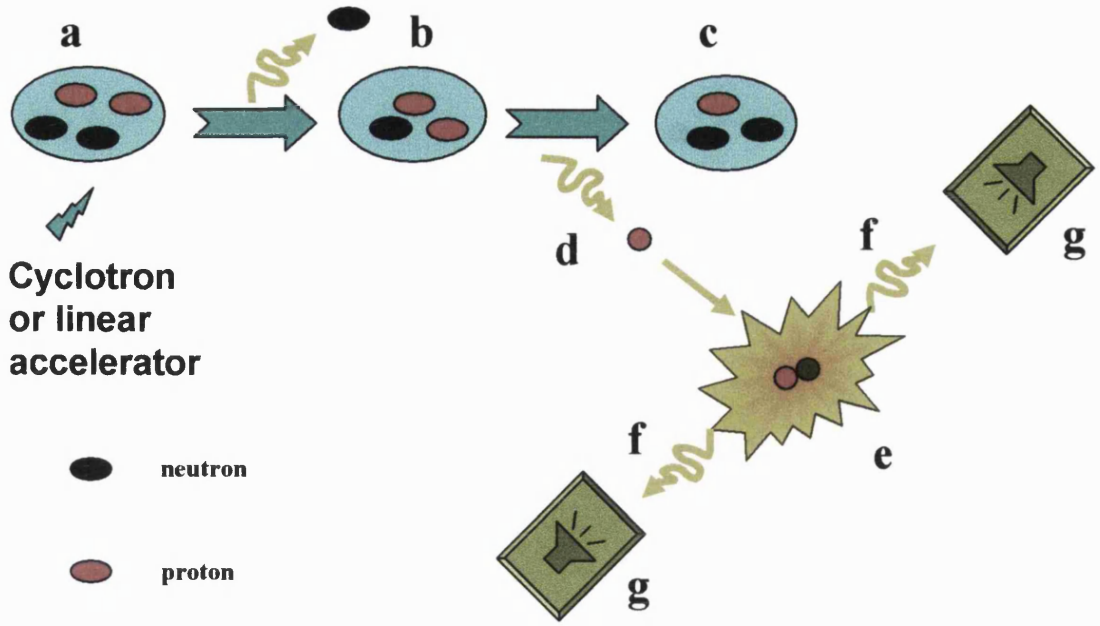


Figure 1.5 A nucleus has equivalent net charge (a), but when bombarded in a linear accelerator or cyclotron a neutron deficient state is induced (b). In order to keep electrostatic equilibrium (c) a proton transmutates into a neutron and expels a positron (d). This collides with an orbiting electron to momentarily form a positronium before annihilation takes place (e). The resultant energy is discharged as two 511KeV photons (f) that travel at 180^0 to each other. These coincidence events can be detected by PET assemblies (g)

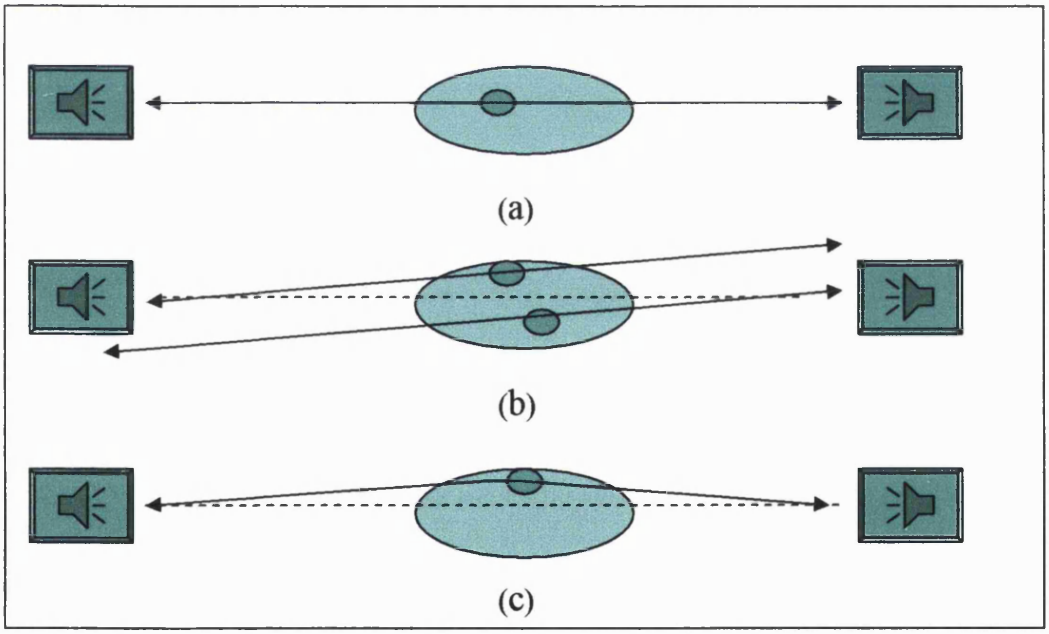


Figure 1.6 The type of coincident events that can be detected in PET; (a), true coincidence; (b), random or accidental coincidence; (c), scatter coincidence.

finite time window used for annihilation detection, two photons created by different annihilation events are registered by the two opposing detectors (figure 1.6). The projected line will now give an inaccurate estimation of the point of annihilation. Alteration of the time window for coincidence detection using specifically designed camera configuration can minimise this error.

The second phenomenon that must be accounted for is the detection of photons that may be scattered within the body (figure1.6). Again coincidence detection of these scattered photons will result in the inaccurate placement of the original annihilation event. For 511KeV photons the predominant scattering process is Compton (inelastic) scattering. Both these events contribute to background noise and their accurate removal is a prerequisite for image quantification.

Correction for absorbed coincidences takes into account the heterogeneous absorption of photon pairs as they travel trough the body's tissues on their way to the detector. This requires attenuation correction and can be done using a standard transmission source. The routinely used source for transmissions scans is germanium and this correction reduces distortion. This does add time to the procedure, typically 25-50% of the acquisition time. Conventionally, the time for attenuation correction varies with the method of reconstruction, available reconstruction software and the activity of the source and can be between 3 and 10 minutes per bed position.

Positron emitting nuclei do not occur in nature and therefore have to be synthesised in a cyclotron. The cyclotron was developed in the early 1930's and is essentially a particle accelerator with a large evacuated container into which charged particles produced from an ion source are introduced. Two high-voltage electrodes accelerate the particles, which are kept in a circular pathway by a strong magnetic field applied at right angles to the electrical field. A beam of particles is produced and directed towards specific targets. The result is the production of positron-emitting radionuclides. The energy required to penetrate the nucleus of the isotopes used for biomedical imaging (^{11}C, ^{15}O, ^{18}F and ^{13}N – table 1.7) is relatively low as most have between six to nine protons in their nucleus therefore the repulsive forces encountered by accelerated particles which penetrate the nucleus and initiate a reaction is small. These isotopes can be synthesised in a cyclotron or linear accelerator which can

transfer sufficient energy to accelerate protons to the 10-17 MeV range [Fowler JS and Wolf AP, 1986].

Isotope	^{11}C	^{13}N	^{15}O	^{18}F	^{68}Ga
Half life (minutes)	20.4	9.96	2.07	109.7	68.3
Average energy (MeV)	0.3	0.4	0.6	0.2	0.7
Average positioning error (mm)	0.28	-	-	0.22	1.35

Table 1.7 Commonly used biomedical isotopes and their physical properties.

1.3.2 PET Instrumentation

Detector technology:

There are a variety of detectors capable of imaging positron-emitting tracers and these can be broadly divided into four classes: i) the thallium doped sodium iodide (NaI (Tl)) gamma camera with lead collimators; ii) the dual-head rotating NaI (Tl) camera with modified electronics for coincidence detection; iii) the dedicated NaI (Tl) PET camera with a ring detection system and iv) the dedicated bismuth germanate oxide (BGO) PET camera with a ring detection system (with either a full or partial ring). The performance of each camera type depends on the figures of merit of the particular machine and with the wide range in performance comes a wide difference in price. Most Nuclear Medicine departments can afford to run an adapted Anger gamma camera, which is PET capable, but a state-of- the-art full ring, multicrystal dedicated BGO PET camera costs between £1 million and £1.5 million sterling.

The first electronic gamma camera was described by Anger in 1952 and the design remains relatively simple; its primary components are a lead collimator and a large NaI (Tl) scintillation crystal (usually between 40-50cm in diameter and 0.6-1.2cm thick) coupled to a hexagonal array of photomultiplier tubes (PMT). Photons pass through the collimator and interact with the scintillation crystal, which results in the emission of light. The light is detected by the PMT and converted into an electrical

signal. The information produced is a two-dimensional representation of three-dimension radionuclide distribution. The concept of SPECT, also introduced by Anger in 1967, allowed the transition from two-dimensional planar imaging to multiple two-dimensional cross-sectional images. These were produced by rotation of the gamma camera about the patient axis and processing data sets using computer software. The development of the gamma camera favoured imaging isotope decay by electron capture (γ-ray photons in the 50-300 KeV range) rather than positron decay. Imaging positron decay using a NaI (Tl) gamma camera has the disadvantages of lower sensitivity (described below) as well as an intrinsic inefficiency for detection of high-energy photons. I will briefly describe the options available for commercially available detection systems now.

1.3.2.1 NaI (Tl) gamma camera with lead collimators:

The NaI (T1) gamma camera with lead collimators is the cheapest solution for PET. Nuclear Medicine departments can adapt existing cameras, however, with the cost saving comes a low detection sensitivity. The reason for the poor performance of these cameras can be put down to the inefficiency of the lead collimator and secondly, due to the physical properties of the NaI (T1) crystals described above. In order to detect coincident gamma rays a camera can either use coincidence electronics or lead collimators to define the direction of the incident gamma rays. Lead collimators absorb 95% or more of the gamma rays which leads to a decrease in sensitivity by one to two orders of magnitude compared to the electronic devices [Wong WH et al., 1999].

The NaI (Tl) crystals are the components of the system that actually detect the incoming gamma rays. Unfortunately, the NaI (Tl) crystals used are very thin and optimized for detecting 140 KeV gamma rays produced in technetium (^{99m}Tc) imaging. The high-energy 511 KeV gamma rays produced by positron emitting isotopes penetrate the crystal leading to approximately 70% escaping detection. Overall, only 2% of the emitted gamma ray pairs are detected resulting in an image resolution of 2.5-3cm.

1.3.2.2 Dual-head rotating NaI (T1) camera with modified electronics for coincidence detection

This is a rotating dual-head NaI (Tl) camera with coincidence electronics. Elimination of the lead collimator increases the detection sensitivity by 20-fold, but the penetration and therefore loss of 511 KeV gamma rays remains a problem with the NaI (Tl) crystals. Overall, this camera assembly is 5-10 times more sensitive than the standard NaI (Tl) gamma camera and can detect lesions between 1.5-2cm [Ziegler et al., 1997]. The draw back of this system is that the camera behaves as one large detector, which becomes inactive as soon as a gamma ray is detected. It remains in this state until all the stimulated scintillation light has been emitted. Therefore, if there were a second gamma ray coming in the signal would "pile up" leading to inaccurate detection of energy. This does not occur with a lead collimator and the only way to reduce signal pile up is to reduce the injected dose of tracer (by upto 80% of that used for the more sophisticated dedicated BGO PET camera). This further reduces image quality and reduces the detection efficiency by nine to ten times.

In addition, the coincidence detection efficiency is geometrically dependent resulting in a high efficiency at the centre of rotation and low efficiency at the periphery. The solution is to ensure that the camera field is significantly larger than the field of view. This camera does have certain advantages in terms of increased detection sensitivity over the simple NaI (Tl) gamma camera, but this has to be weighed against the disadvantages of having to reduce the injected dose and limitations of the geometry of the assembly.

1.3.2.3 Dedicated NaI (Tl) PET camera with a ring detection system

This system is comprised of six NaI (Tl) heads with coincidence detection electronics placed in a fixed ring that surrounds the patient [Karp et al., 1990]. In addition, the thickness of the NaI (T1) detectors is 2.5cm compared to the 1cm thickness of a dual-head detector. As well as producing a uniform detection field around the patient the detection sensitivity is increased by four times compared to the dual-head coincidence camera. The problem of signal pile up remains and even though electronic processing of the detected activity can reduce the dead time of these cameras, the injected dose of

radiotracer has to be reduced by 60-80% of a dedicated BGO PET camera [Karp et al., 1990].

This dedicated PET camera is a cost effective alternative to the expensive state-of-the-art BGO PET cameras, but it is a compromise in terms of absolute detector sensitivity and resolution.

1.3.2.4 Dedicated BGO PET camera with a ring detection system

The gold standard PET camera is the dedicated BGO PET camera. Unlike the other cameras already described this assembly consists of several thousand small BGO crystal detectors, which are constructed into a ring that surrounds the patient [Degrado et al., 1994]. This system has two advantages. Firstly, the BGO crystals improve sensitivity because they are better suited for the 511KeV photons produced due to their higher density compared to NaI (Tl). The multicrystal layout lets the operator work with much higher count rates so that the injected dose can be increased, which in turn improves image quality. In addition, eliminating the rotation of the detector ring means that the quality of studies using short-lived isotopes such as ^{15}O and ^{13}N is improved. Overall, these improvements in hardware mean that the practical spatial resolution of these cameras is far superior to those previously discussed and currently is reported at between 4.5 and 6mm. Ultimately, the resolution of BGO PET detectors for cancer lesions depends very much on the differential uptake of tracer between tumour and normal tissue. The current view is that malignant lesions of 6 – 10 mm can be accurately detected.

Image reconstruction and quantitation

The key advantage of functional imaging with PET is the ability to relate detected radioactivity to specific metabolic parameters. This allows comparison between lesions in one patient over time, for example to monitor treatment, or between different patients in order to compare disease. So that one is able to understand the complex and contentious debate surrounding the application of quantitation to routine clinical use I need to first describe the process of image reconstruction.
A comprehensive review of the physics of image reconstruction is not attempted. I will, however, give a brief overview of the basic details that a clinician should be

familiar with. Images can be acquired after tracer injection in a static or dynamic mode. In the former, the body is imaged in sections of 15cm for both emitted activity and then transmitted activity from a germanium source. This is done at a point in time after tracer injection and gives activity data sets at that particular point in time. Dynamic imaging is the acquisition of multiple images over a set time period over a region or regions of the body. Dynamic imaging can be used initially to optimise the timing of subsequent imaging with a particular tracer, but can also be used to study tracer distribution and uptake in a specific region of interest. This can be of particular use in breast cancer and its metastatic lesions where [^{18}F]fluoro-2-deoxy-D-glucose (FDG) uptake increases over a three hour period after initial injection [Borner et al., 1999]. Both these techniques allow functional metabolic parameters to be calculated if transport models for the tracer have been validated and blood tracer activity is also known. This means that an area of high FDG uptake could be quantified with respect to glucose metabolism and tissue perfusion, for example.

Image reconstruction is the process of producing a two or three-dimensional image from the stored data sets using one of two methodologies. The two algorithms used are Iterative and Fourier techniques. Iterative reconstruction techniques lead to a more accurate reconstructed image by allowing for the effects of noise. The basic principle employed is that a 'best guess' image is produced and using a number of iterations the image is improved by comparing this 'pseudo-projection' with the raw data. This technique is computationally demanding and therefore, Fourier techniques are more routinely used.

Filtered Back Projection versus Ordered Subsets Expectation Maximisation

The commonest technique used in Fourier reconstruction is filtered back projection (FBP). The fundamental process involves backprojection of the collected projected data onto a reconstruction matrix. Each transaxial slice will have its own matrix and the process is in effect the reverse of the projection process. The resultant image is usually crude and blurred due to overestimation of the activity concentration (figure 1.7). A process known as Ramp filtering is applied prior to backprojection in order to

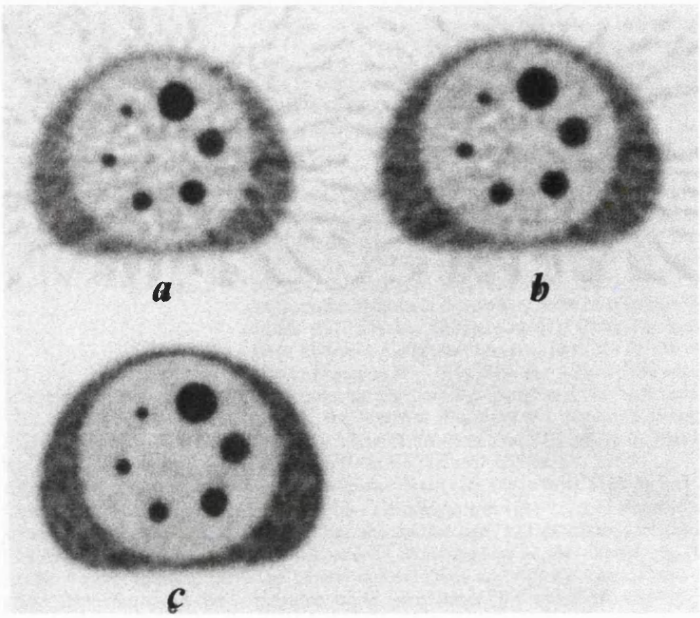


Figure 1.7 The plane containing the hot spheres from the reconstructed images of a phantom (15 min for both emission and transmission). Different image reconstructions are shown: (a) FBP with measured attenuation correction; (b) FBP with segmented attenuation correction; (c) OSEM with segmented attenuation correction [Visvikis et al., 2001]

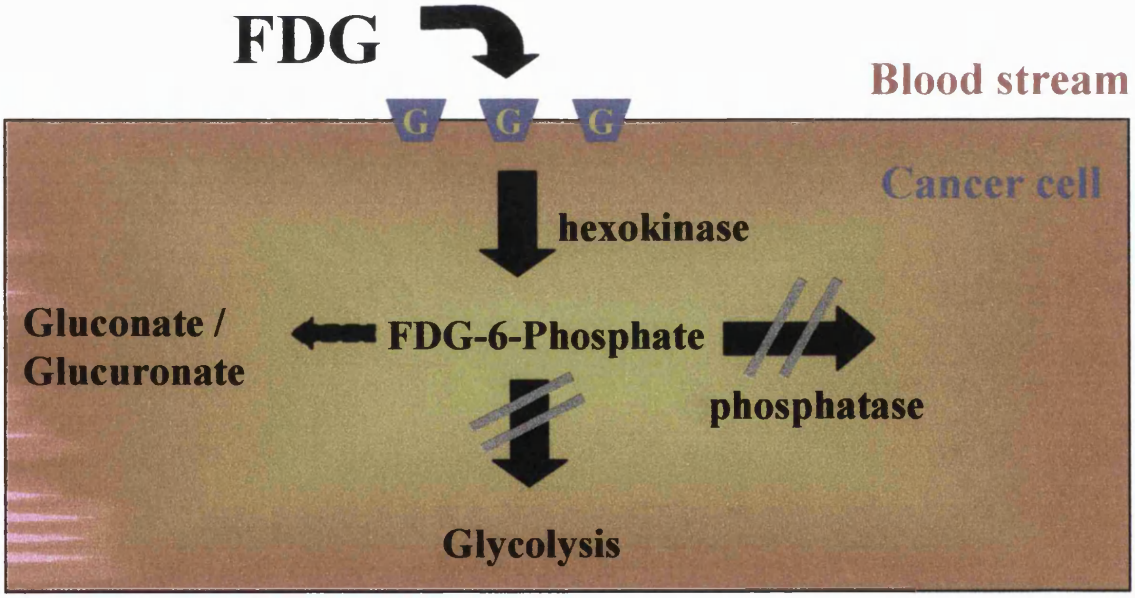


Figure 1.8 Mechanism for metabolic trapping of FDG. FDG in the plasma is transported into cancer cells preferentially by glucose transporter molecules. It is then phosphorylated by hexokinase into FDG-6-phosphate which becomes metabolically trapped. The FDG-6-Phosphate then decays by positron emission.

remove this effect. The use of different reconstruction filters leads to a trade-off between image resolution and noise in the reconstructed image. FBP is relatively quick method of reconstruction, as it does not require complex mathematical computation.

More recently iterative recontructions methods have been described and these do improve image quality without sacrificing image resolution [Knesaurek et al., 1996]. Iterative reconstruction uses less intense smoothing filters for the transmission scan, thus improving image quantification. Many different methods can be used with iterative reconstruction algorithms and segmented attenuation correction is recognised as one of the most efficient [Beni et al., 1994]. This technique has the potential to identify both normal structures as well as detected abnormalities [Akurst et al., 1999]. The technique used in this thesis was iterative reconstruction with segmented attenuation correction performed using an application of the expected maximisation algorithm in emission tomography described by Shepp and Vardi with ordered subsets (OSEM). OSEM was defined as a single pass through all the specified subsets and further iterations could be performed by passing through the same ordered subsets during reconstruction. Using this technque and coupling the availability of high-resolution scanners with increased detector efficiency much smaller lesions can be detected, thus expanding the clinical potential of FDG-PET. Widespread acceptance of this technique has been slow due to concerns over speed of execution and non-linearity in the absolute quantitation necessary in PET [Visvikis et al., 2001].

Image quantification

Having reconstructed the image, it is possible to derive indices that relate detected activity to metabolic parameters. It is impractical to obtain quantitative tracer calculations in routine clinical practice. This is because continuous invasive blood sampling would be required and the procedure would be extremely long. Instead, it has been proposed that FDG uptake is expressed in terms of a semiquantitative standardised uptake value (SUV) [Strauss, 1996]. The number obtained is a measure of the activity concentration in a volume of tissue corrected for the injected activity and the patient's body weight. Interestingly, when calculating SUV for FDG uptake, the blood glucose level is often not taken into consideration [Langen et al., 1993].

This is primarily because a period of fasting is defined and pre-injection blood glucose is checked in order to ensure that levels are not in excess of standard values.

As well as needing to know the injected activity of the tracer, it is necessary to know the tracer concentration in the blood. Any tracer that is used for PET, therefore, needs to be fully characterised not only in terms of tissue uptake over time, but also in relation to blood activity. This means that non-invasive methods of calculating this parameter must first be validated against invasive arterial or arterialised venous blood sampling. For FDG the activity is dependent on the whole body volume of distribution for the radiotracer. The body weight is accepted as an accurate measure of volume of distribution. However, it can be argued that body weight may be a factor that independently influences SUV [Kim & Gupta 1996; Zasadny & Wahl 1993] and instead SUV variants such as body surface area and lean body mass are proposed as better correlates of volume of distribution [Kim & Gupta 1996; Schomburg et al., 1996; Zasadny & Wahl 1993]. This debate is only partially resolved and I intend to explore this aspect of FDG-PET in chapter 3. The SUV may be calculated as reported in the literature [Takeuchi et al., 1999;Fischmann, 1996]:

SUV = Tumour activity concentration (MBq/l) × Body Weight (Kg) / injected activity (MBq)

These indices can be useful in distinguishing inflammatory from neoplastic tissue uptake and monitoring disease versus time and/or therapy, but significant spread of this type of data must be taken into account. The use of a minimum SUV of 3 to diagnose malignant tissue, derived from FDG-PET studies of patients with CRC, may help to increase the specificity for CRC [Gupta and Bradfield, 1996]. This method of analysing FDG accumulation has, however, been criticised [Niederhuber, 1998] and normal gastrointestinal uptake with SUV's of 5 to 10 in the stomach, liver and intestine have been reported [Delaloye and Wahl, 1995]. The calculation of SUV remains an area of some debate and some have voiced scepticism [Keyes, 1995; Hamberg et al., 1994]. The main concerns remain the fact that SUV varies with patient size, time after tracer injection to the time of the scan, plasma glucose levels and partial volume effects. It is also evident that the processing of emission and transmission data sets is time consuming and labour intensive. The cost of PET is driven down by the omission of attenuation correction, but at a cost in terms of accuracy. On the other hand the overall accuracy of PET may be enhanced by using

external markers in order to co-register conventional imaging with those acquired using FDG uptake. This is an area of development currently undergoing rapid expansion.

1.3.3 PET tracers for colorectal cancer:

The radiotracers used in oncological applications of PET range from the glucose analogue FDG to ^{11}C methionine and ^{11}C thymidine (table 1.8). A detailed description of PET tracers used in the field of oncology can be found elsewhere [Wieler HJ and Coleman, 2000]. Those tracers used most commonly for clinical applications in CRC imaging are discussed below.

Tracer	Abbreviation	Reaction studied
2-[^{18}F] fluoro-2-deoxy-D-glucose	FDG	Glucose metabolism
[^{18}F]Fluorouracil	[^{18}F]FU	Uptake of chemotherapeutic agent
^{11}C methionine	-	Amino acid synthesis
^{11}C thymidine	-	DNA synthesis (cellular proliferation)
[^{18}F]Fluorothymidine	FLT	DNA synthesis (cellular proliferation)

Table 1.8 Positron-emitting tracers used to study CRC

The tracer most frequently used for oncological applications of PET is the fluorinated glucose analogue FDG. FDG-PET is described in detail for CRC imaging and many studies demonstrate its' high sensitivity and specificity [Huebner et al., 2000], although the latter can be a problem due to false positive FDG uptake in highly metabolic benign lesions, most notably inflammatory tissue.

Other tracers such as [^{18}F]Fluorouracil ([^{18}F]FU) are available to predict and monitor treatment response[Strauss and Conti, 1991]. This tracer is an analogue of 5-FU, a chemotherapy agent used in the treatment of metastatic CRC. ^{15}O water has also been used for assessing CRC metastases. This tracer is a marker of tissue perfusion and vascularity [Dimitrakopoulou et al., 1993].

^{11}C methionine is a marker of amino acid metabolism. This is not widely used in routine clinical practice. Likewise, ^{11}C thymidine is a marker of cellular proliferation as this compound is a substrate for DNA synthesis. Unfortunately, ^{11}C thymidine is rapidly metabolised in the body and is not therefore as helpful as other tracers. I have

analysed in detail the benefits and disadvantages of positron-labelled thymidine analogues in chapter 7, therefore description in this section has been brief. The field of tracer development in CRC imaging continues to expand and we speculate that one of the fluorinated thymidine analogues may prove to be of great value in this respect.

The biological basis for the use of FDG in oncological applications of PET

FDG is commonly used in oncological applications of PET because this compound is able to target malignant tissue on the basis of cellular glucose metabolism. The biological basis for PET centres on the observations made by Warburg [Warburg, 1931;Warburg, 1956] that cancer cells exhibit enhanced glycolysis. Glucose is preferentially concentrated in malignant cells due to an increase in membrane glucose transporters [Hatanaka, 1974;Flier et al., 1987] as well as an increase in some of the principal enzymes such as hexokinase, phosphofructokinase and pyruvate dehydrogenase [Monakhov et al., 1978;Weber, 1977;Flier et al., 1987].

The mechanism by which FDG accumulates in cells is based on the upregulation of expression of glucose transporter molecules on the surface of human cancer cells [Hartung et al., 1994;Yamamoto et al., 1990;Nishioka et al., 1992]. The activation of the gene coding for the synthesis of the glucose transporter, GLUT1, is a major early marker of cellular malignant transformation [Hiraki et al., 1988]. Once transported into the cell, FDG is phosphorylated to FDG-6-phosphate by hexokinase, but takes no further part in the glycolytic or glycogen synthetic pathway. FDG-6-phosphate cannot diffuse out of the cell and becomes metabolically trapped as accessory metabolic pathways are too slow for the half-life of FDG. So like unlabelled glucose, FDG concentrates in malignant cells, however, the tracer becomes metabolically trapped and decays by positron emission. The detected activity of ^{18}F fluorine closely approximates to the accumulated FDG-6-phosphate and the glycolytic activity for exogenous glucose [Sokoloff et al., 1977;Gallagher et al., 1978]. Figure 1. 8 schematically illustrates this process.

Although this model is widely accepted, there are certain important physiological factors that influence FDG uptake. These include tissue oxygenation and glucose utilisation, regional blood flow and the inflammatory reaction surrounding the tumour [Clavo and Wahl, 1996;Lindholm et al., 1993;Yao et al., 1995]. Hence the signal

recorded from FDG may be a composite area and interfere with the specificity of FDG-PET for malignant tissue [Lindholm et al., 1993;Yao et al., 1995]. For example, there may be difficulty in differentiating tumour from active inflammation in the pelvis as FDG uptake reflects the metabolic activity of a tissue [Strauss et al., 1989;Delbeke et al., 1997;Schlag et al., 1989].

1.3.4 Application of PET to oncology

The metabolic imaging of cancer tissue using FDG-PET can be broadly divided into specific applications:

1. Detecting primary tumours
2. Staging primary tumours
3. Detecting recurrence
4. Evaluating the extent of recurrence
5. Monitoring subclinical response to therapy

FDG-PET has been successfully applied to the imaging of a variety of cancers. Initially, FDG-PET was a research tool that was used to study cerebral tumours, but rapid development of hardware, computer software as well as tracer production has seen an exponential rise in its application [Bomanji JB et al., 2001]. The main indications for the use of FDG-PET are listed in table 1.9.

Other than CRC, FDG-PET has an important role in detecting and staging lung cancers, especially non-small cell lung cancer [Dwamena et al., 1999;Pieterman et al., 2000]; lymphoma [Kostakoglu and Goldsmith, 2000]; melanoma [Tyler et al., 2000]. The role of FDG-PET in head and neck cancer and breast cancer remains to be clarified [Bomanji JB et al., 2001]. Table 1.10 lists tumours for which FDG-PET has been used in clinical practice.

Main indications
Pre-operative staging of non-small cell lung cancer
Staging of recurrent disease in lymphoma and colorectal cancer
Assessment of melanoma greater than stage II
Investigation of a solitary pulmonary nodule
Secondary indications
Pre-operative staging of head and neck cancer
Staging of recurrent breast cancer
Distinction between scar or recurrence or tissue necrosis or recurrence
Brain tumour grading
Emerging indications
Assessment of tumour response to therapy
In vivo imaging of drug action

Table 1.9 The current indications for FDG-PET imaging in oncology - from Bomanji, JB, et al [Bomanji JB et al., 2001].

Lung
Gastrointestinal
Oesophageal & Gastric
Colorectal
Pancreas
Liver and hepatoma
Lymphoma
Head and Neck
Breast
Melanoma
Endocrine
Thyroid and parathyroid
Adrenal
Neuroendocrine
Pituitary
Muskuloskeletal
Ovarian
Genitourinary
Brain

Table 1.10 : Malignancies that have been studied with FDG-PET

1.4 Imaging in colorectal cancer and the role of FDG-PET

1.4.1 Detection of primary colorectal cancer

The detection of primary CRC can be subdivided into diagnosis of CRC in asymptomatic individuals, in other words screening and secondly, into detection in symptomatic individuals. Currently there are several means of screening, which have have been discussed in section1.1. In principle, early diagnosis may lead to detection of disease at a point where the metastatic process has not been initiated or at worst is limited and amenable to intervention. Most importantly, however, knowledge of the natural history of CRC points to the possibility of reducing the incidence of the disease by the identification and removal of adenomatous polyps. Therefore, there is a place for an improved screening technique.

The detection of CRC in symptomatic individuals is relatively accurate with current diagnostic methods (table 1.11). Improving detection rates combined with offering patients a minimally-invasive investigation are the facets of a new technique that are most likely to warrant its' introduction. Of course, this must be in conjunction with high sensitivity and specificity and low unit cost.

Ba enema -/+ sigmoidoscopy
Colonoscopy
CTC
Hydrocolonic sonography
MR

Table 1.11 Methods of detecting CRC

There is no substantial published data for the use of FDG-PET in screening for asymptomatic CRC although polyp detection is possible [Yasuda et al., 2001]. The availability of PET and the cost (a PET study currently costs approximately twice that of a CT of the abdomen and pelvis at University College London Hospitals (UCLH) NHS Trust and this seems consistent with other reports [Falk et al., 1994]) are two important contributory factors. Furthermore, the inclusion of patients with low disease probability increases the likelihood of false positive PET scans, therefore this technique is unsuitable for unselected screening programmes. These are also the

conclusions of Yasuda and colleagues who have analysed 5575 screening sessions, but with only short term follow up of 10 months [Yasuda et al., 2000].

The situation is, to a certain extent, similar for diagnosis of CRC in symptomatic individuals. Published data is scarce compared to that on recurrent CRC, but it is possible to detect primary lesions in symptomatic patients with PET [Mukai et al., 2000;Takeuchi et al., 1999]. Ruhlmann [Ruhlmann et al., 1997], Takeuchi [Takeuchi et al., 1999] and Mukai [Mukai et al., 2000] identified patients with primary CRC. Ruhlmann et al [Ruhlmann et al., 1997] described one patient diagnosed confidently with PET and confirmed the absence of tumour in two patients. Takeuchi et al [Takeuchi et al., 1999]confirmed the diagnosis in six patients with histologically proven CRC. Both reports were part of larger studies of the use of PET for imaging recurrent CRC. There is more published data on PET for recurrent CRC than for PET used in primary CRC.

There are, however, several factors that make FDG-PET less attractive than other imaging techniques. Currently endoscopy and barium enema detect over 90% of CRC's [Feczko and Halpert, 1986]. These investigations are more readily available and cheaper than PET. CTC is gaining popularity and is cost effective because the technique is not only sensitive and specific for CRC, but is minimally invasive with a low morbidity [Harvey et al., 1998]. The study by Harvey et al. [Harvey et al., 1998] showed that in 52 patients 47 diagnostic studies were obtained and none of the malignant lesions were misdiagnosed. The application of three-dimensional reconstruction to CT allows a 'virtual' colonoscopy viewing the colonic mucosa from anus to caecum [Fenlon et al., 1999], but further refinement is needed along with improved software processing [Rex et al., 1999]. Finally, hydrocolonic sonography, which is highly accurate (97% sensitivity), is also becoming available and has the potential to become a valuable diagnostic tool [Limberg, 1992]. The accuracy, reliability and availability of current imaging modalities mean that PET is unlikely to play a significant role in diagnosing primary CRC, although its' use as a targeted screening investigation in high risk groups is yet to be fully evaluated.

1.4.2 Staging primary colorectal cancer

Staging primary CRC is inadequate with current imaging modalities. It is estimated that 70% of patients presenting to the clinician with a primary cancer of the colon or rectum are suitable for a so-called curative resection. Unfortunately, approximately 30% of these patients go on to develop recurrence [Sagar and Pemberton, 1996] usually within the first 18 to 24 months [Galandiuk et al., 1992]. Half of all patients diagnosed with CRC eventually die of the disease. One of the possible causes of this high recurrence rate is the development of recurrent or metastatic disease from occult foci of CRC, which have not been adequately treated initially or may be in a dormant state [Taylor, 1996]. By implication there are weaknesses in the initial staging process and there is evidence that current methods of imaging patients with CRC are not sufficiently accurate [Moss, 1989]. CT is commonly used for the staging of primary CRC, however, it has a low staging sensitivity [Thoeni, 1997]. Intraoperative USS improves the detection of liver lesions, but this information cannot be provided pre-operatively and therefore cannot contribute to preoperative patient management [Leen et al., 1995]. This must be taken within the context of arguments for the optimal management of CLM [Sarela and O'Riordain 2001].

The aim of pre-operative staging investigations for patients with CRC is to identify the extent of local infiltration, involvement of lymph nodes, and finally metastases to the liver. Accurate staging allows planning of the surgical procedure and informed decisions to be made on additional treatments, for example, neoadjuvant radiotherapy [Gerard et al., 1988;Stockholm Rectal Cancer Study Group, 1990]. This allows all foci of cancer to be treated by an appropriate combination of surgical excision, chemotherapy and radiotherapy so as to minimise the chance of recurrence. CRC's were histologically staged according to the modified Dukes' classification [Dukes CE, 1932] and many centres still continue this practice. In order to standardise histopathological staging, however, the UICC TNM classification is now established [Sobin LH and Wittekind C, 1997] (table 1.4). A cancer of the colon or rectum can now be specifically classified according to the TNM status, which makes comparison between centres more standardised.

Local infiltration:

CT has been accepted as an accurate method of assessing local infiltration especially in advanced tumours. Sensitivities of 61%, 55% and over 70% have been reported [Balthazar, 1991; Freeny et al., 1986; Zerhouni et al., 1996]. Accurate delineation of the extent of local infiltration allows planning of resection by allowing the surgeon to assess if a tumour is resectable and which procedure is of maximum oncological benefit. This information is also necessary to assess the need for additional treatments such as neoadjuvant radiotherapy [Stockholm Rectal Cancer Study Group, 1990]. The accuracy of CT for low stage tumours (Dukes A and B / T_{0-2}) can be poor, but the overall detection and characterisation of transmural penetration is deemed acceptable. Endoanal USS provides useful clinical evaluation of the depth of invasion of rectal cancers with a sensitivity of 96% and specificity of 89% for T_{1-3} rectal tumours [Hildebrandt et al., 1994; Napoleon et al., 1991; Hildebrandt and Feifel, 1995]. This is a substantial improvement on transabdominal USS. However, as with transabdominal USS the information is only targeted to one region and complementary imaging is also required. The development of sophisticated endoluminal MR coils will augment CT for the evaluation of rectal cancer [Zerhouni et al., 1996].

Involvement of lymph nodes and extrahepatic intraabdominal spread:

Standard evaluation of lymph nodes and extrahepatic, intra-abdominal spread with CT and MR is inadequate [Freeny et al., 1986; Guinet et al., 1988; Thompson et al., 1986; Balthazar et al., 1988]. This is primarily because judging a lymph node to be malignant on size criteria alone is misleading as nodes less than one centimetre (the usual CT criterion for malignancy) can be malignant and this stage migration effect is well described in small lymph nodes retrieved at resection of gastric cancers [Noda et al., 1998]. Approximately 30-40% of lymph nodes involved in CRC are 4mm or less [Dworak 1989; Rodriguez-Bigas et al., 1996]. Reported accuracy for CT range between 25-73% (overall sensitivity is 45% [Thoeni, 1997]) with a 40% sensitivity for MR. Laparoscopy with or without USS may further improve staging accuracy [Hildebrandt et al., 1994; Easter et al., 1992], but this must be weighed against its' invasive nature. Also information that could alter treatment is not available prior to definitive surgery.

Histological examination of biopsy tissue may give an accurate estimation of the risk of lymph node spread in rectal carcinoma [Hermanek 1990]. Low risk individuals are those in whom histological evaluation reveals a low grade of differentiation and absence of microscopic lymphatic invasion. They will have a 3% or less chance of lymph node metastasis if histological examination is favourable.

Immunoscintigraphy has been shown to be significantly more sensitive for pelvic (74%) and intra-abdominal disease (66%) disease when compared to CT (57% and 34% respectively) [Collier et al., 1992], however, other reports have questioned this accuracy (sensitivity of 23%, positive predictive value (PPV) of 33%, negative predictive value (NPV) of 37% [Holting et al., 1989]). Recently emerging evidence suggests that this technique is accurate and has potentially useful clinical applications [Veroux et al., 1999].

Metastases to the liver:

Liver metastases are found in 10-25% of patients at the time of initial operation for their primary CRC. Of these patients 25% are candidates for resection [Adson, 1987]. In the United States approximately 14,000 patients per year present with isolated CLM at their first recurrence [Foster and Lundy, 1981] and about 20% of these patients die with metastases exclusively to the liver. Ferrucci [Ferrucci, 1990] suggests that the following questions should be answered when investigating the liver: 1) Are tumours present? 2) Are all lesions visible? 3) Are they malignant? 4) Are they resectable? The sensitivity of transabdominal USS is too low to exclude small lesions in the liver [Stevenson, 1995]. CT has a reported sensitivity of 72.2% and specificity of 98.9% with MR having similar results [Freeny et al., 1986;Rummeny et al., 1992], but published series show that CT failed to demonstrate lesions in 7% and underestimated the number of lobes involved in 33% of cases [Steele, Jr. et al., 1991]. Intraoperative USS has been shown to be a sensitive investigation and is possible laparoscopically [Hartley et al., 2000], but its use is not universal. Immunoscintigraphy has shown promise in this aspect of staging [Haseman et al., 1992;Patt et al., 1990;Patt et al., 1988;Lamki et al., 1990] with CLM not evident on CT being detected using Indium-111-labelled anti-CEA antibodies. Although the sensitivity of immunoscintigraphy is high, specificity can be a problem along with poor spatial resolution when compared to FDG-PET.

***The role of PET*:**

Studies by Falk [Falk et al., 1994], Abdel-Nabi [Abdel-Nabi et al., 1998], Ogunbiyi [Ogunbiyi et al., 1997] and Mukai [Mukai et al., 2000] all report varying degrees of superiority for FDG-PET in the staging of primary CRC when compared to CT (table 1.12). It should also be noted that synchronous tumours can be detected when FDG-PET is used [Pin et al., 2000] and this can potentially influence the extent of surgical resection. FDG-PET does not give sufficient anatomical detail with regard to local infiltration unless image co-registration with CT or MR is performed. Falk's study showed that in a cohort of 16 patients with 15 foci of CRC, FDG-PET was superior to CT for staging (PPV 93% and NPV 50% for FDG- PET versus PPV of 100% and NPV of 27% for CT). However, the group contained patients with primary and recurrent CRC and it should be noted that one liver focus (2-3mm in size) and one mesenteric metastasis were missed by FDG-PET. In another study Abdel-Nabi et al [Abdel-Nabi et al., 1998] investigated 48 patients with CRC (44 with biopsy proven CRC and 4 who were highly suspicious). FDG-PET had a PPV of 90% and NPV of 100%, but sensitivity for lymph node metastases was only 29% and similar to that of CT. Detection of liver metastases by FDG-PET was superior to CT (sensitivities of 88% versus 38%). This study was not controlled and PET reporters were not blinded to CT reports. Mukai and colleagues [Mukai et al., 2000] reported sensitivity of 22.2% (2/9) for lymph nodes with specificity of 86.7% (13/15) which possibly raise further questions about the precise role of PET in a much debated area of CRC management.

Author	**Patients**	**FDG –PET Sensitivity (%)**	**CT Sensitivity (%)**
Gupta (1993)	16	90	60
Falk (1994)	16	87	47
Ogunbiyi (1997)	11	95	74
Abdel-Nabi (1998)	23	Lymph nodes 29 Liver 88	29 38
Mukai (2000)	24	22.9	86.7

Table 1.12 Sensitivity of FDG-PET for staging primary CRC

Thus, there appears to be a place for the use of FDG-PET in staging primary CRC and PET has the advantage of studying the whole body thus submitting the patient to

only one staging investigation. FDG-PET has been shown to be accurate for the detection of metastases to the liver in a small study group, but the accuracy for the detection of metastatic lymph nodes is not fully established. Further evaluation of PET for staging primary CRC is required in order to quantify benefits to the patient, in terms of decreased rate of recurrence, increased disease free survival and decreased mortality. Rigorous cost analysis is also needed in order to justify the cost/benefit to the healthcare system. Staging primary CRC remains controversial and the effect on patient outcome for all modalities needs to be re-evaluated, especially with the advent of fast, high resolution, thin slice CT. PET, however, will be invaluable for the diagnosis of equivocal lesions both in the peritoneal cavity and within the liver.

1.4.3 Detecting recurrent colorectal cancer

The current weaknesses in the staging of primary CRC contribute to the significant proportion of patients who go on to develop recurrent and metastatic disease. This problem is compounded further by the difficulties encountered diagnosing recurrence early and with certainty. With respect to rectal cancer, the reported rates of recurrence after so called "curative" surgery vary from 3-32% [Karanjia et al., 1990;Hurst et al., 1982]. Recurrent rectal cancer carries a particularly poor prognosis, with survival being between 7 to 10 months from time of diagnosis.

Sensitivity (59%) and specificity (84%) for recurrence with serial measurement of CEA is low [Moertel et al., 1993]. Routine surveillance with CT has gained acceptance and the sensitivity for detecting intra-abdominal and pelvic abnormalities is high. However, differentiating benign fibrosis from tumour recurrence following treatment for primary CRC is difficult if not impossible, without the use of a metabolic signal. This is especially so in the pelvis, where CT is not sufficiently specific [Moss, 1989]. MR may give additional information and technology continues to improve, but there have been reports questioning its ability to distinguish recurrent tumour from fibrosis [Ebner et al., 1988;Krestin et al., 1988;de Lange et al., 1989]. Immunoscintigraphy with 111-Indium labelled B72.3 (sensitivity 74%) [Doerr et al., 1990], 99Tc anti-CEA Mab (sensitivity 91%) [Baum et al., 1989] and 99mTc BW431/26 (sensitivity 92%) [Lind, 1990] all show promise in the detection of recurrent CRC and this technique has been shown to be superior than CT for differentiating scar from tumour in the pelvis [Doerr et al., 1991]. These findings

have been confirmed by Lunniss et al [Lunniss et al., 1999] who used ^{99m}Tc labelled PR1A3 antibody for detecting recurrent CRC (sensitivity 96%, specificity 50%, PPV 73%, NPV 89%). Although curative surgical strategies could not be offered to all patients in whom recurrence was detected, management was altered in more than a third of patients with the small subgroup who had operable disease benefiting most from early, accurate detection. The results demonstrate that this technique has its' own problems as the reported specificity was only 50%.

This is not the only problem faced when following up patients with CRC. CEA may begin to rise, but conventional imaging modalities may not clearly identify a focus of tumour. The dilemma arises of what course to take when CEA rises in association with minimal symptoms and normal imaging. Subjecting a patient to a series of investigations may ultimately prove fruitless and only result in anxiety on the part of the patient. Observation may result in losing the opportunity to resect a curable recurrence, but aggressive investigation leads to psychological and physical patient morbidity, as well as significant financial cost. In this context tissue biopsy has been shown to have a false negative rate due to sampling error [Grabbe and Winkler, 1985;Somers et al., 1993] even with CT guidance. Second look laparotomy can lead to a definite diagnosis in 90% of cases, yet between 12-60% of these patients are unsuitable for resection [Cohen et al., 1993] and suffer substantial morbidity. These findings contribute to the on going debate regarding the need for aggressive follow-up for detecting recurrence following treatment for CRC [Tornqvist et al., 1982; Renehan et al., 2002]. It is apparent from the group in Ulm who evaluated patients treated for CRC, intense follow up protocols aimed at identifying curable recurrence are cost effective [Staib et al., 2000a]. It is therefore of great interest to determine the comparative accuracy of FDG-PET to conventional investigations.

PET vs. conventional imaging: Strauss [Strauss et al., 1989], Schlag[Schlag et al., 1989], Ito [Ito et al., 1992] and Schiepers [Schiepers et al., 1995] have all confirmed the value of FDG-PET when trying to differentiate scar from local recurrence.
In Schiepers' study [Schiepers et al., 1995] 76 patients with confirmed or suspected recurrence were evaluated with FDG-PET against routine imaging (CT, USS, plain radiograph). Sensitivity for disease in the pelvis was 93% with FDG-PET against 60% with CT. The study also emphasised the value of FDG-PET in detecting both hepatic disease (sensitivity of 94% with PET vs. 85% with CT/USS) and extrahepatic disease

(14 foci in 10 patients). Takeuchi et al [Takeuchi et al., 1999] also reported the accuracy of FDG-PET for the diagnosis of pelvic recurrence in fifteen out of sixteen patients with histologically proven pelvic recurrences (4 of these patients had equivocal CT or MR). The authors stated that by retrospectively analysing the SUV's and clinical findings an SUV cut off value of 2.8 would have resulted in diagnoses with 100% accuracy. It is also noteworthy that CEA was normal in five patients with recurrent lesions detected on FDG PET

The emerging evidence for the use of FDG-PET in the management of patients with recurrent or metastatic CRC is impressive [Whiteford et al., 2000; Staib et al., 2000b; Imdahl et al., 2000]. Whiteford and colleagues [Whiteford et al., 2000] retrospectively looked at the records of 105 patients who underwent both FDG-PET and CT for suspected recurrence. This group reported a sensitivity of 87% and a specificity of 68% for FDG-PET compared to 66% and 59% respectively for CT.

PET vs. CEA: Flanagan et al [Flanagan et al., 1998] assessed the potential role of FDG-PET in patients with unexplained elevation in CEA and normal CT scans. In 17 out of 22 patients PET was abnormal and tissue sampling and/or follow up confirmed recurrence. Biopsy was performed in seven patients of whom four underwent curative surgical intervention. The clinical course and radiological follow-up confirmed extensive disease in 8 out of 10 patients who did not undergo biopsy or operation. PET had a PPV of 89% and NPV of 100%. These results are encouraging, but should be analysed cautiously, as the study was small with the possibility of inherent biases associated with retrospective analysis. The follow up period of 6 months with CT or MR to confirm a false positive PET is probably insufficient based on knowledge of the natural history of CRC. Finally, the method of analysis used to calculate FDG accumulation has been criticised and a more rigorous calculation of actual glucose metabolism suggested [Niederhuber, 1998]. Valk and colleagues also assessed a group of 44 patients with elevated CEA. Twenty seven of these patients had a negative CT, while 17 patients had no CT performed. Of the 27 patients with negative CT, 19 (70%) were true positive on FDG-PET. In the remaining 17 patients FDG-PET was true positive in 8 and false positive in only 2.There were two false negative FDG-PET studies in the 15 patients with negative FDG-PET. The superior accuracy of PET over CEA for the detection of recurrent CRC has also been discussed by

Schiepers [Schiepers et al., 1995], Takeuchi [Takeuchi et al., 1999], Delbeke [Delbeke et al., 1997], Beets [Beets et al., 1994] and colleagues.

1.4.4 Evaluating the extent of recurrent/metastatic colorectal cancer

For the clinician who is deciding whether to resect what appears to be localised rectal recurrence or a solitary hepatic or pulmonary metastasis it is absolutely essential that the true extent of disease is known. This will prevent poor prognosis patients undergoing surgical intervention that carries a high failure rate with a significant morbidity attached. Good results are reported for surgery for patients with isolated pelvic recurrence [Suzuki et al., 1996]. Current investigations are not sufficiently sensitive enough to differentiate isolated resectable disease from disseminated metastases. Reported sites most commonly affected by metastases from CRC vary with one study reporting 13% to the liver, 4% to abdominal lymph nodes, 3% to lung, 2% peritoneal, 0.9% to bone, 0.7% to brain [Ferrucci, 1990]. Another report suggests the liver is affected in 33% of cases, lung 22%, locoregional 21%, intraabdominal 18%, retroperitoneal 10% and intraluminal 6% [Galandiuk et al., 1992]. PET offers a highly sensitivity, minimally-invasive means by which to detect recurrence and select the most appropriate treatment. Early reports suggest that FDG-PET is more accurate than CT for the purpose of staging recurrent CRC [Beets et al., 1994;Schiepers et al., 1995].

Hepatic metastases: Beets et al [Beets et al., 1994] demonstrated the value of whole body FDG-PET for detecting CLM. Schiepers et al [Schiepers et al., 1995] confirmed a higher sensitivity and accuracy with FDG-PET (94% and 98% respectively) compared to CT/USS (85% and 93%) for the detection of CLM. There were no false positives for FDG-PET and 1 for CT/USS. There were two false negative FDG-PET scans for two nodules discovered in the liver at surgery. In each of the two patients the nodule was less than 1cm and not detected by CT. Delbeke et al [Delbeke et al., 1997] compared FDG-PET with CT and CT portagram (CTP). 52 patients were evaluated on 61 occasions (CTP was not performed in all patients). Final diagnosis was made by histopathology in 44 cases and clinical/radiological follow up in the remainder. For the 127 hepatic lesions identified in these patients, FDG-PET had a sensitivity of 91% compared with 81% and 97% for CT and CTP respectively. For the 39 extrahepatic lesions sensitivity of PET was 100% compared with 74% for CT.

Ogunbiyi et al [Ogunbiyi et al., 1997] looked at 40 patients with recurrent CRC and reported a high sensitivity (95%) and specificity (100%) for FDG-PET compared to CT (74% and 85% respectively) for the detection of CLM and a higher accuracy than CT for delineating multiple liver lesions. More recent studies have demonstrated the value of FDG-PET for the detection of both hepatic and extrahepatic metastases from CRC [Vitola et al., 1996;Delbeke et al., 1997;Zhuang et al., 2000;Topal, 2001]. The available evidence suggests that optimal evaluation of patients with CLM should include FDG-PET and Topal et al [Topal, 2001] demonstrate this in a large series of 91 consecutive patients. In this study FDG-PET provided additional information in 11% of patients. This could be the difference between a curative resection being attempted or therapies such as radiofrequency thermoablation and chemotherapy being initiated. In this context the impact not only for the patient, but for healthcare resource management is significant.

Extrahepatic metastases: Lai et al[Lai et al., 1996] compared FDG-PET with conventional imaging (CT n=34, CXR n=15, CT chest n=19). Thirty four patients were evaluated with FDG-PET and unsuspected extrahepatic disease was confirmed in 11 (32%) patients. Clinical management was altered in 10 patients. Schiepers [Schiepers et al., 1995] also reported that a significant number of unexpected extrahepatic metastases could be demonstrated using FDG-PET. In this study, a total of 14 out of the 25 abnormal foci detected with FDG-PET were confirmed by biopsy as metastases, and the 11 false positives were all in the thorax. With image correlation and careful patient selection the false positive rate may be reduced.

The crucial advantage that FDG-PET must confer to patient management in order to become an acceptable clinical tool is that it should alter clinical management for the benefit of the patient. This may be by avoiding surgery, early commencement of non-surgical treatments or selecting patients suitable for surgical re-intervention. FDG-PET is highly sensitive and accurate for the diagnosing and staging recurrent CRC as demonstrated by Huebner and colleagues [Huebner et al., 2000]. The meta-analysis of eleven studies showed a sensitivity of 97%, specificity of 76% and impact on clinical management in 29% of cases. Detection of unsuspected metastases by FDG-PET ranges from 13-32% [Beets et al., 1994;Schiepers et al., 1995;Valk et al., 1999]. A multicentre study by the Institute of Clinical PET (ICP) examined the cost effectiveness of 14 PET centres (reviewing 267 CRC patient records). The conclusion

was that a potentially large saving could be made if PET was incorporated into the routine management algorithm for recurrent CRC on the basis of a reduction in unnecessary laparotomies (from 20 to 10%) and the increased number of resections with curative intent [Larson, 1994]. These results add still more weight to Huebner's analysis, which supports the incorporation of FDG-PET in the routine clinical algorithm for patients with recurrent CRC [Huebner et al., 2000].

1.4.5 Monitoring treatment of colorectal cancer

Accurate information regarding the anti-tumour effect of RT and/or chemotherapy in patients being treated for CRC would provide useful guidance in planning and revising ongoing adjuvant therapy. Nagata [Nagata et al., 1990] and co-workers showed a correlation between FDG uptake and tumour response in patients with primary or metastatic liver lesions who were treated. Studies assessing the uptake of FDG measured by PET and correlation with the anti-tumour effects of chemotherapy have been reported for certain tumour types including CRC [Findlay et al., 1996;Ichiya et al., 1991;Okada et al., 1991;Nakata et al., 1997;Dimitrakopoulou-Strauss et al., 1998].

Chemotherapy: The potential use of FDG-PET for monitoring chemotherapy in advanced CRC appears very promising. The available data suggests highest concentration of [^{18}F]FU in responsive tumours[Shani et al., 1982]. Strauss [Strauss and Conti, 1991] demonstrated that lesions with low [^{18}F]FU uptake had a significant increase in volume and no response to treatment. Findlay et al [Findlay et al., 1996] evaluated the metabolism of CLM using FDG-PET before and at intervals after treatment. The findings were compared with tumour outcome conventionally assessed using change in size on CT. Twenty patients were studied of whom 18 had assessable liver metastases. The results were expressed as a ratio of FDG uptake in tumour and normal liver (T:L). Pre-treatment T:L ratio did not correlate with response. The T:L ratio 4-5 weeks after treatment was able to discriminate response from non response both in a lesion-by-lesion and overall patient response (sensitivity 100%, specificity 90% and 75% respectively).

Based on pharmacokinetic studies, debate continues as to whether [^{18}F]FU is superior to FDG in predicting the response to treatment on an individual patient basis

[Dimitrakopoulou et al., 1993;Moehler et al., 1998]. This is subject to ongoing clinical evaluation. The encouraging results of Couper et al [Couper et al., 1998] who studied FDG uptake and therapy response in patients with upper gastrointestinal malignancies appears be applicable to the evaluation of CRC also.

In 1994 a meeting of EC PET oncology concerted action group and the EORTC PET study group brought together many of the 31 European PET centres [Price and Jones, 1995]. Their collaboration with oncologists had led to the study of tumour response to chemotherapy in 12 groups and to radiotherapy in 3 groups. Although there was wide variation in the methodology between centres, assessment of FDG uptake was thought to be a satisfactory method for functionally imaging tumours, assessing metabolic rate and providing information on response to treatment. Those patients with the biggest reduction in FDG uptake showed the best clinical response and the use of ^{11}C thymidine or ^{11}C amino acids as tracers may provide an even more specific marker of cellular proliferation. These conclusions along with the proposals to advance PET methodology, run PET studies in parallel with phase I/II clinical trials and collect more information regarding the application of PET to specific tumours provide an indication of the potential role of PET in this aspect of the management of CRC.

Radiotherapy: Similar promise was thought to be present for PET in the evaluation of RT response. There are some problems, most notably demonstrated by Haberkorn [Haberkorn et al., 1991] who evaluated FDG-PET in 21 patients (41 examinations) with recurrent CRC undergoing pelvic RT. A correlation was made between the palliative benefit and reduction in FDG uptake in 50% of patients (this was also more accurate than CEA). However, this figure was lower than the actual number of patients who responded, probably because the benign inflammatory response to RT may have caused an increase in FDG accumulation wrongly interpreted as residual tumour. An arbitrary delay in post treatment FDG-PET evaluation of 6 months may increase the accuracy for assessing tumour response. The findings mirror the results of Abe et al [Abe et al., 1986] and Engenhart et al [Engenhart et al., 1992].

More recently, Guillem and colleagues [Guillem et al., 2000] have demonstrated that FDG-PET augments conventional morphological imaging modalities when used to pre-operatively assess response to chemoradiation for rectal carcinoma. Twenty-one

patients with T_3, N_1 rectal cancers were treated with 5040 cGY RT to the pelvis and two cycles of bolus 5-FU and leucovorin. Assessment of response on FDG-PET was made using SUV, size criteria and two novel parameters, visual response score and the total lesion glycolysis. Of the 15 patients that responded, FDG-PET detected response in 100% of cases compared to 78% with CT. The implication for the surgeon is that sphincter saving surgery can be accurately planned prior to operation and the additional information gathered on FDG-PET complements CT and MR.

Another enticing prospect is the ability to reduce RT treatment fields by restricting the target volume to the metabolically active tumour. This is usually smaller than the target volume designated by conventional CT [Kiffer et al., 1998;Rosenman, 2001]. Such an assessment could possibly reduce unwanted side-effects of RT. This is still an area of ongoing clinical evaluation.

1.5 Summary

It is evident that the CRC is a common problem throughout the world, particularly in Europe and North America. Significant advances have been made with surgical and adjuvant therapies, but the accurate imaging of CRC is one aspect of the clinical process that may be improved significantly. The main points on the management path of a patient with the disease where such improvements may be of benefit are 1) early detection and accurate staging of primary CRC; 2) early detection of recurrence; 3) accurate determination of the extent of recurrent disease; 4) evaluation of subclinical treatment response. On the evidence of data I have presented, PET may be of significant benefit in the management of patients with CRC.

The application of FDG-PET to oncology and in particular to the management of CRC continues to gain acceptance. The main advantages of PET rest on the fact that it is a minimally invasive technique that images the whole body. FDG-PET also has the potential for detecting foci of CRC earlier than conventional cross-sectional imaging modalities.

1.6 Aims of thesis

The scope of this thesis covers three specific areas:

i) FDG-PET for imaging primary colorectal cancer

An assessment as to the optimum SUV variant to compare CRC lesions when using FDG-PET with iterative reconstruction and segmented attenuation correction is undertaken. Secondly, an investigation of FDG-PET for staging of primary CRC and its potential as a modality that offers prognostic information is carried out. This may result in more approriate treatment being administered in the first instance.

ii) Comparison of FDG-PET with spiral CT in the management of recurrent colorectal cancer

FDG-PET is compared with spiral CT in order to assess whether it is feasible to use this imaging technique to routinely follow up patients treated for CRC. A separate comparison is made between FDG-PET and spiral CT for the detection of local recurrence and metastatic disease, in individuals with a high suspicion of disease.

iii) Investigation of a novel tracer for PET in oncology

Fluorothymidine, FLT, is investigated as a candidate for PET imaging in CRC. The aim being, firstly, to charaterise the time-activity curves for FLT in normal tissue and CRC lesions. Secondly, to compare time-activity curves for FLT and FDG in normal tissue and CRC lesions. Thirdly, to correlate uptake of FLT in arterial blood with uptake values derived from reconstructed FLT-PET images at a standard reference point. Fourthly, to evaluate breakdown of the parent tracer compound in the human body over time.As well as characterising the tissue/metabolic activity of FLT in CRC patients, a direct comparison is made with FDG. This study aims to establish experience with FLT as an oncological tracer.

CHAPTER 2

Materials and methods

2. Materials and Methods

Overview

Different protocols for specific clinical studies are described in the next five chapters. However, the methodology for FDG-PET as well as that for CT remains common. I have, therefore, described the common imaging methods used in these studies in this chapter to avoid repetition. Methodology for FLT-PET is described in chapter 7.

2.1 Patient recruitment

In order to conduct the studies described in this thesis relevant approval was obtained from the Ethics Committees of University College London (UCL) and University College London Hospitals NHS Trust (UCLH). These can be found in Appendix B. In addition to this an application was made to the Administration of Radioactive Substances Advisory Committee (ARSAC) for licences to carry out FDG-PET studies. Patients were required to give consent after reading a patient information leaflet and having the opportunity to discuss the study (Appendix B). All patients were recruited from those with confirmed or suspected CRC referred to the CRC multidisciplinary team (MDT) at UCLH. Once patients were recruited demographic and disease data were recorded. This data set included name, age, date of birth, contact address and telephone number, clinical indication for investigation and imaging results (once performed). This data was stored in a Microsoft Excel™ spreadsheet on a personal computer (Dell Computer Corporation). All data storage and handling was compliant with the Data Protection Act. Imaging was scheduled so as not to hinder the process of investigation or treatment.

2.1 FDG-PET scan

2.1.1 Arrival and calibration of FDG

FDG was obtained on a commercial basis from two sources for studies in this thesis:

1. The Wolfson Brain Injury Centre, Addenbrookes Hospital, Hills Road, Cambridge

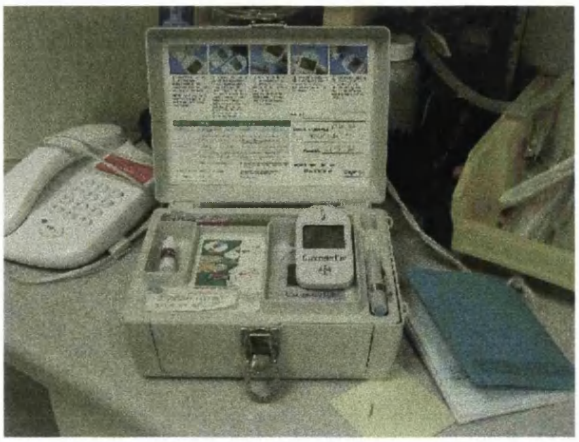
2. MRC Cyclotron Unit, Hammersmith Hospital, Ducane Road, London

Tracer arrived between 10.45 and 11.00 am after the producing cyclotron had notified the Institute of Nuclear Medicine (INM) that it had passed quality control for that particular day. For transfer, the vial containing tracer is within a shielded pot within a separate container. The dose comes with a regular trained driver by road and UK law governing transfer of radioactive substances is strictly adhered to. On arrival the activity of the consignment of tracer was measured by a designated technician in a dose calibrator in the PET suite (figure 2.1a). The procedure is documented in a standard protocol (a) in Appendix D along with the INM PET suite recording sheet for the process. The dose calibrator underwent quality control checks daily according to INM protocol (b) in Appendix D.

2.1.2 Patient preparation for whole body FDG-PET scan

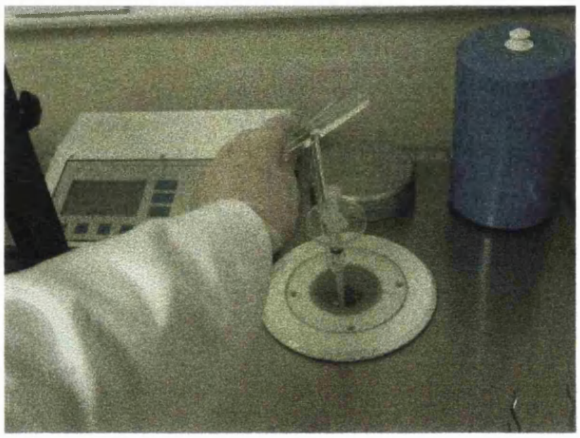
Patients were scanned fasting in order to both maximise FDG uptake in tissues and minimise blood insulin levels. All protocols are documented in Appendix B. Patients were requested to abstain from any oral intake of food or drink for four hours prior to the scan. The only exception to this rule was the intake of plain water in order to maximase hydration thus encouraging diuresis and washout of confounding tracer accumulation in the urinary tract. This is because FDG is renally excreted and tracer within the ureters or a bladder diverticulum could be a potential source for misinterpretation when analysing images of the pelvis. All instructions were given in writing. Patients attended the PET suite at the INM at UCLH either as

a



b

c



d

Figure 2.1 (a) Dose calibrator for checking the activity of a sample of tracer. (b) Glucometer Elite which is used to read blood glucose levels. (c) and (d) show shield and apparatus for drawing up a dose of tracer using a 5ml syringe.

inpatients or outpatients. All patients had height and weight recorded for the purposes of calculating SUV from the acquired data. Patients then lay on a couch and underwent intravenous cannulation, most frequently in a forearm vein, with a 16 gauge cannula. At this time a sample of venous blood was taken through the cannula and serum glucose was measured in a commercially available glucometer (Glucometer Elite, Bayer Pharmaceuticals – figure 2.1b). The timing of this blood sample was noted.

In anxious patients an anxiolytic/myorelaxant was given in order to minimise confounding FDG uptake in contracting muscle. The drug used was diazepam, given as an oral dose of 5mg. This procedure normally took place immediately after venous cannulation. Uptake in normal bowel, another potentially confounding factor, can be reduced by administration of hyoscine butylbromide. This drug reduces muscular activity and therefore FDG uptake in intestinal mural smooth muscle.This was not used in any of the patients studied so that a standardised technique was adhered to in all patients studied.

Patient dose measurement was carried out in the dose calibrator previously described and followed the protocol (c) in Appendix D. FDG, which had a mean activity of 370MBq (range 330-380 MBq) was drawn up in a shielded 5ml syringe (figure 2.1c & d). If a larger volume was required then a second volume would be drawn up in a 5ml syringe. This dose was administered to the patient using a sheilded dispensing unit and through the intravenous cannula. The time of injection was noted.

Patients were not routinely catheterised or given frusemide, a diuretic. Both these techniques can be used to reduce renal tract FDG accumulation for the reasons mentioned above. Again, in order to standardise the methodology the procedures were not undertaken. Patients rested quietly for approximately 45 minutes after injection. Patients were then moved to the couch of the PET scanner (figure 2.2) and emission scanning was carried out at 60 minutes post injection. Residual activity was measured in the dose calibrator and could help estimate activity in spills. The syringe and cannula were then disposed of in a shielded sharps bin. This was stored overnight in the INM and disposed of the next day when activity would be negligible.

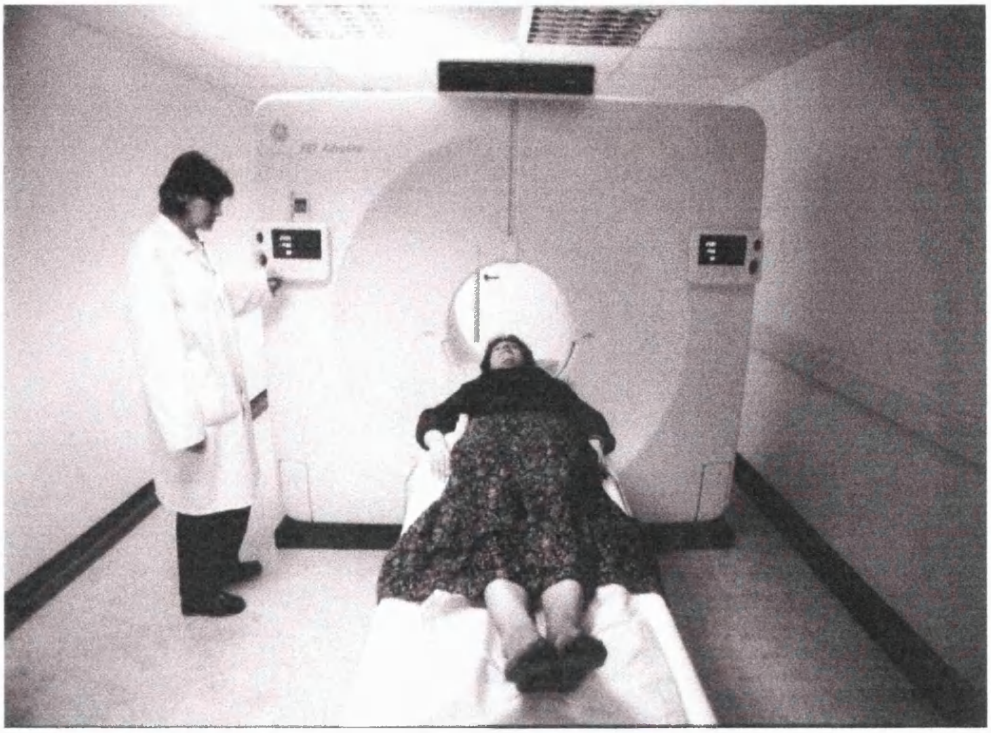


Figure 2.2 A patient lying on the couch of a GE Advance™ dedicated PET scanner. This machine has a full-ring, multi-crystal BGO detector system and was used to study all patients described in chapters 3 to 6 inclusive (courtesy of the Institute of Nuclear Medicine, Royal Free & University College Medical School)

2.1.3 Protocol for whole-body FDG-PET scan

FDG-PET imaging was performed using a GE Advance™ dedicated PET scanner (General Electrics Medical Systems, Milwaukee, USA). The scanning sequence was optimised from the base of the skull to the upper third of the lower limb. Data sets were obtained from both tracer emission and transmission, for optimal analysis and quantification.

A whole body emission scan was taken (5 minutes per bed position), followed by a post-injection transmission scan using germanium sources (3 minutes per bed position).

2.1.4 Data analysis

Coincidence events detected by opposing scintllation crystal result in an electrical signal being registered on the processing workstation. The registered data was processed and reconstructed on a Sun Microsystems workstation (Palo Alto, California, USA). Transaxial images of $4.3\times4.3\times4.25mm^3$ (matrix size $128\times128\times35$) were reconstructed using Ordered Subsets-Expectation Maximisation (Iterative reconstruction) and segmented attenuation correction. These slices were re-orientated to produce whole body coronal and sagittal images.

Reconstructed orthogonal FDG-PET scans were then visually inspected in order to identify areas of maximal uptake and regions of interset (ROI) as well as to make a diagnosis. The slice number judged to visually represent the maximum uptake was noted. Data sets were then reloaded on screen in the single slice display mode and the slice number previously noted was retrieved. Activity was calculated using ROI drawn within the area of maximal uptake on the specified slice and similar areas in the immediately adjacent slices. A 1.5cm diameter circle was used to standardise the area of the ROI being analysed and this was drawn on screen. The activity data within this ROI was displayed in MBq/l as soon as it was drawn on the slice. SUV's were calculated as follows:

SUV corrected for weight:

$$\frac{[\text{average tumour activity concentration (MBq/l)} \times \text{body weight (kg)}]}{[\text{Injected activity (MBq)}]} \quad (1)$$

SUV corrected for body surface area

$$\frac{[\text{average tumour activity concentration (MBq/l)} \times \text{body surface area (m}^2\text{)}]}{[\text{Injected activity (MBq)}]} \quad (2)$$

Body surface area was calculated as follows:

$$\text{BSA} = [4\times \text{body weight (kg)}]/\ [\text{body weight (kg)} + 90] \quad (3)$$

SUV corrected for weight and glucose

$$\frac{[\text{average tumour activity concentration (MBq/l)} \times \text{body weight (kg)}] \times \text{blood glucose (mmol/l)}}{[\text{Injected activity (MBq)}]} \quad (4)$$

Nearly all available published SUV data that is available has been calculated from FBP reconstructed images. More recently, iterative reconstruction has been described as a clinically useful means of image reconstruction primarily due to improved resolution and ability to detect lesions. The studies in this thesis use this method of reconstruction although there remain concerns about the time required to produce these images. Therefore, for SUV reference purposes the data published recently by Ramos and colleagues has been used and a table of "normal" values reproduced (below) from this paper:

Site	Test	Number	Maximum SUV			Average SUV		
			Mean	(SD)	CV	Mean	(SD)	CV
Aorta	FBP	20	2.06	(0.47)	22.66	1.43	(0.32)	22.67
	IRSAC	20	2.16	(0.38)	17.6	1.67	(0.30)	17.91
Bone marrow:	FBP	20	2.07	(0.62)	29.92	1.30	(0.54)	41.8
Lumbar spine	IRSAC	20	1.98	(0.56)	28.47	1.52	(0.39)	25.97
Bone marrow:	FBP	20	0.72	(0.24)	33.43	0.26	(0.19)	72.48
Humerus	IRSAC	20	0.69	(0.24)	34.9	0.44	(0.17)	39.24
Bone marrow:	FBP	20	2.11	(0.56)	26.47	1.61	(0.38)	23.68
Thoracic spine	IRSAC	20	1.98	(0.43)	21.9	1.55	(0.36)	22.87
Breast	FBP	11	0.98	(0.46)	47.19	0.43	(0.21)	47.94
	IRSAC	11	0.74	(0.35)	47.03	0.43	(0.21)	49.15
Oesphagus	FBP	15	1.60	(0.22)	13.64	1.32	(0.22)	16.83
	IRSAC	15	1.89	(0.29)	15.53	1.58	(0.27)	16.9
Heart: blood pool	FBP	20	2.10	(0.48)	22.66	1.42	(0.33)	23.34
	IRSAC	20	2.12	(0.41)	19.36	1.63	(0.31)	19.11
Heart: myocardium	FBP	12	6.08	(3.15)	51.77	4.44	(2.50)	56.31
	IRSAC	12	6.72	(3.64)	54.22	4.99	(2.90)	58.13
Intestine: large	FBP	17	2.23	(0.57)	25.55	1.44	(0.51)	35.68
	IRSAC	17	2.12	(0.56)	26.3	1.54	(0.46)	29.63
Intestine: small	FBP	20	2.37	(0.42)	17.89	1.53	(0.19)	12.57
	IRSAC	20	2.34	(0.50)	21.52	1.64	(0.27)	16.49
Kidney: parenchyma	FBP	20	2.71	(0.60)	22.16	1.74	(0.39)	22.12
	IRSAC	20	3.31	(0.72)	21.85	2.33	(0.48)	20.49
Kidney: collecting	FBP	20	20.70	(15.48)	74.76	12.63	(9.23)	73.07
system	IRSAC	20	35.02	(30.43)	86.89	16.78	(13.21)	78.72
Larygeal muscle	FBP	20	3.31	(2.62)	79.2	2.88	(2.15)	74.61
	IRSAC	20	4.14	(3.32)	80.35	3.27	(2.54)	77.85
Liver	FBP	20	3.34	(0.59)	17.66	1.86	(0.27)	14.45
	IRSAC	20	3.17	(0.60)	18.99	2.17	(0.33)	15.15
Lung	FBP	20	1.14	(0.36)	31.23	0.40	(0.06)	16.29
	IRSAC	20	0.80	(0.24)	30.17	0.48	(0.10)	20.02
Pulmonary hilum	FBP	20	1.77	(0.42)	24.01	1.21	(0.22)	18.18
	IRSAC	20	1.74	(0.36)	20.67	1.37	(0.24)	17.39
Salivary gland:	FBP	20	2.80	(0.90)	32.31	2.23	(0.67)	30.08
sublingual	IRSAC	20	3.10	(1.13)	36.53	2.36	(0.73)	31.08
Salivary gland:	FBP	20	2.16	(0.34)	15.6	1.77	(0.28)	15.66
submandibular	IRSAC	20	2.38	(0.46)	19.33	1.90	(0.37)	19.64
Salivary gland: parotid	FBP	20	1.84	(0.40)	21.73	1.49	(0.37)	24.75
	IRSAC	20	1.93	(0.51)	26.28	1.50	(0.43)	28.55
Shoulders: capsule	FBP	20	1.33	(0.42)	31.23	0.85	(0.26)	30.83
	IRSAC	20	1.38	(0.39)	28.46	1.02	(0.28)	27.47
Skin (axillary region)	FBP	20	1.25	(0.26)	20.42	0.79	(0.15)	18.4
	IRSAC	20	1.32	(0.32)	23.87	0.94	(0.19)	19.7
Spinal cord	FBP	20	1.84	(0.36)	19.68	1.56	(0.29)	18.64
	IRSAC	20	2.25	(0.43)	18.94	1.79	(0.31)	17.57
Spleen	FBP	20	2.34	(0.51)	21.77	1.26	(0.23)	18.51
	IRSAC	20	2.31	(0.44)	19.28	1.65	(0.29)	17.51

Site	Test	Number	Maximum SUV			Average SUV		
			Mean	(SD)	CV	Mean	(SD)	CV
Stomach	FBP	20	2.95	(0.68)	23.15	1.99	(0.53)	26.73
	IRSAC	20	3.21	(0.84)	26.14	2.34	(0.59)	25.12
Tonsil: lingual	FBP	20	2.91	(1.19)	41.02	2.47	(1.01)	40.65
	IRSAC	20	3.49	(1.37)	39.3	2.83	(1.18)	41.61
Tonsil: palatine	FBP	20	2.84	(0.87)	30.74	2.39	(0.72)	30.09
	IRSAC	20	3.45	(1.31)	37.94	2.73	(0.95)	34.87
Trapezius muscle	FBP	20	1.13	(0.26)	23.08	0.69	(0.23)	33.16
	IRSAC	20	1.05	(0.23)	22.25	0.76	(0.23)	30.75
Ureter	FBP	16	3.96	(2.22)	56.04	2.78	(1.59)	57.25
	IRSAC	16	5.53	(4.24)	76.66	3.48	(2.35)	67.44

Table 2.1 SUV's in normal anatomical structures. Mean of SUV_{max} and SUV_{avg} in mg/ml; SD = standard deviation; CV = coefficient of variation (SD/mean, expressed as a percentage) from Ramos et al, 2001.

2.1.5 Image analysis for whole-body FDG-PET scan

Whole body data was analysed in terms of the pattern of distribution of labelled FDG and also with respect to the measurement of tracer uptake at a specific site. The quality of the data obtained depends significantly on the figures of merit of the instrument used, software available and amount of tracer administered. A typical normal whole body scan for FDG is seen in figure 2.3. Normal and significant FDG uptake is always seen in the brain, frequently, but variably, in the myocardium, stomach, liver, spleen, muscle and the lumen of the gastrointestinal tract. The bone marrow is seen, with variable intensity, often reflecting response to chemotherapy. The FDG tracer is eliminated by the kidneys, which are depicted along with the urinary bladder. Since the data is recorded in 3D, data sets formatted into any plane (transaxial, coronal, and sagittal) can be displayed and inspected. A pathological FDG-PET scan is shown in figure 2.4.

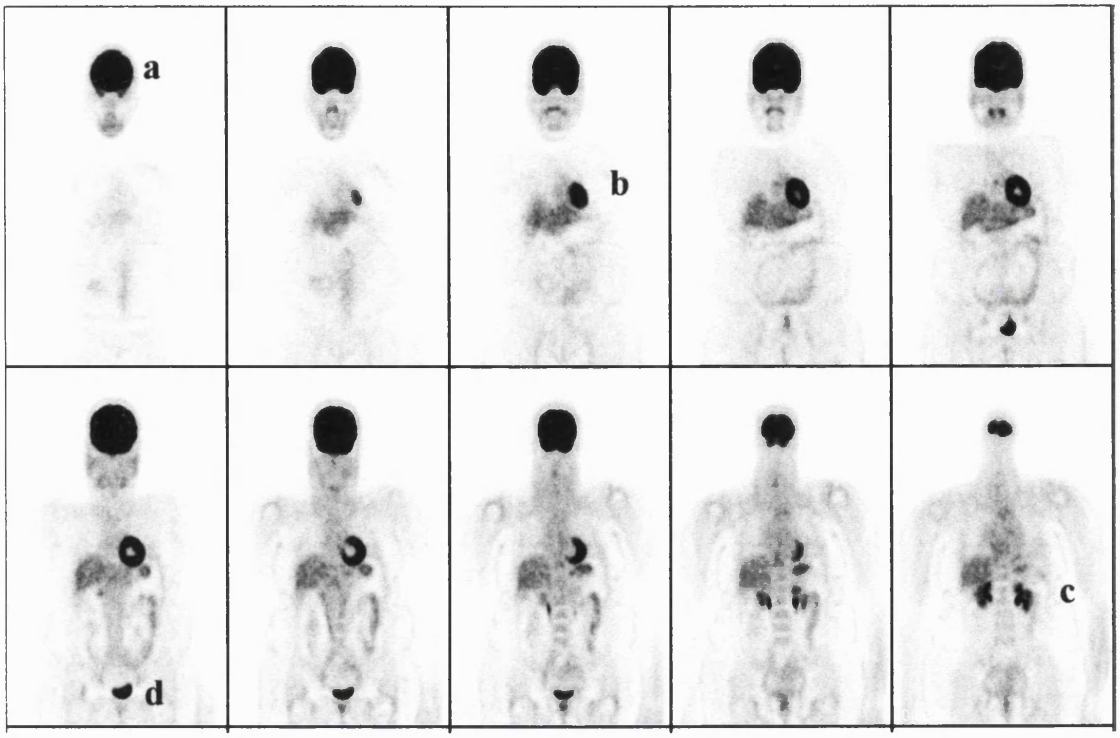


Figure 2.3 Coronal slices printed out from a normal FDG-PET examination. Normal FDG uptake can be seen in the brain (a), myocardium (b), kidney collecting system (c) and urinary bladder (d).

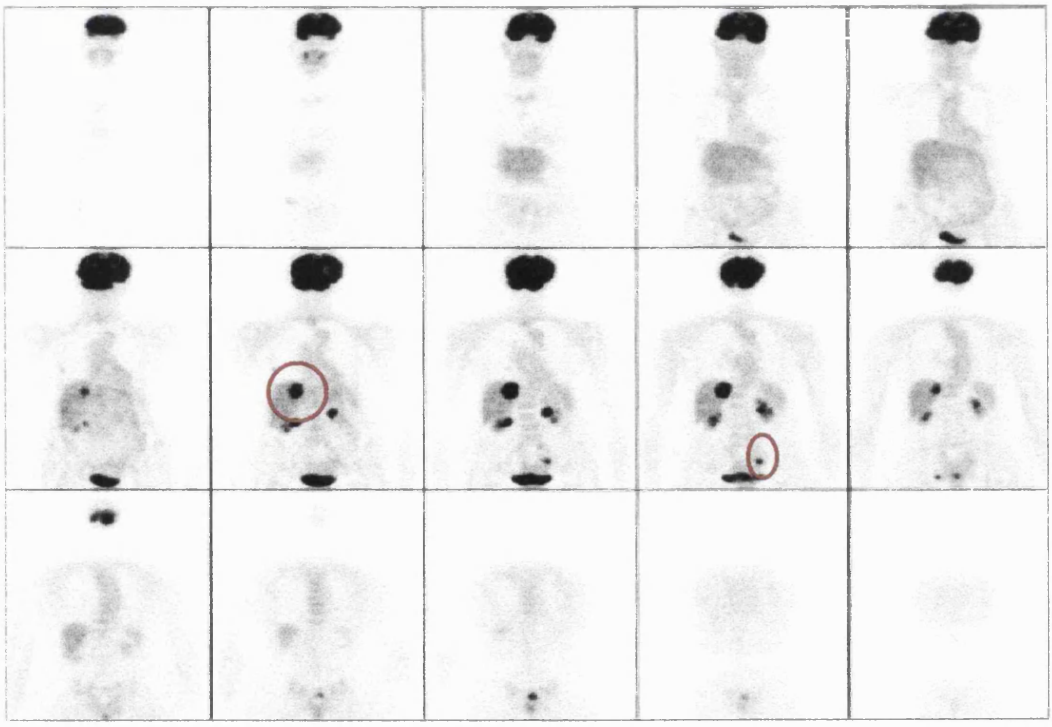


Figure 2.4 Coronal slices printed out from an abnormal FDG-PET examination. A CLM and pelvic recurrence of a rectal tumour are seen (circled)

Consensus reporting was used to analyse and issue a clinical report on each FDG-PET scan. This procedure involved visual inspection of coronal, sagittal and transaxial images for each patient. Those present at each reporting session would include at least 2 nuclear medicine physicians of consultant grade and the physicist and radiographer who carried out the injection and imaging. Each report took approximately 15 minutes and reports were issued under a standard format of:

1. FDG protocol used
2. Clinical indication for scan
3. FDG distribution and findings
4. Conclusion

Once a report was made the images that best demonstrated the findings were printed on photographic paper and accompanied the written report to the referring clinician. The written report was used to document FDG-PET findings for the purposes of the studies described in this thesis.

2.3 Spiral CT

2.3.1 Preparation

CT abdomen, pelvis, liver and chest

Patients are asked to not eat anything for four hours prior to the scan and can drink non-fizzy drinks upto one hour before the scan. No other special preparation is required. Oral contrast may be given just prior to CT of the abdomen and pelvis.

CTC (CT pneumocolon)

Bowel preparation in order to clean the colon is required and this took place the day before the examination. Preparation involves ingestion of one sachet of oral picolax the day before the CTC (between 7.30 and 9 am for a morning appointment and before 7pm for an afternoon appointment). Patients are encouraged to drink clear fluids (approximately 500ml per hour) continuously and a low residue diet is allowed until approximately 18 hours prior to the scan. Immediately before the scan, patients were required to drink two glasses of water.

2.3.2 Image acquisition

Abdomen, pelvis and liver

CT scans of the abdomen and pelvis were contrast enhanced and performed in either a Somatom Plus 4 or a Somatom Plus 4 Volume Zoom (both Siemens AG Medical Engineering Group, Forchheim, Germany). The contrast used was Omnipaque 350 (Nycomed Amersham plc, Amersham Place, Little Chalfont, Buckinghamshire). Scanning protocol with the Somatom Plus 4 for the abdomen and pelvis involved 5mm contiguous slices after giving 100ml intravenous contrast at 4ml per second with a 45-second delay. For bi- or triphasic liver imaging patients were scanned at 20s, 50s, 180s with slices being 5mm thick at 2.5mm intervals. For the Plus 4 Volume Zoom CT scanner, abdomen and pelvis imaging involved dynamic multislice imaging with 3mm contiguous reconstructions after giving 100ml intravenous contrast at 4ml per second with a 45 second delay. For bi- or triphasic liver imaging patients were scanned at 35s, 50s, 180s with slices being 3mm thick at 1.5mm intervals.

Chest

Standard, non-contrast enhanced scans were performed as detailed above.

CTC (CT pneumocolon)

Patients were given 120ml of Omnipaque 350 intravenously at a rate of 5ml per second and scanned after a 25 second delay. Scanning took place in the prone and supine positions (in order to reduce faecal artefact that may obscure mucosal lesions) after an initial scanogram was taken.

2.3.3 Image reconstruction

All data was processed on the CT scanner Siemens workstation where images were reconstructed according to appropriate software package used. Images were usually formatted into the transaxial plane, but when necessary coronal and sagittal prints were produced on a SUN microsystems workstation.

2.3.4 Image analysis

A Radiologist of specialist registrar or consultant grade evaluated all images. In addition, all CT scans were presented at a weekly CRC MDT meeting where they were re-evaluated by a Radiologist of consultant grade. All films were visually analysed.

2.4 Comparative analysis of imaging

Multidisciplinary Oncology Meeting

In line with guidelines issued by the government on optimal individualised care for cancer patients, an MDT managed all those with a confirmed diagnosis of CRC. This group consisted of both medical and allied healthcare professionals. Included in the group were radiologists, nuclear medicine physicians, surgeons, medical and clinical oncologists as well as nursing staff. The objective of the MDT is to offer the CRC patient the optimal care by harnessing the expertise of a variety of medical specialities, rapid refferal between the specialists and maintenance of high standards through audit.

This group made consensus decisions regarding the clinical management of complex cases and therefore formed and ideal forum to present CT data, decide management based on this and relevant clinical information.

Comparison between FDG-PET and CT

All diagnoses were confirmed either on histological evidence or by careful clinical and radiological follow-up within the CRC MDT. However, in order to compare CT and FDG-PET the management was noted as dictated by CT, then FDG-PET results were presented. If there was a difference in imaging data obtained, a change in management plan was then documented. In a majority of cases FDG-PET detected abnormalitites, which on review of CT scans proved to be lesions interpreted as being non-significant. Diagnosis was then verified as explained above and the result of each imaging modality was designated true positive (TP), true negative (TN), false positive (FP) or false negative (FN).

2.5 Statistical analysis

Standard statistical analysis of acquired data is discussed in each of the relevant chapters. Once a change in management has been established this was recorded for each of the patients in each of the different series. The statistical significance of these changes were evaluated using the McNemar test. I would like to clarify here the use of the McNemar test, which is specifically used in the series of studies described. This is a variant of the Chi squared test that is particularly well suited for tesing the significance of changes in studies with "before and after" designs and in which each subject acts as his or her own control. In this thesis the significance of the change resulting from FDG-PET on clinical management is tested.

In order to test any observed change by this method it is neccesary to construct a fourfold table of frequencies in order to represent the management before FDG-PET (i.e. with CT) and then after FDG-PET (table 2.2).

	Disease negative on FDG-PET (after FDG-PET)	Disease positive on FDG-PET (after FDG-PET)
Disease positive on CT (before FDG-PET)	**A**	**B**
Disease negative on CT (before FDG-PET)	**C**	**D**

Table 2.2 fourfold table for use in testing the significance of change using the McNemar test.

The total number of people in whom responses changed is A+D. The null hypothesis is that the numberof changes in each direction is equally likely. That is, of the A+D individual who changed, we would expect (A+D)/2 individuals to change from positive to negative and the same number to change the other way. When H_0 is true the expected frequency in each cell is (A+D)/2.

We know that :

$$X^2 = \Sigma (O_i - E_i)^2 / E_i \qquad (5)$$

In the McNemar test we are only interested in the cells where change occurs:

$$X^2 = \frac{[A - (A+D)/2]^2}{(A+D)/2} + \frac{[D - (A+D)/2]^2}{(A+D)/2} \qquad (6)$$

Therefore:

$$X^2 = \frac{[A - D)]^2}{(A+D)} \qquad (7)$$

Standard Chi squared tables are then used to obtain values and for this series of studies significance was taken at $p< 0.5$.

CHAPTER 3

Detection of primary colorectal cancer

3. Detection of primary colorectal cancer

3.1 Background

A variety of relatively cheap, accurate and widely available methods for detecting primary CRC exist and have been described in Section 1.4. In this chapter I concentrate on patients with symptomatic CRC. In these patients the phenomenon of variable bowel uptake of FDG is seen. This chapter is a study to reconfirm the accuracy of FDG-PET for detecting primary CRC.

However, the main focus of this investigation is the SUV that is derived for primary CRC lesions. There is evidence that body size and blood glucose level influence SUV. The reason for this is that SUV corrected for total body weight (SUV_W) overestimates FDG uptake in heavy patients since their fraction of body fat (with low FDG uptake) is often increased [Zasadny & Wahl, 1993]. One proposed solution to minimize this is to use the SUV corrected for body surface area (SUV_{BSA}) [Kim & Gupta, 1996]. I have set out to assess the correlation between SUV variants, specifically the SUV_W, SUV_{BSA} and SUV corrected for blood glucose (SUV_G). Having established which variant is of most use when evaluating patients with primary CRC, I have then gone on to assess whether the SUV correlates with histological status of the particular tumours used for this study.

3.2 Aims

The aims of this chapter are:

1. To confirm the capability of FDG-PET for detecting primary CRC lesions.
2. To investigate SUV's of CRC lesions and establish the optimum SUV variant to study CRC. This will then be used for the entire thesis including the study in chapter 7, which investigates a new PET tracer and directly compares tissue characteristics with those of FDG.
3. To compare FDG-PET SUV's in CRC lesions with histological features of these lesions.

3.3 Methods

Patient selection

Patients with a confirmed diagnosis of CRC were prospectively recruited to undergo FDG-PET scan in addition to standard investigations designed to detect CRC. All patients were managed by a CRC multidisciplinary team (MDT). At the hospital where this study was conducted the investigations used included double contrast ba enema, flexible and/or rigid sigmoidoscopy, colonoscopy and CTC. Diagnoses were all confirmed histologically.

Procedure

All patients underwent FDG-PET scans as detailed in chapter 2, with the majority seen as outpatients. In order to calculate SUV, body weight and height was recorded for each individual. All investigations were completed before any treatment was initiated. If CT or CTC were performed they were carried out as detailed in chapter 2. Standard techniques were used for colonoscopy and rigid or flexible sigmoidoscopy. Patients underwent surgery as decided by the clinician responsible for the patient. Resected specimens were sent for standard histopathological analysis as carried out at UCLH.

Analysis

Reconstructed orthogonal FDG-PET scans were then visually inspected in order to make a diagnosis and identifying regions of interest for subsequent SUV calculation. SUV's were calculated with correction for total body weight, body surface area and glucose according to the formulae and protocol detailed in chapter 2. Histopathology reports were retrieved in order to confirm the final diagnosis and grade of tumour which was then compared with SUV data.

Statistical analysis

SUV variants were plotted against each other and a linear regression analysis was made giving an r value and regression equation. Standard regression analysis was carried out using a Microsoft Excel™ 97 package. All graphs were plotted using data entered into this database.

3.4 Results

In total 13 patients were recruited. There were 9 males and 4 females with a median age 76 years (range 53 years and one month to 86 years, 9 months). Table C1 (Appendix C) shows the pre-operative investigations performed, FDG-PET result and final diagnosis for all patients. I will first present the results for the use of FDG-PET for the detection of confirmed primary CRC. The second section of the results will be devoted to SUV analysis and correlation between SUV variants as well as with histological features of the tumour.

Detection of primary colorectal cancer

Detection of the primary tumour with FDG-PET was confirmed unequivocally in all cases by differential tracer uptake. Figure 3.1 is an example of an FDG-PET study in a patient with an adenocarcinoma of the descending colon.

SUV analysis

SUV variants were calculated for regions of interest drawn on to areas of maximum uptake (table 3.1). Parameters such as height, total body weight, blood glucose and injected activity are documented for all patients in appendix C, table C2.

SUV_W and SUV_{BSA}

When this data was represented graphically (figure 3.2) an extremely good correlation between SUV_W and SUV_{BSA} was seen in these primary CRC tumours. The regression coefficient was r=0.7572 with only one patient lying well away from the line. This patient weighed 101kg and was well outside the normal range of total body weight for patients investigated. We can say from this data that there is good correlation between SUV_W and SUV_{BSA} in primary CRC within a normal range for total body weight. The one patient who fell outside this range demonstrates very well the overestimation of SUV when correcting for total body weight alone in heavy patients: that is since the fraction of body fat, which has a low FDG-uptake, increases then overestimation takes

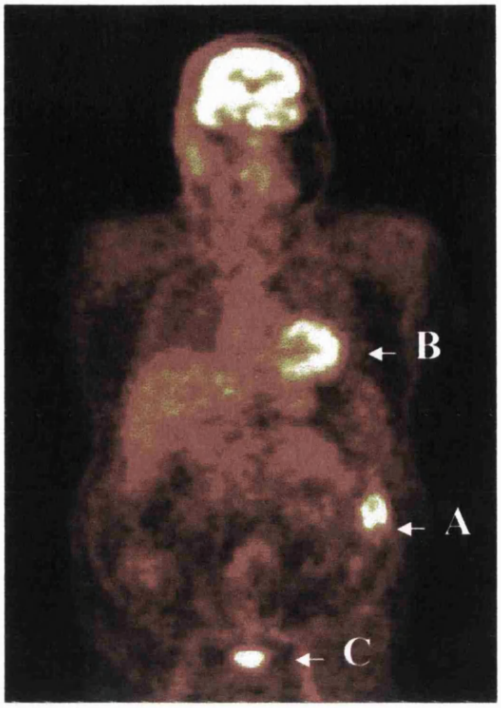


Figure 3.1 FDG-PET study in a 61 year old male with symptoms of left sided abdominal pain and change in bowel habit. At level "A" one can see intense uptake of FDG. This area was histologically confirmed to be a Dukes B carcinoma of the colon. B = heart and C= urinary bladder.

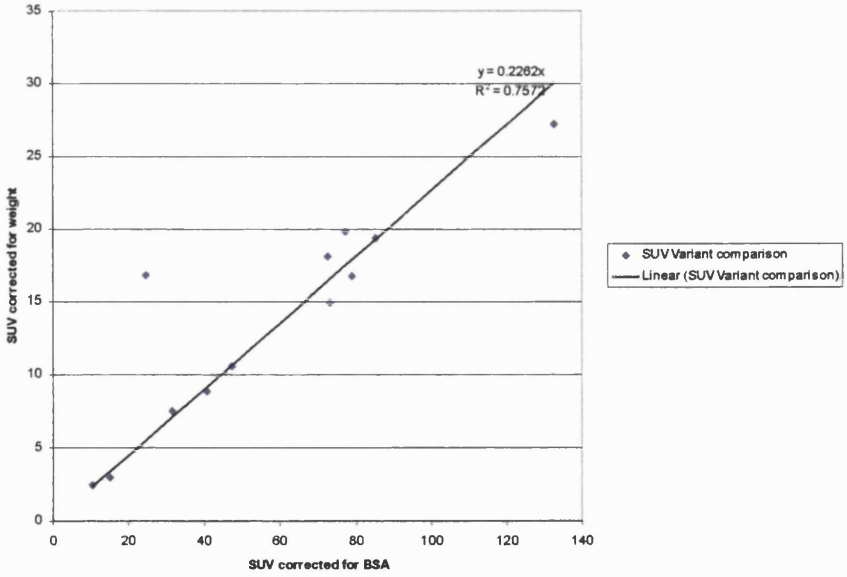


Figure 3.2 SUV_W plotted against SUV_{BSA} for patients with primary CRC

place. With only 13 patients it would be inaccurate to state an upper limit for body weight above which SUV_{BSA} would be the recommended SUV variant to use.

SUV_W and SUV_G

Similar results were seen when comparing SUV corrected for blood glucose and that for total body weight (figure 3.3). The regression coefficient was r=0.5536 and the only significant outlying value was in a patient who had a blood glucose of 10.9mmol/l. The median blood sugar was 5.5mmol/l (range 3.8-10.9mmol/l). Similar to the comments regarding SUV_W, blood sugar is usually kept within certain limits prior to scanning. This was the case in 11 of the 12 patients. If patients present with a blood sugar that is significantly elevated as in the 12th case, scanning should be postponed or adequate correction made.

Comparison of SUV with histological status

It was the original intention of this study to compare SUV_W with histological grade. Unfortunately, table C4 (appendix C) reveals that all the primary CRC assessed were moderately differentiated making real comparisons impossible. The data available from histolological analysis regarding vascular, lymphatic and perineural infiltration was also extremely varied making assessment of any correlation with SUV impossible.

PATIENT	SUV_W Av g/ml	SUV_W Max g/ml	SUV_{BSA} Av cm^2/ml	SUV_{BSA} Max cm^2/ml	SUV_G
1	16.822	19.156	24.678	28.102	62.924
2	14.994	16.932	73.092	82.54	73.470
3	7.534	8.701	31.56	39.787	42.190
4	27.207	33.858	132.894	165.381	138.756
5	16.764	19.31	79.012	91.01	90.526
6	19.831	25.684	77.367	100.905	124.935
7	*	*	*	*	*
8	8.866	10.484	40.57	47.974	69.155
9	18.125	38.769	72.573	155.231	197.563
10	2.982	3.505	15.16	17.816	14.015
11	2.45	2.653	10.476	11.342	24.255
12	19.379	25.004	85.335	110.1	116.27
13	10.612	12.285	47.257	54.7	55.182
Mean	**13.797**	**18.028**	**57.498**	**75.407**	**84.104**
sd	**7.416**	**11.347**	**35.589**	**51.100**	**52.636**

Table 3.1 SUV variants calculated for regions of interest drawn over site of maximal FDG uptake within the primary tumour. (Derived from raw data in table C1). * Note that in one patient (7) stored data was corrupted and it was not possible to retrieve or analyse any information. Abbreviations: Av=average; Max= maximum)

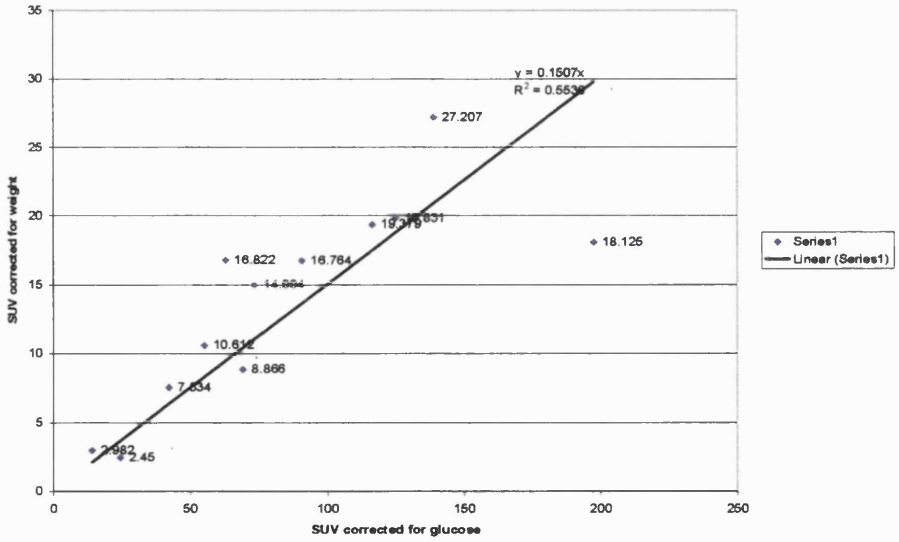


Figure 3.3 SUV_W plotted against SUV_G for patients with primary CRC

3.5 Discussion

In chapter 1 (1.4) I have discussed in detail why, at present, FDG-PET is unlikely to play a role in unselected population screening for primary CRC in asymptomatic individuals because of the cost and lack of specificity. This situation may change in the near future as the first validated publications demonstrating that adenomatous polyps can be detected using FDG-PET start to appear in the scientific literature [Yasuda et al., 2001]. If polyp detection using FDG-PET is shown to be accurate then comparative studies with colonoscopy and CTC will be justified. While FDG-PET relies on metabolic activity, CTC polyp detection is based on size criteria and reports suggest that polyps of less than 10mm may be picked up. In addition, asymptomatic cancers that are likely to be at a very early stage and flat adenomas might be detected. Therefore, as well as potentially preventing the development of new cancers, treatment of established CRC may be improved. The most significant problem when looking for primary CRC appears to be the fact that FDG is taken up in a heterogeneous fashion in normal bowel mucosa as well as in mucosa with pathology. This means that visual and semiquantitative analysis may be inaccurate. In patients at low risk for disease, there tends to be a high proportion of false positive FDG-PET images [Rigo et al., 1996]. This, along with cost, is a significant factor counting against FDG-PET being used in unselected screening programmes.

These problems are seen to a much lesser extent in patients with symptomatic primary CRC that were assessed in this chapter. The results of FDG-PET detection of primary CRC presented here reiterates the work of others who demonstrated nearly 100% sensitivity for detecting primary CRC [Mukai et al., 2000; Takeuchi et al., 1999; Ruhlmann et al., 1997]. The advantage of accuracy for FDG-PET is, however, offset by its cost. Ba enema and flexible sigmoidoscopy, colonoscopy and finally, CTC are cheaper by varying degrees. They are also currently more accessible to the clinician. Therefore, the use of FDG-PET to soley diagnose primary CRC in symptomatic individuals is unlikely to be in great demand. There are two situations which may be combined with this role and make FDG-PET more cost effective for the evaluation of primary CRC. The first of these is if FDG-PET were to be used as a whole-body staging investigation. The number of FDG-PET investigations ordered would be much less than if it were to be used to diagnose all patients with symptoms suggestive of CRC. The issue of FDG-PET as a staging investigation is addressed in chapter 4.

The second use that FDG-PET could be put to is to give the clinician information about the biological aggressiveness and behaviour of the tumour. This assumes that FDG-PET can give the same type of metabolic information that allows correlation of SUV and histological grade of certain brain tumours. The basis for this statement comes from the fact that authors have correlated absolute glucose consumption values with histological grade in gliomas. Patronas suggested that within the high grade glioma sub-group, FDG uptake may be more important as a prognostic factor than histological grade. There were flaws in this study as many of the cases included were recurrences. So, although this correlation is well documented for cerebral tumours, it is an area of controversy [Di Chiro, 1986; Di Chiro et al, 1988; Kim et al., 1991; Schmidt et al, 1996]. Currently, the best prognostic indicators are a combination of clinical and radiological evaluation of the patient along with the careful histopathological analysis of the resected specimen. In order to ascertain information from an FDG-PET study that could correlate with tumour biology one needs to use the SUV's that can be derived. Unfortunately, in the work presented in this chapter a suitable correlation with histological features was not possible. This was because a large proportion of the tumours were moderately differentiated and the documentation of other features such as vascular, lymphatic and perineural infiltration was variable.

Interestingly, however, before I tried to correlate SUV to histological type it was necessary to decide which SUV variant I used. It is widely assumed that SUV_W is the most accurate semiquantitative index. Studies have, however, shown that SUV can be influenced by body size, blood glucose concentration and scan time after injection [Zasadny & Wahl 1993; Kim & Gupta 1996; Cremerius et al., 1998]. Scan time after injection was kept uniform according to prearranged protocol. As part of the preliminary investigation, therefore, I analysed whether there was any correlation between these SUV variants (SUV_W, SUV_{BSA} and SUV_G) in primary CRC. Data regarding these parameters is available for lung cancer, but this may not apply to CRC. An important consideration when trying to put SUV data presented in this and future chapters into context is that almost all available data in the literature regarding SUV range in various tumours, cut off values for malignancies and SUV in normal tissues have been calculated from FBP reconstructed images. It is for this reason that I have specifically referred to the reference values for iterative reconstruction with segmented attenuation correction publised by Ramos and colleagues. These values are tabulated in chapter 2 (table 2.1) as a means of reference for "normal" values and I

use these as they are calculated from high quality images comparable to those reconstructed for this study.

My findings demonstrate good correlation between all three variants; therefore, it is appropriate to use SUV_W when assessing primary CRC lesions. The benefit of this information is that this variant is easier to calculate from basic patient data obtained on admission to the PET facility.

The drawbacks of this study are primarily that it has examined a relatively small number of patients. A larger spread of data would enable the investigator to pick up small degrees of difference in sensitivity and specificity. This information is a prerequisite if the modality were to be compared directly with other methods of diagnosing primary CRC. To a lesser extent this applies to the comparison of SUV variants, but the correlation is quite apparent from this small sample. One of the biggest benefits of a larger study population would be a greater spread of histology. This would enable the investigator to make firm conclusions as to any potential for SUV's to be correlated to grade. A standardised histopathology reporting format as produced by the Association of Coloproctology of Great Britain and Ireland would also ensure specific microscopic features such as vascular, lymphatic and perineural invasion would be documented for comparison with SUV. This, along with long term follow up, would allow evaluation of SUV as a predictor of histological nature of the tumour and prognostic indicator.

In summary, this chapter has demonstrated the high accuracy of FDG-PET to detect primary CRC as well as indicating that SUV_W is an appropriate semiquantitative index to use when evaluating primary CRC lesions.

Future directions

Prognostic indicators for patients with primary CRC are primarily related to the resected tissue specimen. Study of FDG-PET for the evaluation of the biological nature of a diagnosed primary CRC has many knock on effects. If FDG-PET could accurately predict the biological nature of the tumour it would possible to use this and histological information to decide on adjuvant therapy. One could speculate that if, infact, there is a subpopulation within the Dukes B stage of CRC that would benefit

from chemotherapy, FDG-PET may be able to identify these patients on metabolic grounds. Another avenue worth consideration is the comparison of FDG-PET SUV data and the presence of MS instability. Patients with MSI tend to have a better prognosis [Thibodeau et al., 1993] and an imaging technique such as FDG-PET may be an effective way of identifying these patients. The advantage of FDG-PET in these scenarios is that complex histological and immunohistochemical tissue processing may be avoided while giving important biological information. This is in addition to the primary function of identifying the presence of a tumour.

CHAPTER 4

Staging primary colorectal cancer

4. Staging primary colorectal cancer

4.1 Background

The optimal treatment of CRC requires accurate delineation of all foci of disease. This means that not only does the surgeon need to know the degree of local infiltration, but also the presence of malignant lymphadenopathy, CLM and distant spread. This ensures that the patient receives treatment appropriate to the disease present. An example of this would be the detection of a CLM in a patient with a confirmed CRC primary. These may be present at the time of surgery to the primary intestinal lesion in 25% of cases [Ballantyne and Quin, 1993]. If detected treatment would be commenced depending on whether the lesion was suitable for surgical resection or an alternative treatment modality, such as physical ablation or chemotherapy. So, from the outset, the patient commences appropriate treatment tailored to the extent of his or her own disease. Too often, the surgeon discovers a metastatic liver lesion several months after initiating treatment for the primary intestinal cancer and the chance to offer potentially curative surgical treatment is missed.

4.2 Aims

The area of weakness that results in inadequate staging of primary CRC is the initial radiological staging of the disease. This study aims to compare FDG-PET with CT for detection of additional metastatic lesions in patients being treated for confirmed primary CRC. The objective is to assess whether FDG-PET, which is costly and labour intensive, improves staging primary CRC to such an extent that it is a feasible option for patients with primary CRC. An assessment is made as to the impact of FDG-PET on clinical management, which helps answer, this question.

4.3 Methods

Patient selection

Patients with primary CRC who were referred to the CRC MDT of UCLH NHS Trust were recruited to the study and are the same patients who underwent SUV variant analysis in chapter 3. All patients were asked to give informed consent in order to take part in the study (Appendix B). Patients with a contraindication to FDG-PET were excluded from the study.

Procedure

Patients underwent routine staging investigations, which included CT scan of the abdomen (and pelvis if the tumour was a rectal cancer). Some patients also underwent endorectal USS and/or MR of the pelvis on the request of the supervising clinician. Patients also underwent a staging whole body FDG-PET scan. Both FDG-PET and CT were carried out pre-operatively as described in chapter 2.

Data analysis

The parameters used for the purposes of evaluation were TP, FN, TN, and FP for the presence of metastatic lesions for each method of imaging. FDG-PET scans were also analysed as described in chapter 2 so as to designate an SUV to all abnormal lesions detected. All diagnoses were confirmed either histologically or on radiological and clinical follow-up. In order to assess the impact on clinical decision-making the independent reports were analysed prior to presentation at the weekly CRC MDT meeting where final management was decided. The management plan directed by CT was noted and then any alteration as a result of new or different information obtained from FDG-PET was documented.

Statistical analysis

The difference in the ability of FDG-PET and CT to detect metastatic disease correctly and then to alter management was evaluated using McNemar's test for matched pairs. These were considered to be significant if $p<0.05$.

4.4 Results

Thirteen patients were recruited to the study, 9 male and 4 female. The median age was 76 years (range 53 years and one month to 86 years, 9 months). At the point of data analysis follow up had been for a mean of 11 months. One patient (patient number five) was excluded from the final data analysis because she did not undergo complete pre-operative staging investigations with CT, thus making comparison with FDG-PET invalid.

Table 4.1 lists the patients, the site and histopathological staging of the primary cancer and any site of metastatic disease.

Patient	Age (years)	Sex	Dukes Stage	Site of Primary CRC	Metastasis/ Synchronous Disease	PET result	CT result	SUV_W Av g/ml
1	61.83	M	B	Descending Colon	Tubulovillous adenoma	TP	FN	16.822
2	53.08	M	C_2	Rectal Cancer	Liver and lymph nodes	TP/ TP	TP/ TP	14.994
3	77.67	F	B	Transverse Colon	None	TN	TN	7.534
4	74.67	F	B	Ascending Colon	Lymph node and luminal	FP/ TP/ TP	FP/ FN/ FN	27.207
5	76.42	M	B	Rectal Cancer	None	TN	TN	16.764
6	80.08	M	B	Ascending Colon	None	TN	TN	19.831
7	86.75	F	*	Rectal Cancer	None	TN	TN	*
8	76	M	B	Rectal Cancer	None	TN	TN	8.866
9	81.33	F	A	Rectal Cancer	None	TN	TN	18.125
10	56	M	*	Rectal Cancer	None	FP	TN	2.982
11	65.08	M	C_1	Sigmoid Colon	Liver and Lymph nodes	TP/ FN	FN/ FN	2.45
12	74.92	M	C_1	Rectal Cancer	Lymph nodes	FN	FN	19.379
13	77.92	M	C_1	Rectal Cancer	Lymph nodes	FN	FN	10.612
	Median 76							

Table 4.1 Patient and histopathological details of patients evaluated with FDG-PET and CT for staging primary CRC.

The sensitivity, specificity and predictive values for both FDG-PET and CT are noted in table 4.2. Nine metastatic lesions were present in six patients (patients 1,2,4,11,12 and 13). In total three of these patients (1,4 and 11) were upstaged as a direct result of FDG-PET, that is patients had additional metastatic disease that was FDG-PET positive and CT negative. There was one false negative FDG-PET lesion (11) in one of these patients and one false positive FDG-PET (4) lesion in in another. In both cases CT scan gave the same result and management was not altered. In two patients with metastatic disease (12 and 13) FDG-PET was false negative. In the sixth case (2) both modalities detected metastatic lesions and management was not altered.

In the seven patients with no metastatic disease (3 and 5-10) FDG-PET was true negative in all but one case (10). The seven cases where FDG-PET differed from CT or was incorrect are discussed in greater detail below.

	TP	FN	TN	FP	PPV (%)	NPV (%)	Sensitivity %	Specificity %
PET	6	3	6	2	75	67	67	75
CT	2	7	7	1	67	50	29	88

Table 4.2 The accuracy of FDG-PET and CT for staging primary CRC lesions. Abbreviations used: TP = true positive, FN = false negative, TN = true negative, FP = false positive

Patients upstaged by FDG-PET

Three patients (1,4 and 11) were upstaged as a direct result of FDG-PET and in each case management was altered in order to tailor treatment to new foci of disease that were detected. Of the 13 patients clinical management was altered in only these three patients despite inaccuracies in FDG-PET in other cases. The reasons for this become evident when one analyses the TP, FN and FP FDG-PET studies.

Patient 1: One additional lesion detected by FDG-PET and not by CT

The first patient had a tumour of the descending colon seen on FDG-PET. However, a second focus of FDG uptake was seen more proximally in the transverse colon (figure 4.1). At laparotomy an equivocal abnormality, possibly a mucosal polyp, was

palpated and the patient underwent an extended left hemicolectomy. Histological evaluation clearly showed that the patient had a Dukes B carcinoma of the descending colon. However, of significant interest was the finding that a 2.5 × 1.5 cm broad based polyp was present in the proximal colon, which was microscopically identified as a tubulovillous adenoma with focal stromal invasion. The position of this polyp coincided exactly with the site of increased FDG uptake.

Patient 4: ***Two lesions detected by FDG-PET and not by CT; both modalities false positive for a third lesion***

The second patient had two foci of metastatic colon cancer in the small bowel that was identified on FDG-PET, but not CT. These were confirmed both at laparotomy and on histological evaluation of the resected segment of jejunum and ileum. A local lymph node was diagnosed malignant by both modalities (FP) and this will be discussed in the next section (false positive PET scans).

Patient 11: ***One lesion detected by FDG-PET but not CT; a second lesion missed by both modalities***

This patient was a 64 year-old gentleman who had a confirmed carcinoma of the sigmoid colon. A CT scan detected a "vascular blush", the nature of which was uncertain and close radiological follow up was suggested (figure 4.2a). FDG-PET clearly showed multiple liver metastasis (figure 4.2b). The patient therefore underwent sigmoid colectomy and histological evaluation of the tumour confirmed it to be a Dukes C_1. Although, FDG-PET demonstrated the CLM, a local lymph node was not apparent on FDG-PET and I will discuss this in the following section on false negative FDG-PET studies and CT. The plan was to perform delayed laparotomy for attempted resection of the CLM. Unfortunately, due to tumour location, resection was not technically possible, but the patient underwent radiofrequency thermoablation

False negative FDG-PET scans (patients 11, 12 and 13)

In three cases FDG-PET and CT did not demonstrate histologically apparent local lymph nodes, i.e. those with histologically Dukes C_1 tumours. One of these was patient 11 who had a CLM detected by FDG-PET but not CT. Interestingly; FDG-PET did clearly demonstrate regional lymphadenopathy in the one patient with a Dukes C_2 tumour (patient 2). It is possible to speculate that the proximity of local

lymph nodes to the primary lesion makes differentiating a region of intense activity from two separate lesions difficult. This may be an inherent problem with resolution for detected activity. This also explains why more proximal lymphadenopathy is easily characterised in patient 2. CT, being an anatomical imaging modality does not suffer from this limitation, but there are still well documented problems when trying to diagnose malignancy in normal sized lymph nodes. This possibly explains why both FDG-PET and CT were negative for the three patients with Dukes C_1 tumours (patients 11, 12 and 13).

False positive FDG-PET scans (patients 10 and 4)

In one patient with a false positive FDG-PET uptake was noted in the right adrenal gland, but an incorrect interpretation of metastatic CRC was made. CT scan did not show any abnormality and there was no growth seen over a period of 15 months. FDG activity was present on subsequent scanning, but CT remained negative while tumour markers and the patient's clinical condition did not indicate metastatic disease. No cause could therefore be assigned for the abnormal uptake and there was no evidence of any cause for an increase in metabolic activity or tissue prefusion to this region.

In the second patient (number 4) FDG-PET and CT suggested the presence of malignant local lymph nodes.This patient had also been identified by FDG-PET, but not CT as having small bowel metastases from an ascending colonic carcinoma. It is unclear why increased FDG uptake was seen in this lymph node as no histological abnormality was identified. Subsequent FDG-PET suggested the lymph node had been excised.

Correlation of SUV and the presence of metastatic disease

SUV_W were calculated as described in chapter 2 (table 4.1). These values were then paired with the Dukes staging for that individual patient in order to assess whether this would enhance the ability of the clinician to predict the presence of metastatic disease. There is no correlation between the the SUV_W and the presence of metastatic disease although thee is a trend towards a lower SUV for patients who do not have metastases (mean SUV 12.35 versus 15.24). This is primarily because the spread of data is inadequate to yield step-wise cut off values for each Dukes stage. It is likely that in order to comment on this subject one would need significant numbers of

primary CRC's to analyse and this would only be feasible in a multi-institutional setting.

Altered management

Of the 13 patients, management was altered for the benefit of 3 patients (1, 4 and 11). Despite incorrect FDG-PET scans in both patients 4 and 11, the surgical resection was not altered and histopathology directed adjuvant therapy. This is because a segmental resection of the colon was carried out in both cases. In patient 4 FDG-PET suggested the presence of a metastatic lymph node which was not seen in the resected specimen. Subsequent FDG-PET scan was negative. The patient therefore underwent adjuvant chemotherapy based on the extent of disease. In the second patient, although malignant mesenteric nodes were present FDG-PET was negative, possibly due to their proximity to the primary lesion. These nodes were still resected as part of a segmental resection of the sigmoid colon.

In two further patients (12 and 13) FDG-PET was false negative for the same reasons as in patient 11. Again clinical management was unaltered. In patient 10, the discovery of uptake in the adrenal gland lead to more intensive radiological imaging, but it could have resulted in an invasive approach and possibly commencement of chemotherapy. Therefore FDG-PET altered management in 4 patients, 3 of whom had a beneficial change. The hypothesis that FDG-PET altered management for the benfit of the patient is not statistically significant ($p>0.5$). The spread of data is small and this must be taken into account.

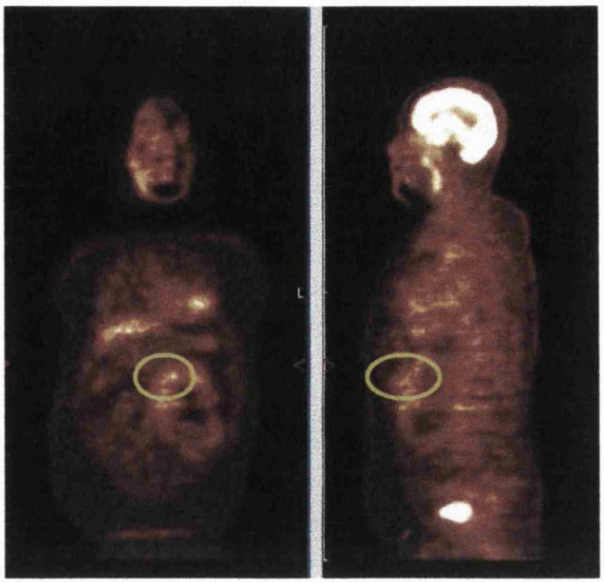


Figure 4.1 Coronal and sagittal FDG-PET showing abnormal FDG uptake (circle) in the large intestine. One particularly avid (best seen in the coronal slice) area was interpreted as a polyp which was confirmed at surgery.

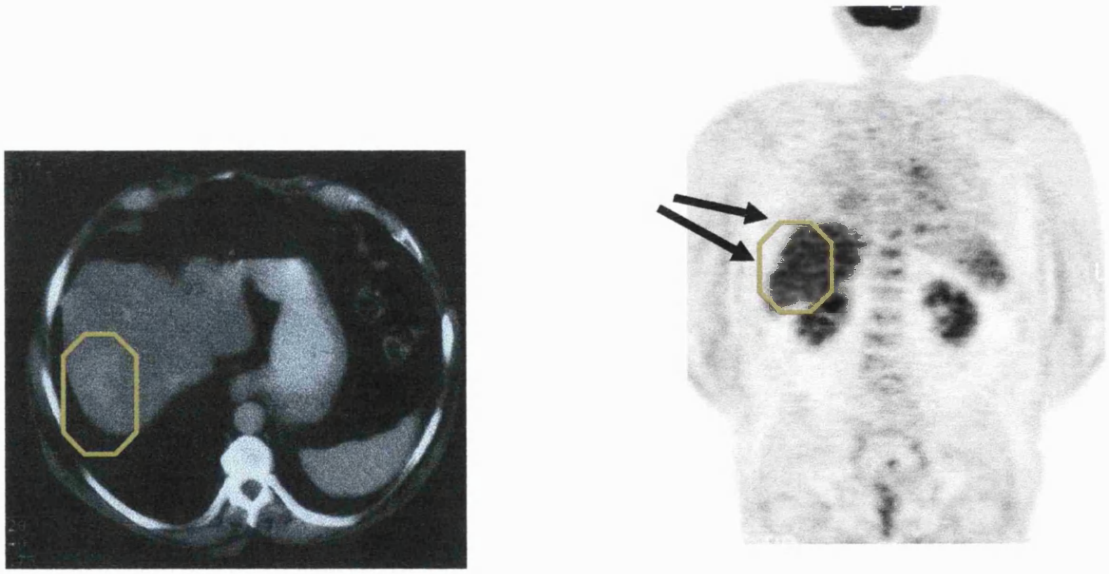


Figure 4.2 Transaxial CT liver (a) showing "vascular blush" (circled). The coronal FDG-PET (b) shows multiple areas of tracer uptake (arrowed circle) which were confirmed in each plane and then at surgery.

4.5 Discussion

Accurate pre-operative staging of primary CRC allows patients to receive appropriate treatment, which in turn optimises the chance of cure. This study demonstrates that when assessment of local infiltration is excluded, FDG-PET does have a marginal superiority to CT for staging primary CRC. CT and other anatomical imaging modalities have significant advantages for evaluating local infiltration of CRC. When assesing the extent of CLM the data indicates that FDG-PET is able to detect additional foci more accurately. This is not the case with assessing lymph node involvement.These results must be taken within the context of this small study, but certain important points are demonstrated.

Firstly, detection of malignant lymph nodes on size criteria has been shown to be inaccurate [Rodriguez-Bigas et al., 1996]. FDG-PET is more accurate for detecting malignancy in normal sized lymph nodes, but in CRC patients it must be borne in mind that differentiating the primary tumour from adjacent malignant lymph nodes is difficult. This is very much the case in the study presented here. In fact, the poor sensitivity of FDG-PET for detection of malignant lymph nodes has been reported by others [Mukai et al. 2000; Abdel-Nabi et al., 1998], but in both studies further analysis as to the possible reasons is lacking. Both authors reported sensitivity of between 22.2% and 29%. Mukai looked at 24 patients with CRC and of the 9 patients with positive lymph nodes FDG-PET was positive in 2 patients. Only one of these was N_1 (i.e. a Dukes C_1 tumour). There were 2 false positive FDG-PET scans for regional lymphadenopathy. Abdel-Nabi investigated 48 patients and found only 4 out of 14 patients with positive lymph nodes were detected by FDG-PET (29%). The point is made by Mukai, that although we expect FDG-PET to be accurate in this situation, the reality is that FDG-PET is inaccurate for pre-operatively assessing regional lymphadenopathy in CRC patients with primary disease.

The fact that FDG-PET was FN in all three patients with Dukes C_1 tumours and TP positive in the patient with a Dukes C_2 tumour suggests that the resolution of FDG-PET for activity in two adjacent areas may not be sufficient for the purpose of accurate CRC staging. The contribution of partial volume effects to this is difficult to estimate. In this study more proximal regional lymph nodes can, however, be differentiated from the primary cancer and this suggests that there may be a problem

with resolution. This is particularly interesting as one of the theoretical advantages of FDG-PET is the ability to detect malignant lymphadenopathy whatever the morphology of the node.

These findings are contrary to the extremely good published results for FDG-PET detection of malignant lymphadenopathy in non-small cell lung cancer (NSCLC) and lymphoma [Dwamena et al., 1999; Kostakoglu and Goldsmith, 2000]. Dwamena and colleauges looked at pooled data from 14 PET studies (514 patients) and 29 CT studies (2226 patients) in patients with NSCLC. The sensitivity and and specificity for detection of mediastinal lymphadenopathy with FDG-PET was 79% and 91% respectively compared to 60% and 77% with CT. In lymphoma a similar pattern is seen with one study demonstrating FDG-PET upstaging 8% of 60 patients with either Hodgkins or Non-Hodgkins lympoma [Moog et al, 1997]. An explanation for the lack of such compelling data for CRC, not just in this study, but also in the published literature to date is a searching question that remains unanswered. Any comments would be speculative; however, in the recurrent CRC setting the situation is very different (chapter 5). As there is no primary tumour, FDG is avidly taken up by lymph node masses and these are clearly delineated by PET detectors. An important point to note is that CT was no better than FDG-PET in either scenario.

The real benefits of FDG-PET for staging may be in the early detection of CLM. Although only two patients had CLM and one of these was upstaged, FDG-PET may influence clinical management to a greater extent than if malignant lymph nodes were detected. In the course of a proper oncological resection all immediately adjacent draining lymph nodes should be excised. The weakness of FDG-PET is partially made up for by this fact. If FDG-PET detects regional (more proximal) lymph nodes or liver metastases then management is altered. In the former case resection is more extensive. In the latter case, if single or multiple CLM are detected then the extent of CLM need to be evaluated and a decision needs to be made as to the most appropriate treatment. This may involve resection of the primary CRC followed by delayed resection of the CLM. Alternatively, some may argue simultaneous resection of primary CRC and CLM, but this would be regarded as the exception in the UK [Sarela and O'Riordan 2001]. It may, however, be that the only option available is to administer palliative chemotherapy with or without physical ablation of the CLM.

This study only has two patients with CLM, but when taken in the context of the superior results for FDG-PET detection and evaluation of the extent of CLM in chapters 5 and 6 it can be speculated that the preliminary findings here may be extrapolated to those with primary CRC and CLM. If up to 25% of patients do in fact have CLM at diagnosis of primary CRC, then the implications for patient management, resource allocation and ultimate patient outcome are significant. Certainly, Abdel-Nabi demonstrated a clear benefit for FDG-PET in detecting CLM, albeit in only 8 patients [Abdel-Nabi et al., 1998].

As with all imaging techniques FDG-PET is not 100% sensitive or specific. When one looks at the false positive FDG-PET studies, no definitive conclusions can be drawn as to which patients may have a false positive scan. In particular there was no evidence of any inflammatory lesion or abnormal tissue perfusion. It is particularly difficult to explain the false positive FDG-PET scans, but the fact that they are relatively frequent (2 out of 13) both in this study and in Mukai's investigation points the clinician towards a cautious approach.

One other indication of potential benefits of this technique when assessing a primary CRC is the fact that in one patient FDG-PET demonstrated a tubulovillous adenoma. The implications of this intriguing finding are two-fold. Firstly, in the future it may be justifiable to evaluate FDG-PET as a screening tool since polyps and small CRC can be detected. The progression of polyp to invasive carcinoma is primarily a change in cellular biochemical function, which is followed, by a morphological change. One of the first steps in malignant transformation is the increase in mRNA for the synthesis of glucose transporter molecules. This study demonstrates clearly that adenomatous polyps, the pre-malignant precursor to an invasive cancer, can be detected. Secondly, in the staging scenario FDG-PET may yield valuable information on synchronous lesions (polyps or synchronous CRC). This information can lead to more extensive surgical procedures being performed, for example a segmental resection may be converted to a radical resection of the colon. This minimises the chance of occult synchronous lesions progressing as well as the well documented progression of adenomatous polyps into invasive cancers. Interestingly, Abdel Nabi showed that in 35 hyperplastic polyps there was no FDG uptake. This is particularly helpful to the clinician as the clinical significance of these is negligible.

In summary, this study demonstrates that FDG-PET is in fact more accurate than CT for staging primary CRC in specific circumstances. This benefit is principally seen because of the detection of CLM and synchronous lesions, both of which lead to alterations in patient management. The findings of the study help clarify the reasons behind the disappointing yield for malignant lymph nodes. The magnitude of CRC as a clinical problem may justify a more extensive multicentre study of FDG-PET for staging CRC with long term follow up. This would help ascertain the clinical benefit of detecting CLM, possibly at an earlier stage than otherwise. The consequent impact of therapeutic intervention would then need to be assessed in terms of survival. The data may help determine the value of SUV for predicting metastatic disease.

CHAPTER 5

Detecting recurrent colorectal cancer

5. Recurrent colorectal cancer

5.1 Background

CRC is a common condition, but it is accepted that 70% of patients who present with a primary CRC are suitable for so called curative surgery. I have already pointed out that the disease recurs in a large proportion of patients (30-40%) [Renehan et al 2002]. This in itself is disappointing, but there is good evidence that if recurrence or isolated liver or pulmonary metastases are present then "salvage" surgery can be of benefit [Benotti et al., 1992; Zavadsky and Lee, 1994]. This benefit is demonstrated by improved survival. The diagnostic challenge facing the clinician is how best to follow up patients who have been treated for CRC. The ultimate goal of these follow up strategies must be to detect recurrence with certainty and sufficiently early so as to offer the chance for curative surgical reintervention. The assessment of patients is based on the results of taking a clinical history, physical examination and a combination of colonoscopy, CT and serial blood CEA measurement. Although the methods described do detect the majority of recurrences, there are cases where a focus of recurrent disease is missed or diagnosis delayed [Renehan et al 2002].

Clinicians are faced with two challenges when looking after patients who have been treated for CRC; firstly, patients may present with symptoms during the interval between regular outpatient follow up appointments or be found to have abnormal follow up investigations that require further confirmatory tests. These patients are categorised as suspicious of recurrent/metastatic disease. The question posed here is "can the accuracy of diagnosis be improved with a one-off test?". Another aspect of the problem is devising the best routine follow up protocol for treated CRC patients. The diagnostic accuracy of regular follow up investigations and clinical evaluation of patients that have been described above leave scope for significant improvement [Renehan et al 2002].

5.2 Aims

In this chapter I explore the capability of FDG-PET to make an early diagnosis of recurrent/metastatic CRC and analyses the accuracy of FDG-PET in the detection of recurrent CRC compared to the more standard practice of spiral CT. In order to address this subject comprehensively I have first looked at FDG-PET and CT for evaluating symptomatic and high suspicion patients.

In the second half of the chapter I assess the feasibility and safety of using FDG-PET as a regular follow up investigation after resection of CRC. This second group of patients are at lower risk of recurrent disease being present than the group studied in the first section of this chapter. This is because they are unselected and have no clinical suspicion of disease. It is important to assess safety particularly the question of an unacceptable level of false positive examinations with FDG-PET, as this would result in costly, potentially dangerous and anxiety provoking investigations being initiated.

The chapter concludes with a discussion on the advantages and disadvantages for the use of FDG-PET in detecting recurrent CRC. I have specifically omitted any discussion on the ability of FDG-PET to detect additional metastatic lesions; that is the evaluation of the extent of confirmed CRC recurrence/metastasis, as this is dealt with in some detail in chapter 6.

5.3 Comparison of FDG-PET with spiral CT for detecting recurrent colorectal cancer

5.3.1 Methods

Patient selection and procedure

In order to evaluate FDG-PET against CT for the detection of recurrent and metastatic CRC patients were recruited from those referred to the UCLH NHS Trust colorectal MDT. These patients were referred internally as well as those from peripheral district general hospitals. Patients were asked to give consent after a full explanation of the study was given (see Appendix B – patient information sheet and consent forms). Patients recruited were either thought to be highly suspicious of recurrent/metastatic CRC or a definite diagnosis of recurrence had been made elsewhere.

All patients underwent whole body FDG-PET and spiral CT as described in chapter 2. Spiral CT used in the follow up setting for these patients consisted of either CT of the abdomen for colon cancer patients (to assess for local and liver disease) and CT of the abdomen and pelvis for those with rectal cancers. If whole body FDG-PET did detect lesions in a region of the body that had not been scanned by CT, then this was undertaken in order to make a comparison.

Data analysis

Lesions were classified as being TP, FN, TN, and FP for each method of imaging. FDG-PET scans were also analysed as described in chapter 2 so as to designate an SUV to all abnormal lesions detected. All diagnoses were confirmed histologically where possible; otherwise close radiological and clinical follow up was maintained. In order to assess the impact on clinical decision making the independent reports were analyses prior to presentation at the weekly CRC MDT meeting where final management was decided. The management plan directed by CT was noted and then any alteration as a result of new or different information gained on FDG-PET was documented.

Statistical analysis

The difference in the ability of FDG-PET and CT to detect recurrence and metastatic disease correctly and then to alter management was evaluated using McNemar's test for matched pairs. These were considered to be significant if $p<0.05$.

5.3.2 Results

In total forty-two patients were recruited, 23 male and 19 female, with a median age of 68.4 years (range 40.1-84.3 years). At the time of data analysis for this thesis follow-up had been for a mean of 16.6 months after FDG-PET scan or until death (two patients). Patient details, diagnoses and method of confirmation of final diagnosis can be found on table C5 (Appendix C).

Of the forty-two patients investigated, 30 (71 per cent) had a final diagnosis of local recurrence or metastatic disease which was confirmed by histological evidence in 17 cases and on clinical course and follow up radiology in the remainder. The distribution of disease is documented in table 5.1.

Site	Number
No recurrence	12
Local recurrence only	7
Local recurrence and metastases	8
Hepatic metastases – Solitary	4
Hepatic metastases – Multiple	6
Hepatic metastases – plus extrahepatic lesions	5
TOTAL	**42**

Table 5.1 Distribution of recurrent colorectal cancer in 42 patients studied with FDG-PET and CT. All results confirmed by histopathology and/or clinical and radiological follow up.

For the purpose of clarity I will first present the results assessing the accuracy of FDG-PET and CT for detecting recurrence and discuss specific instances where FDG-PET is of benefit to both patient and clinician. I will then present the results evaluating the impact of FDG-PET on clinical management and analyse these in detail.

Detecting recurrent or metastatic colorectal cancer

FDG-PET made a correct diagnosis in 35 out of 42 patients (83 per cent) compared to 31 (74 per cent) with CT. FDG-PET had a sensitivity of 93 per cent and specificity of 58 per cent compared to CT, which had a sensitivity of 73 per cent and a specificity of 75 per cent table 5.2. FDG-PET was falsely negative in two cases and falsely positive in five.

	TP	FN	TN	FP	PPV (%)	NPV (%)	Sensitivity %	Specificity %
PET	28	2	7	5	85	78	93	58
CT	22	8	9	3	88	53	73	75

Table 5.2 The accuracy of FDG-PET and CT for detecting recurrent CRC lesions. Abbreviations used: TP = true positive, FN = false negative, TN = true negative, FP = false positive, PPV = positive predictive value, NPV = negative predictive value.

There were two particular clinical situations in which imaging with a metabolic signal carries significant advantages over conventional anatomical imaging. These were the use of FDG-PET for differentiating benign fibrosis from malignant tumour recurrence and evaluating patients with a rising CEA who had otherwise normal or equivocal imaging. I will now give examples of these two scenarios taken from the study population.

i) Differentiating fibrosis from tumour recurrence

FDG-PET was of benefit for differentiating post-operative and/or post radiotherapy scar from tumour recurrence in several patients assessed. This may only be possible with a metabolic signal. The best example of the capability of FDG-PET in this scenario was in the case of a 59 year old patient had previously undergone sigmoid colectomy for a Dukes B carcinoma of the colon (May 1998). At follow-up CT demonstrated an abnormality in the vicinity of the large bowel anastomosis along with tethering of small bowel loops (figure 5.1). Confirmation as to the nature of this abnormality could not be given based on CT findings.

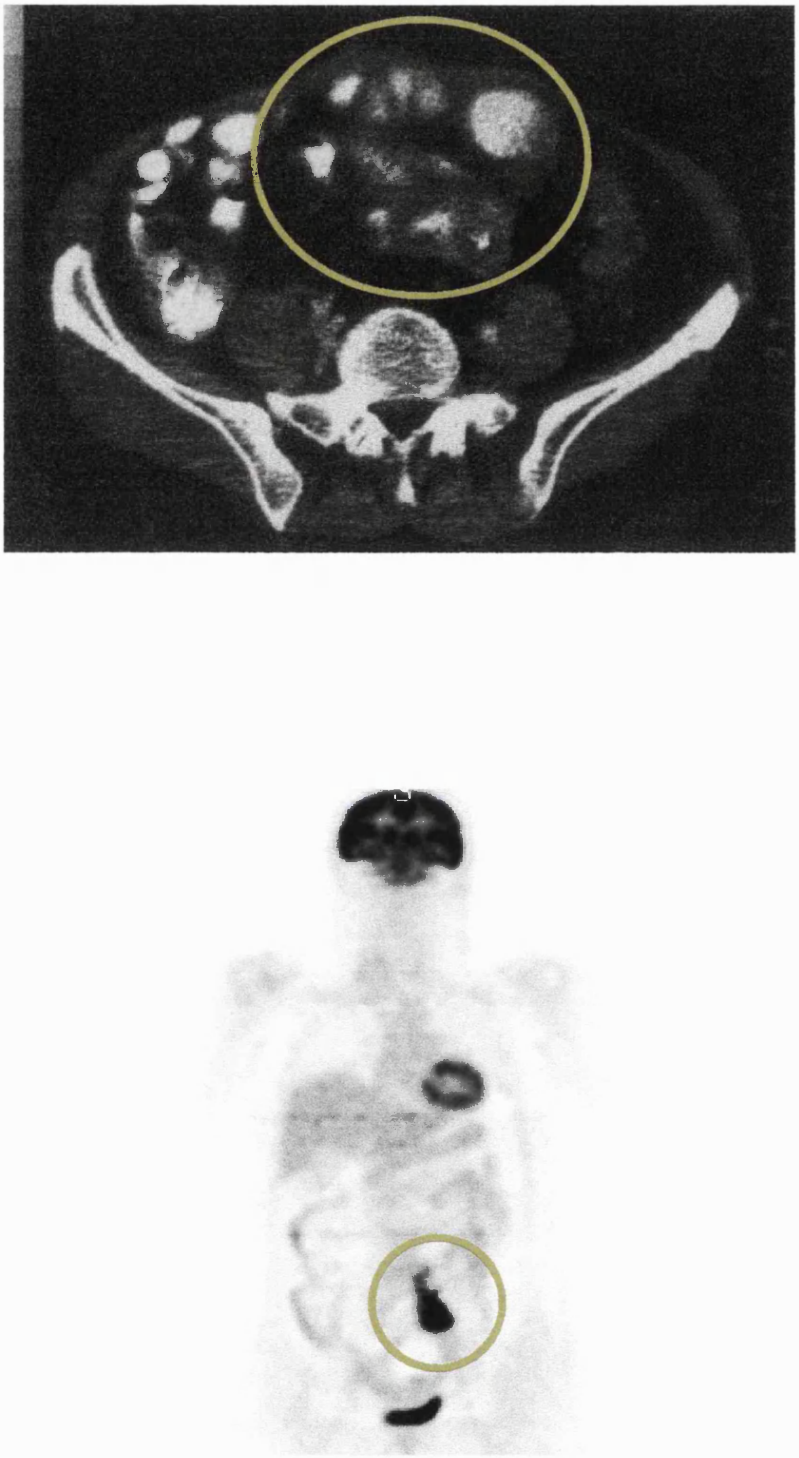


Figure 5.1 Transaxial CT lower abdomen (top) showing contrast in a small bowel mass associated with adhesions to the site of previous anastomosis (circled). The coronal FDG-PET (below) showing tracer uptake in the left side of the lower abdomen (circle) which coincided with the abnormal area on CT and is an area of local recurrence.

The whole body FDG-PET demonstrates avid pathological FDG-uptake in the left lower quadrant at a site, which is anatomically consistent with the abnormality on CT (figure 5.1). This does represent tumour recurrence. The pattern of disease on follow up is unequivocal and FDG-PET does in fact demonstrate a pulmonary metastasis in the apex if the right lung in addition to the local recurrence. The significance of this latter finding is that even if the local recurrence was amenable to surgical intervention (which it was deemed not on radiological grounds), the presence of distant disease makes the patient a high risk candidate for treatment failure as other occult foci are likely to be present. In fact, additional metastatic lesions were found in 8 patients with confirmed local recurrence of CRC (see table 6.3).

ii) Evaluating patients with a rising CEA

The management of patients with rising CEA and normal or equivocal imaging is extremely taxing. FDG-PET is a very useful modality in this situation and this can be illustrated using a patient in this study. The seventy-two year old lady presented to routine follow clinic with an elevated CEA (11μg/l, normal range 5μg/l). She had been clinically asymptomatic and all surveillance investigations were reported as being normal (these included clinical examination, colonoscopy and CT scan). Initially she had undergone anterior resection of the rectum for a Dukes B adenocarcinoma in August 1998. An FDG-PET scan clearly demonstrated uptake of tracer in the pelvis, just above and behind the urinary bladder (figure 5.2). A concurrent CT scan of the pelvis was re-reported in the light of these findings and an abnormality was detected that correlated with the FDG-PET findings (figure 5.2). The abnormality was diagnosed as either a bulky or fibroid uterus.

Although the diagnosis of a uterine fibroid is unlikely in a seventy-two year old woman, the possibility of a second gynaecological malignancy had to be taken seriously. The patient underwent a second laparotomy, therefore, and an isolated 8 × 6 × 4.5 cm mass corresponding to the lesion seen on FDG-PET and CT was identified. This mass completely infiltrated the left ovary. The lesion was resected and histopathological examination confirmed a recurrent rectal adenocarcinoma. It could be speculated that CT would have picked up the presence of the tumour if follow up CT were to be performed at three months after initial discovery of the abnormality. It must, however, be noted that the CT detected abnormality was

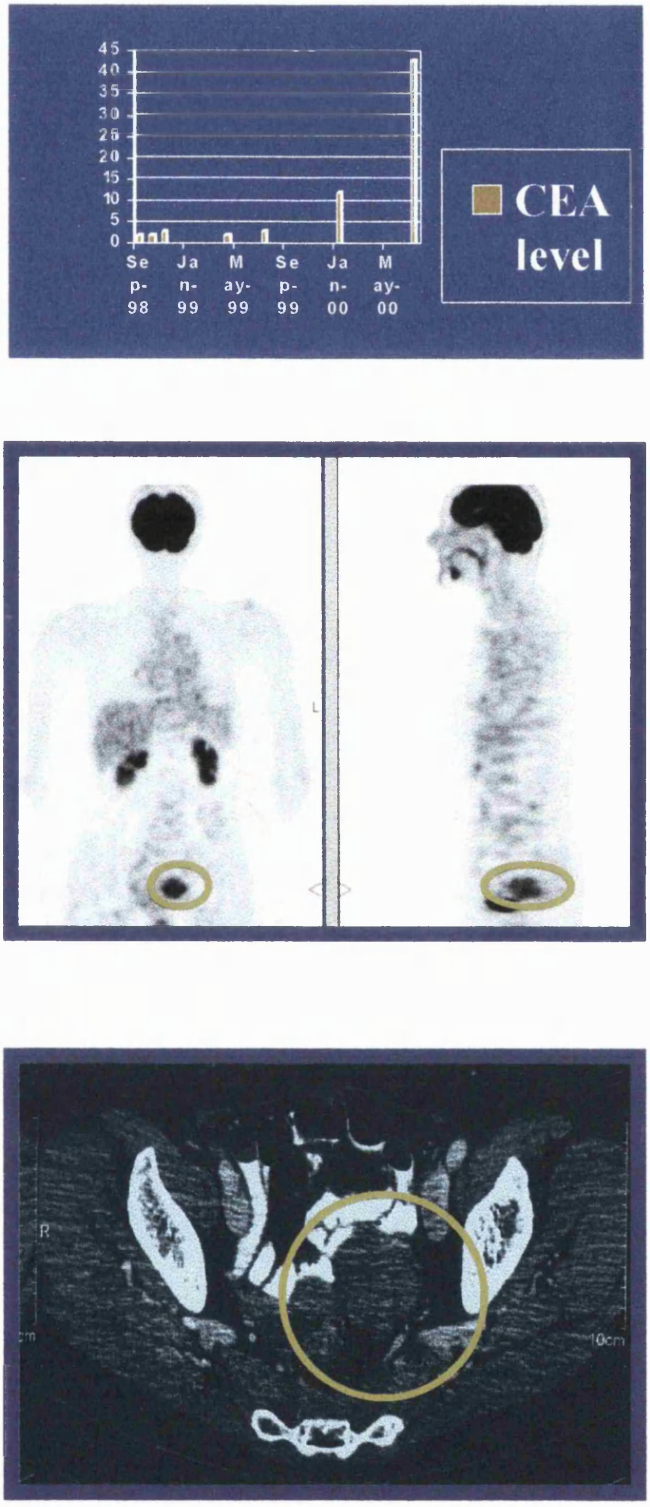


Figure 5.2 Plot of CEA against time in a patient who developed local recurrence of a rectal carcinoma. The coronal and sagittal FDG-PET (middle) show tracer uptake above and to the left of the urinary bladder in the pelvis (circle). Transaxial CT pelvis (bottom) shows an abnormal pelvic mass, the nature of which was uncertain (circled). This coincided with the abnormal area on FDG-PET and is an area of local recurrence.

prompted by FDG-PET. Furthermore, a delay of three months may have rendered surgical resection more difficult if not impossible. The benefit of the FDG-PET is, therefore, clearly demonstrated.

Incorrect FDG-PET scans

FDG-PET was extremely sensitive for detecting local recurrence and metastatic disease, but we also demonstrate that there were incorrect FDG-PET reports and I will discuss these here.

False Negative FDG-PET (n=2): In one false negative FDG-PET study a patient had a pelvic recurrence of rectal carcinoma, which was radiologically and histologically proven. The FDG-PET showed high tracer uptake that was interpreted to be in the bladder or a bladder diverticulum. SUV for this lesion was 27.8 compared to a mean SUV of 6.4 (s.d. +/- 1.70) for confirmed recurrent lesions in the pelvis. In the other patient there was no FDG uptake in a known solitary CRC liver metastasis. Treatment was not altered and the patient underwent resection. The patient had completed chemotherapy 3 weeks previously and the liver lesion, which was metabolically silent on FDG-PET was confirmed to be necrotic on histological analysis. There were no cases where CRC was confirmed, but where FDG-PET was entirely normal.

False positive FDG-PET (n=5): One patient had a false positive FDG-PET scan (figure 5.3), although CT and MRI were negative for recurrence. Eight months prior to FDG-PET, the patient had undergone anterior resection of the rectum, which was complicated by pelvic sepsis. A flexible sigmoidoscopy revealed a false inflammatory cavity in continuity with the rectum. Multiple biopsies demonstrated the presence of inflammatory tissue, which was responsible for the uptake of tracer. Another patient had a focus of borderline tracer uptake in the lung, which was suspicious on initial FDG-PET, but negative on CT and subsequent FDG-PET revealed minimal uptake. In two patients, a suspicious focus of uptake in the pelvis was negative on biopsy in one and follow up imaging in the other. The uptake was attributed to reactive pelvic lymph nodes. The fifth false positive FDG-PET was in a patient with a rising carcinoembryonic antigen (CEA) and normal imaging. FDG-PET was falsely positive

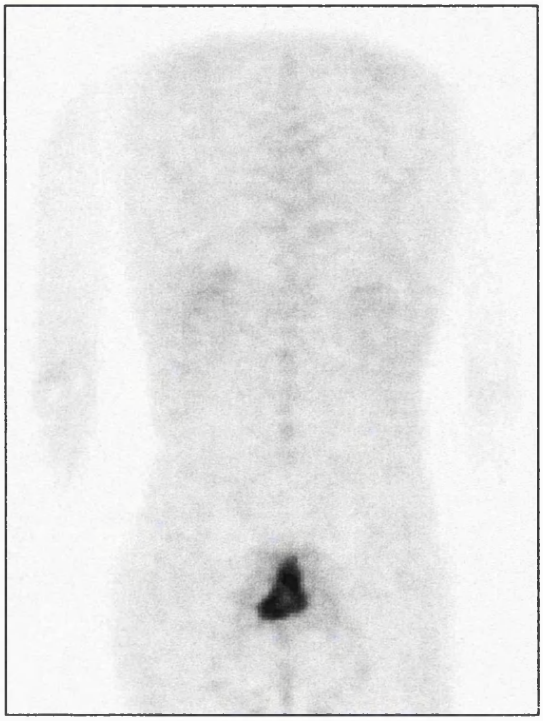


Figure 5.3 Coronal FDG-PET showing tracer uptake in the pelvis. This was not evident on CT. Flexible sigmoidoscopy and biopsy confirmed that this was a benign inflammatory area.

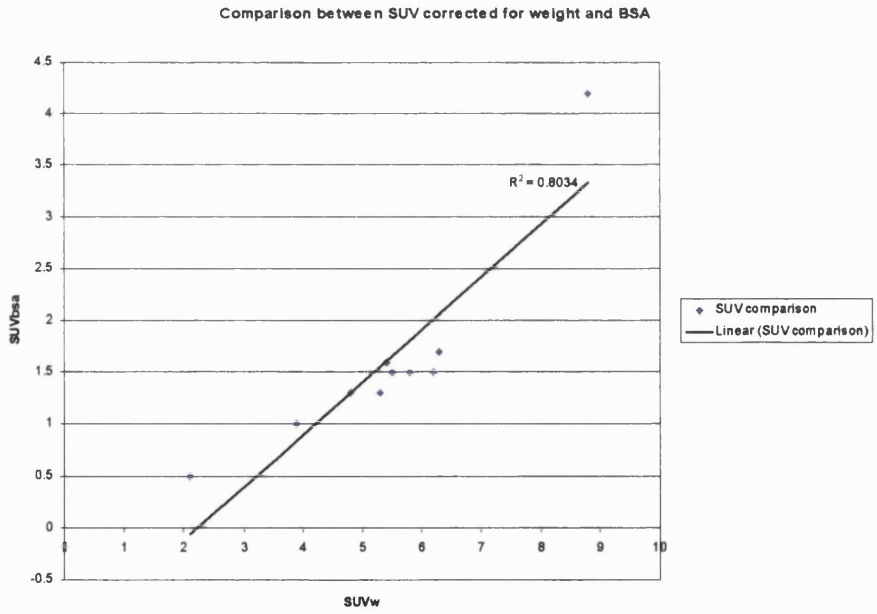


Figure 5.4 SUV_{BSA} plotted against SUV_W in patients with recurrent/metastatic CRC

for local recurrence and a lung metastasis, but this has not been proven on clinical follow up and serial imaging studies to date.

Visual analysis could be criticised as, often, normal tracer uptake is misinterpreted. The interpretation of FDG-PET scans is dependent on knowledge and experience of normal tracer biodistribution and the use of SUV is not always helpful. Interpretation may be extremely difficult when tracer uptake is borderline or inflammatory processes are present. In this study the mean SUV for recurrent pelvic lesions was 6.4 (s.d. +/- 1.70) compared to SUV of 5.1 (s.d. +/-1.73) for the four false positive pelvic lesions (table 5.3 and 5.4). The mean SUV for pulmonary metastases was 5.3 (s.d. +/- 0.87) compared to a mean SUV of 5.0 (s.d. +/-2.56) for the false positive pulmonary lesions. In both instances there is the suggestion that a cut off value could be applied for malignant lesions, but due to an insufficient spread of data this cannot yet be statistically evaluated. An SUV of 3 has been suggested in the past, but in the gastrointestinal tract variable FDG uptake means that benign lesions can have SUV's of between 5 and 10 [Delaloye and Wahl, 1995]. We corrected SUV for body surface area and showed correlation with SUV corrected for total body weight (figure 5.4). The use of SUV corrected for body surface area is, therefore, no more helpful than SUV corrected for weight in deciding if a lesion is malignant. It appears that at present visual analysis remains the preferred method of assessment in this application of FDG-PET.

Definite Pelvic recurrence		
Patient	**SUVw**	**SUVbsa**
A	6.2	1.5
B	8.8	4.2
C	5.8	1.5
D	4.8	1.3
Mean	**6.4**	**2.125**
SD	**1.704**	**1.386**
Definite lung metastasis		
Patient	**SUVw**	**SUVbsa**
E	2.1	0.5
F	6.3	1.7
G	5.5	1.5
H	5.4	1.6
I	5.3	1.3
J	3.9	1
Mean	**5.28**	**1.42**
SD	**0.867**	**0.277**

Table 5.3 SUV corrected for total body weight and body surface area in patients with confirmed local recurrence or extrahepatic metastases.

False positive in pelvis		
Patient	**SUVw**	**SUVbsa**
T	5.4	1.1
U	2.9	0.8
W	7.1	1.9
X	5.1	1.4
Mean	**5.125**	**1.3**
SD	**1.72506**	**0.469**
False positive in the lung		
Patient	**SUVw**	**SUVbsa**
Y	6.2	1.5
Z	2.1	0.5
T	6.8	1.8
Mean	**5.033**	**1.267**
SD	**2.558**	**0.681**

Table 5.4 SUV corrected for total body weight and body surface area in patients with false positive FDG-PET lesions in the pelvis and lung.

FDG-PET directed alteration in clinical management

Clinical management was altered in 11 cases. In two of these invasive investigations (CT guided biopsy of a pelvic lymph node in one patient and flexible sigmoidoscopy in the other) were initiated when in fact no disease was present (as a result of false positive FDG-PET scans). In the 9 other cases FDG-PET led to a definite diagnosis of recurrence when CT was reported as normal. This was judged to be of benefit to the patient and statistically significant ($p<0.05$).

Patient	*Diagnosis*	*CT*	*PET*	*Diagnosis Confirmation*	*Altered management*
1	*Local recurrence*	*FN*	*TP*	*H*	*Commenced local radiotherapy followed by radiofrequency ablation*
2	*Local recurrence*	*FN*	*TP*	*H*	*Resection of local recurrence*
3	*Pulmonary metastases*	*FN*	*TP*	*H*	*Recurrent disease detected and resection of lung lesions*
4	*Pulmonary metastases*	*TP*	*TP*	*C*	*PET directed chest CT, then commenced chemotherapy*
5	*Local and pulmonary metastases*	*FN*	*TP*	*C*	*Commenced chemotherapy*
6	*Local recurrence*	*FN*	*TP*	*H*	*Commenced chemotherapy*
7	*Local recurrence*	*FN*	*TP*	*H*	*Resection of local recurrence*
8	*Local recurrence*	*FN*	*TP*	*H*	*Chemotherapy commenced*
9	*Local recurrence*	*FN*	*TP*	*H*	*Resection of local recurrence*
15	*? pelvic recurrence of rectal cancer*	*TN*	*FP*	*H*	*Sigmoidoscopy and biopsy were negative for tumour cells, but positive for inflammatory cells*
16	*recurrence in a pelvic lymph node*	*TN*	*FP*	*H*	*CT guided biopsy*

Table 5.5 FDG-PET directed alteration in clinical management in patients with suspected or confirmed CRC (n=11). Abbreviations used : True positive (TP), false negative (FN), true negative (TN), false positive (FP), histological diagnosis (H), clinical and radiological confirmation of diagnosis (C). (patient number NOT related to table C5)

FDG-PET significantly altered clinical management ($p< 0.05$) for the benefit of 9 patients (table 5.5). In two other patients, FDG-PET led to invasive investigations, which ultimately did not benefit patient management. In both cases histological confirmation of the diagnosis was obtained. One of these patients had a inflammatory process in a cavity associated with the anastomotic site following anterior resection of the rectum. The second patient had a reactive pelvic lymph node.

In the nine patients where FDG-PET was of benefit, the modality detected local recurrences, which were either resected, or non-surgical treatments were commenced. These interventions would not have occurred on CT criteria alone. The final diagnosis was confirmed histologically in 7 cases and clinically and radiologically in the remaining two cases. These nine patients included 2 patients who not only had recurrence detected, but also unsuspected distant metastases.

In summary, therefore, FDG-PET was found to be more sensitive that CT for detecting malignant recurrence and metastases from CRC. Specificity of FDG-PET was problematic in my study group. Clinical management was altered for the benefit of 21% of patients in this study. Significantly, FDG-PET was demonstrably more accurate than CT for the two scenarios mentioned in the overview to this section namely differentiating fibrosis from recurrence and evaluating patients with a rising CEA and normal imaging.

5.4 Comparison of FDG-PET with spiral CT for routine follow up after surgery for primary colorectal cancer

5.4.1 Methods

Patients who participated in this study were recruited from those with confirmed primary CRC that were treated by the CRC MDT at UCLH NHS Trust. Patients underwent clinical follow up as per standard protocol at UCLH NHS Trust. This involved regular clinical examination, serial CEA measurement, colonoscopy and six-monthly CT scan. CT scans were designed to detect liver metastases as well as local recurrence in colon cancer patients. In those with rectal cancer, CT with or without MR (contrast enhanced) of the pelvis was performed. CT scan protocols are described in chapter 2. All patients underwent concurrent six-monthly FDG-PET scans for a maximum of two years or until first recurrence.

Data analysis

The detection of new metastatic lesions were classified as TP, FN, TN, and FP for each method of imaging. All diagnoses were confirmed histologically where possible; otherwise close radiological and clinical follow up was maintained. In order to assess the impact on clinical decision making the independent reports were analyses prior to presentation at the weekly CRC MDT meeting where final management was decided. The management plan directed by CT was noted and then any alteration as a result of new or different information gained on FDG-PET was documented.

5.4.2 Results

Nine patients were recruited to the study. There were 6 males and 3 females with a median age of 66 years and 11 months (range 53 years and 10 months and 86 years). The mean follow-up has been 14.5 months. Basic demographic data is detailed in table C6 (appendix C). Table 5.6, which is derived from table C6 shows the follow-up period, number of FDG-PET scans and the patients in whom new disease was detected as a result of surveillance. Also shown on this table are the false positive FDG-PET studies.

Patient	Follow-up	PETs	Recurrence or Progression	Mode of detection	False positive results (scan where fasle result was noted)
1	12	2	No	-	FP activity in both adrenals (1)
2	16	3	**Yes**	PET	-
3	18	4	No	-	-
4	14	3	No	-	FP activity (3)
5	10	2	No	-	-
6	15	2	No	-	-
7	17	3	**Yes**	Both	-
8	12	2	No	-	-
9	16	3	No	-	-

Table 5.6 The incidence of recurrence or progression of metastatic CRC in patients who previously underwent treatment of CRC. The mode of detection for recurrence/progression and false positive FDG-PET studies are shown.

The follow up has reached 18 months in one patient and it must be noted that some patients were unable to undergo FDG-PET scans at 6 months due to ongoing chemotherapy schedules. In 7 of the 9 patients no recurrence has been noted over the course of follow-up. Although, this is at the lower limit for the period when recurrences occur, we believe that both CT and FDG-PET have made the correct diagnosis. CEA did not rise in any of these patients (table 5.7).

Months	1	2	3	4	5	6	7	8	9	10	11	12	11	13	14	16	19	22
Patient 1	1		1			3		3				2						
Patient 2		3	2			3		6		4		9				14		
Patient 3	1	2		1			2				2							
Patient 4	1		1	2	3		3				5			2				
Patient 5	2		2	2	2	3	4		2									
Patient 6	2	2	2								2		2	2	2		2	1
Patient 7	12	17	16	17	14													
Patient 8	1	2			2		2	2										
Patient 9		3						3			3		3					

Table 5.7 CEA levels (ng/l) in patients who had received treatment for CRC versus time after treatment in months.

I will therefore concentrate on evaluating the two patients in whom disease progression was documented and the two patients in whom FDG-PET was false positive.

Recurrent disease detected on follow up

Patient 7:

I will discuss this patient first as the both imaging modalities detected progression of disease in a patient with previously confirmed CLM. This was detected at the second scan, which presented the first opportunity to detect this. Clearly from table 5.7 and figure 5.5 one is able to observe that CEA was grossly elevated and both modalities detected CLM. From the level of CEA this would have been predictable.

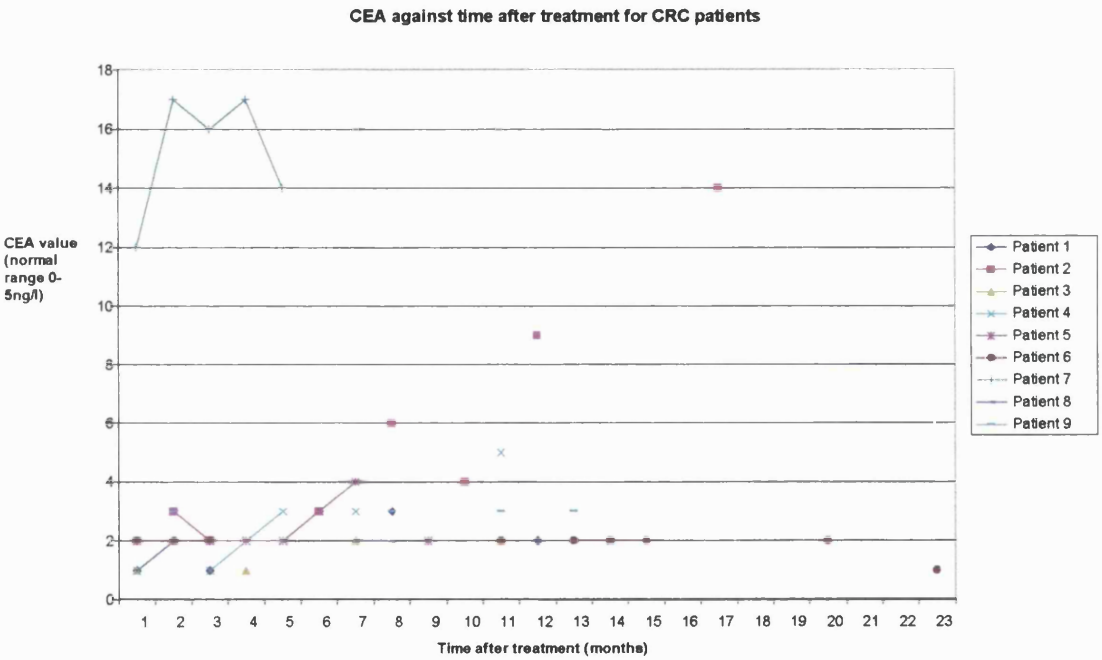


Figure 5.5 CEA levels (ng/l) in patients who had received treatment for CRC versus time after treatment in months.

Patient 2:

This case is of greater interest as there was a significant time period between FDG-PET becoming positive (scan 2 out of 3 – six months post treatment) and the CT being reported as positive. The patient underwent anterior resection of the rectum for a Dukes B adenocarcinoma of the rectum in April 2000. Although, the patient

received chemotherapy under the auspices of a clinical trial, RT was not given to the pelvis. Review of the histology shows that the circumferential margin was only one millimetre. The patient was therefore at risk of developing a local recurrence. FDG-PET performed six months after surgery confirmed that there was abnormal, malignant FDG uptake in the pelvis and in the left lung (figure 5.6). Concurrent CT and MR pelvis were reported as being negative. The findings in the pelvis were thought to be post surgical scar tissue and the lung lesion was not characteristic of a metastasis. The findings were exactly the same six months later, that is a year after surgery. At this point biopsies of both pelvic and lung lesion were carried out confirming malignant recurrence. During this time CEA gradually began to rise and a clear trend can be seen in figure 5.5 (patient 2) compared to the other 7 patients with no recurrent disease. Interestingly, this rise in CEA post dated the FDG-PET scan being positive. That is FDG-PET was positive before serum tumour markers and morphological imaging (figure 5.7).

False positive FDG-PET studies

There were two false positive FDG-PET studies. None of these patients demonstrated an elevation in serum CEA (table 5.7 and figure 5.5). In patient one the abnormal uptake in the adrenal glands was bilateral. There is no evidence that metastases are present on conventional imaging or clinically. No histological diagnosis is available, but an inflammatory process is unlikely. Abnormal uptake in metabolically active adrenal glands is possible, but there is no corroborating evidence for any pathological process. In the second patient, abnormal uptake is reported in the right iliac fossa. CT scan is negative and biopsy has not been performed due to the inability to localise pathology. This finding has occurred in the third FDG-PET study and follow up is only two months. It is therefore unclear what the true diagnosis is in this case. It may be that FDG-PET will eventually be proved correct. The patient has therefore been kept on a more intensive follow up schedule in order to detect recurrence at the earliest opportunity by conventional means.

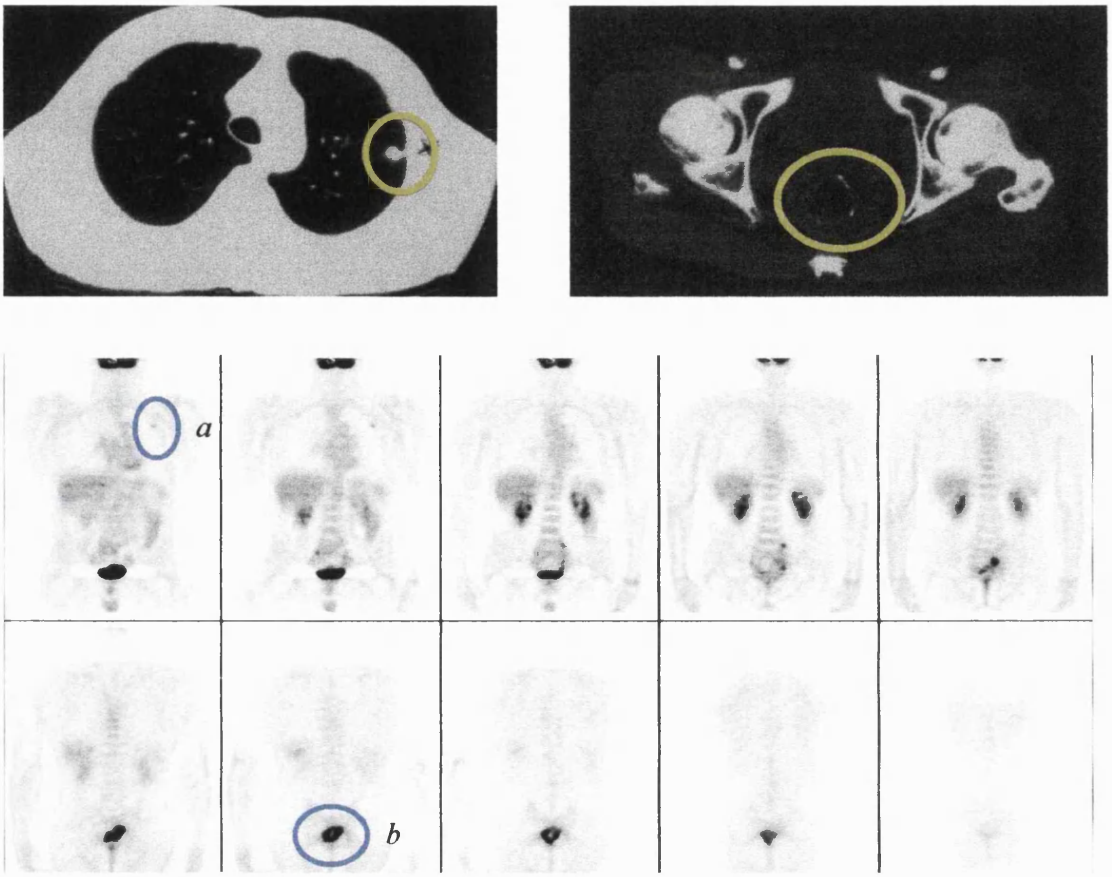


Figure 5.6 CT thorax and pelvis which show a reportedly benign lesion in the lung and an abnormal area of "fibrosis" in the pelvis around the rectum (both circled). Below is the concurrent FDG-PET showing a lesion in the lung and pelvis (a & b). Both these were malignant on biopsy.

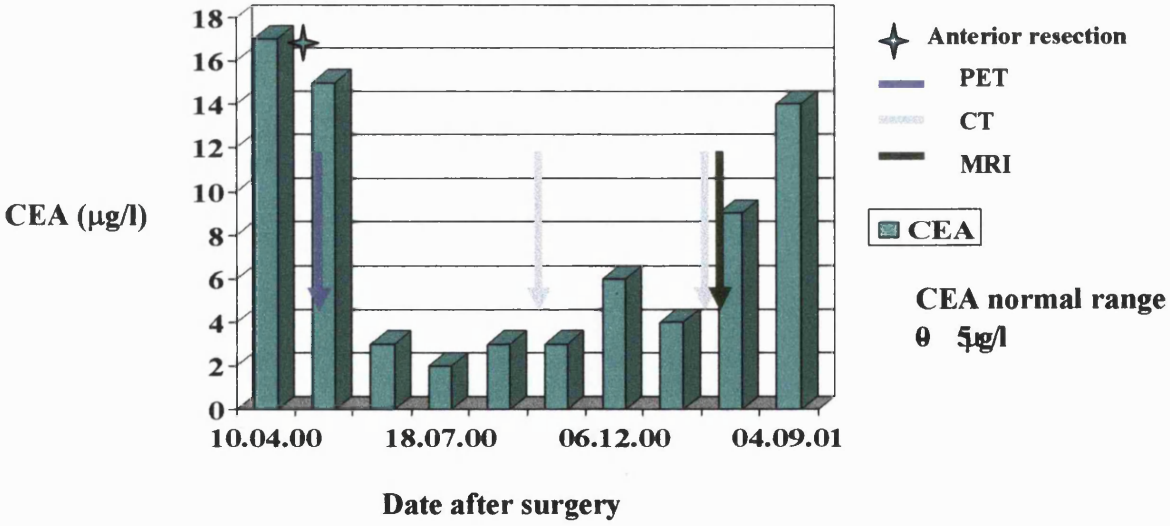


Figure 5..7 Bar chart representing serum CEA in the same patient as in figure 5.6 over time after operation. Also marked are the investigations that he underwent during this period.

5.5 Discussion

There are particular instances when anatomical imaging modalities fail to make a diagnosis with sufficient certainty. The two best examples of this are firstly, the inability of both CT and MR to differentiate post-operative /RT fibrosis form tumour recurrence (patient 16) and secondly the inaccuracy of anatomical imaging modalities to locate malignant recurrence when tumour markers are elevated (patient 23). The latter is classically seen in CRC patients who are followed up with serial measurements of CEA. This may be elevated, but all imaging is reported as normal. Both these situations are seen frequently enough to justify the evaluation of alternative techniques for making an accurate diagnosis [Flanagan et al., 1998; Renehan et al., 2002].

Once an early diagnosis is made there must be appropriate treatment options that carry sufficiently good results to justify intensive follow-up. The justification for making an early diagnosis of recurrent/metastatic CRC is dealt with in detail in the discussion to chapter 6, but currently strategies are available to treat such patients. The sceptic would say that a diagnosis of recurrence may be made, but despite intervention, the impact on outcome (survival and quality of life) would remain unchanged. This remains to be debated, but FDG-PET affords the opportunity to offer patients with recurrence or metastatic CRC treatment which previously they may not have. It is therefore, necessary to audit the outcome of such interventions. In addition to this, FDG-PET also provides valuable information on disseminated disease (chapter 6), which may contraindicate surgical intervention. It is clear that decisions regarding patient management can be made with a better knowledge of the disease that is present.

The first section of this chapter deals with the detection of recurrence/metastatic disease in patients who are suspected of the condition. The findings justify the application of FDG-PET as part of the imaging algorithm for patients suspected of recurrence on clinical grounds or as part of currently available surveillance strategies. This is primarily because the group forms a small proportion of the total number of patients who have been treated for CRC and the likelihood of recurrence is high. These findings are not necessarily applicable to the routine follow-up of patients who have been treated for CRC.

The feasibility of using FDG-PET for the routine follow-up protocol of CRC patients based on the findings that FDG-PET is more accurate than CT for detection of recurrence/metastatic disease in high risk follow-up patients is investigated in the second half of the chapter. It appears that in this small group FDG-PET is safe (i.e. no recurrences missed) and in fact in one case detection of recurrence was much earlier than with current methods. This points to a potential use for FDG-PET, but must be considered along side the high number of inexplicable false positive FDG-PET studies.

It is difficult to attribute the false positive scans to a failure of either the detector or method of reconstruction. It is well known that there is variable uptake of FDG in human tissue [Clavo and Wahl, 1996; Lindholm et al., 1993; Yao et. Al, 1995] and the reporting physician does rely on a clear differential uptake of FDG between normal and cancer tissue. In the second of the false positve cases it could be that normal uptake in bowel lumen led to a misinterpretation of the abnormal uptake. The phenomen of FDG uptake in bowel lumen is an area that clearly needs to be addressed as no published data clarifies this issue. The uptake in the adrenal glands of the first false positive patient is much more difficult to explain, but may be similar to the false positive lymph node uptake discussed below. None of the other studies looking at recurrent CRC discuss the issue of false positive FDG-PET in great depth. It must be stressed that this pilot study was in a small group and it is necessary now to consider whether the hypothesis should be tested under the auspices of a randomised controlled study.

In fact, one of the main failings of the both studies was the low specificity. In the first group, all five false positives were investigated and demonstrated a relative weakness of the technique and the importance of acknowledging that there is a learning curve associated with interpreting this data in CRC patients. All the false positives were scanned within the first 6 months of the study commencing and FDG-PET facilities were installed only 6 months prior to this. One of the main learning points was the consistent pattern of tubular FDG uptake seen after anterior resection of the rectum, especially if FDG-PET was performed within the first three months. This pattern of FDG uptake followed the curve of the sacrum and gave the appearance of a tubular structure. In fact, the signal was clearly from inflammatory cells located where

Waldeyer's fascia had been stripped during surgary. Patient 6 (table C5- appendix C) was investigated extensively to show this.

The accurate imaging of patients who have had CRC in the past is crucial if there is to be hope in reducing the deaths from recurrent CRC. FDG-PET appears to have many benefits in this application, which in conjunction with the findings of chapter 6 suggest that incorporation of this modality into management algorithms for patients with recurrent CRC may benefit patients by:

1. Early and accurate diagnosis of recurrence
2. Consideration of surgical re-intervention
3. Improved quality of life if recurrent disease that is not amenable to surgery is treated with chemotherapy

The findings of this chapter must be considered in conjunction with those of chapter 6.

CHAPTER 6

Evaluating the extent of recurrent colorectal cancer

6. Evaluating the extent of recurrent colorectal cancer

6.1 Background

Once local recurrence or metastatic CRC is confirmed management decisions are based on the extent of disease present. For instance, surgery can be successfully attempted in patients with isolated hepatic, pulmonary and rectal lesions, but best outcome in terms of survival is obtained when disease is limited and well circumscribed [Benotti et al., 1992; Zavadsky and Lee, 1994]. It is imperative, therefore, that the true extent of disease is accurately delineated from the outset. Alternative therapeutic strategies, for example radiofrequency thermoablation of CLM, may be deployed with small, but significant improvements in survival [Oshowo et al., 2002].

Most commonly CT is used as the imaging modality of choice for detecting distant metastatic disease in patients with local recurrence as well as liver and pulmonary metastatic disease. In certain instances MR may be used to assess lesions that may be equivocal on CT, but CT remains the mainstay of evaluating the true extent of recurrent/metastatic disease.

Although current imaging is reasonably accurate for evaluating the extent of spread, it is evident from the review of current literature in section 1.4, that the situation could be substantially improved. This chapter explores the feasibility of applying FDG-PET for performing this task. I have divided this analysis into two parts; the first looks specifically at the evaluation of CLM because this condition forms such a significant proportion of the clinical workload. In the second half of the chapter I concentrate on the use of FDG-PET to evaluate local recurrences and other sites of metastatic CRC. The chapter concludes with a discussion on the merits of FDG-PET used in these two clinical settings and specifically the feasibility of PET being used routinely.

6.2 Methods

Patients were selected from those referred to the CRC MDT with an interest and particular expertise in the multimodality treatment of CLM. Inclusion criteria for the study were those with confirmed local recurrence or metastatic CRC from a confirmed primary CRC. The only exclusion criterion was the presence of a contraindication to having an FDG-PET.

The MDT consisted of colorectal and hepatic surgeons, radiologists, oncologists and nurses. All patients underwent whole-body FDG-PET scan and CT concurrently as outlined in chapter two. In patients with CLM, CT of the liver, abdomen and lung bases was carried out. If the primary tumour was rectal, then patients also underwent CT pelvis. For patients with local recurrence or metastatic CRC the lesion was imaged along with a CT of the liver abdomen and lung bases if this had not already been covered. The CT and FDG-PET scans were also reported as described in chapter two and final independent reports were analysed before being presented to the MDT for a decision on clinical management.

An assessment was made as to the presence of the "index" lesion (the lesion being assessed). In addition, both FDG-PET and CT scan were evaluated for the presence of additional metastatic lesions as follows:

a) Intrahepatic (according to the Couinard classification [I-VIII])
b) Extrahepatic, intra abdominal
c) Distant metastases (specifically the lung)

The last group had the potential to bias against CT because the protocol of the study hospital MDT was for CT liver, abdomen and lung bases only. FDG-PET is a whole-body imaging modality, so if an abnormality was detected in the lungs on FDG-PET a full CT thorax was performed for comparison.

If surgery was undertaken, at laparotomy a thorough examination of the abdomen was undertaken in order to detect the presence of macroscopic peritoneal disease or lymph node involvement. The liver was evaluated by inspection and palpation for the presence of hepatic metastases, the number of lesions and the lobes involved.

Intraoperative, radiological assessment of the liver with USS was not performed. Lesions were considered inoperable if multifocal disease involving both lobes was present or if the procedure was technically difficult due to proximity/infiltration of blood vessels. In addition the presence of extrahepatic, intra abdominal disease (porta hepatis and coeliac lymph nodes or peritoneal involvement) were contraindications to resection.

Statistical analysis

The difference in the ability of FDG-PET and CT to detect recurrence and metastatic disease correctly and then to alter management was evaluated using McNemar's test for matched pairs. These were considered to be significant if $p<0.05$.

Results are presented firstly for the evaluation of CLM then for local recurrence and extrahepatic metastatic CRC.

6.3 Evaluating the extent of colorectal liver metastases

6.3.1 Results

Patient details

Fifteen patients were recruited with a median age of 67 years and 8 months (range 40years, 10 months to 77 years, 10 months). There were 6 males and 9 females. Follow up was for a mean of 16 months and diagnosis was confirmed histologically in one patient. In the remaining patients diagnosis was confirmed without doubt by means of clinical and radiological follow up and the pattern of disease. This data is taken from table C7 in appendix C.

In the fifteen patients with CLM, FDG-PET had a sensitivity of 100 per cent for detecting additional disease compared to 45 per cent for CT. Both investigations had a specificity of 100 per cent (table 6.1).

	TP	FN	TN	FP	PPV (%)	NPV (%)	Sensitivity %	Specificity %
PET	11	0	4	0	100	100	100	100
CT	5	6	4	0	40	100	45	100

Table 6.1 Results of FDG-PET and CT for detecting metastatic lesions in patients with confirmed CLM. (n=15). Abbreviations used : True positive (TP), false negative (FN), true negative (TN), false positive (FP), positive predictive value (PPV), negative predictive value (NPV). All results confirmed by histopathology and/or clinical and radiological follow up.

Four patients had truly solitary lesions, six had multiple liver metastases and five had extrahepatic metastases. FDG-PET and spiral CT both identified the four patients with solitary lesions. FDG-PET identified multiple and not solitary liver lesions in all six patients (figure 6.1), whereas CT detected only two out of the six. Spiral CT also failed to detect intraabdominal, extrahepatic metastases that were present on FDG-PET in two patients (figure 6.2). FDG-PET detected additional pulmonary lesions in three patients. This initiated further imaging of the thorax. In all cases CT of the chest

subsequently demonstrated the pulmonary metastases. At the study hospital these lesions would have been missed had it not been for the FDG-PET scan because it is routine practice to perform CT scan of the liver and lung bases only when assessing liver metastases.

Altered clinical management

In five patients with CRC liver metastases management was altered for the benefit of the patient and this was statistically significant ($p<0.05$). In a sixth patient, FDG-PET correctly detected multiple CLM whereas CT suggested solitary disease. This patient was investigated at the beginning of the study and the clinical decision of the MDT was that she should undergo laparotomy. Multiple CLM were confirmed and she underwent repeated radiofrequency thermoablation. The metastases became radiologically apparent 8 months after initial FDG-PET scan. Strictly speaking, therefore, she has not been included as a patient whose management was altered. In two patients with multiple and not solitary CLM and another with additional extrahepatic metastases, hepatic resection was avoided. In all three cases clinical course and follow up radiology confirmed the diagnosis without doubt. In one patient hepatic resection was carried out along with resection of an unexpected and histologically confirmed tumour recurrence in the appendix that was detected on FDG-PET alone. In the fifth patient FDG-PET detected a second liver metastasis in addition to what was thought to be a solitary lesion on CT. The patient was put on a more intensive imaging follow-up schedule and the second lesion became apparent within three months. The patient then underwent successful radiofrequency thermoablation of this lesion.

Patient	*Diagnosis*	*CT*	*PET*	*Diagnosis Confirmation*	*Altered management*
1	*Multiple hepatic metastases*	*FN*	*TP*	*C*	*Surgery avoided and commenced chemotherapy*
2	*Multiple hepatic metastases*	*FN*	*TP*	*C*	*Surgery avoided and commenced chemotherapy*
3	*Pelvic recurrence*	*FN*	*TP*	*C*	*Surgery avoided and commenced chemotherapy*
4	*Additional peritoneal disease*	*FN*	*TP*	*H*	*More extensive surgery carried out*
5	*Second hepatic metastasis*	*FN*	*TP*	*C*	*Resection of first (CT detected) lesion and radiofrequency thermoablation to second lesion once apparent on CT*

Table 6.2 FDG-PET directed alteration in clinical management in patients with CLM (n=5). Abbreviations used : True positive (TP), false negative (FN), true negative (TN), false positive (FP), histological diagnosis (H), clinical and radiological confirmation of diagnosis (C).

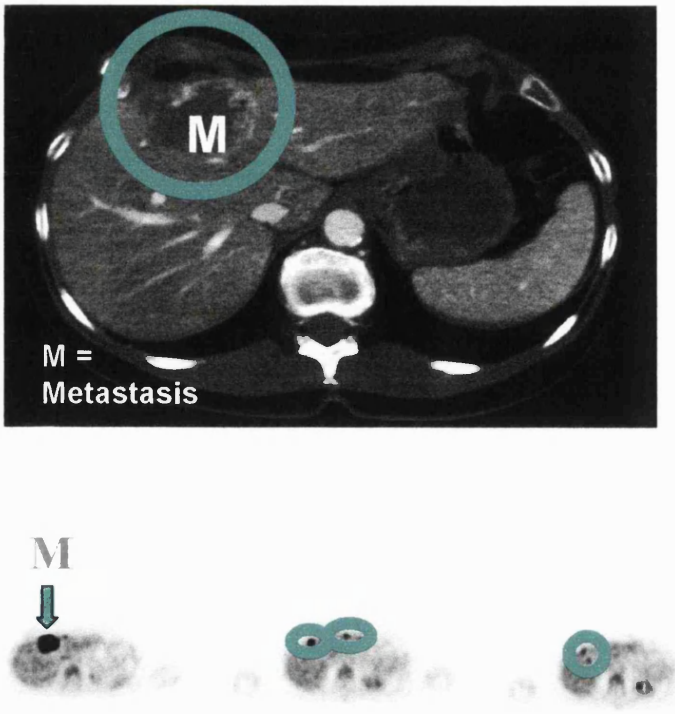


Figure 6.1 CT of the liver which shows what is thought to be a solitary liver metastasis (M). No other lesions were evident on CT. Transaxial FDG-PET scans at various levels through the liver (below) confirm the metastasis M, but show other areas of FDG-uptake (circled)

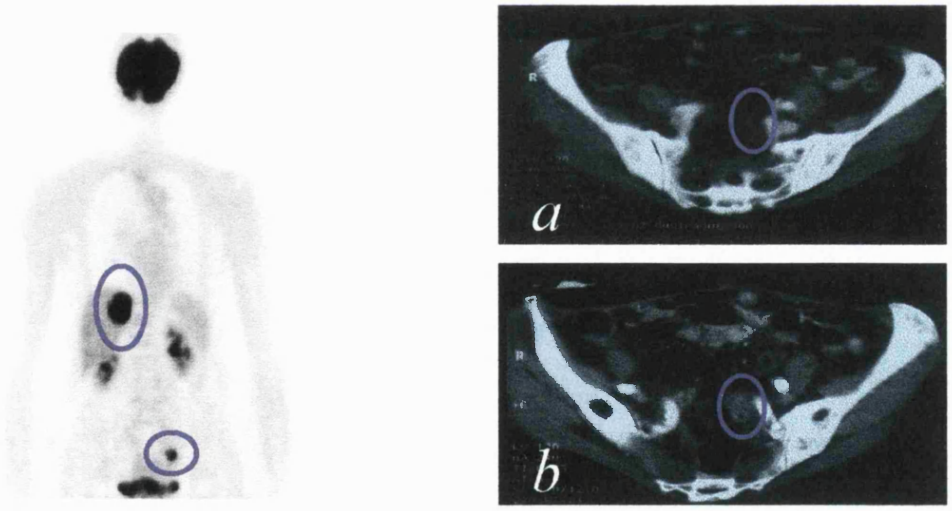


Figure 6.2 Coronal FDG-PET showing a CLM and local recurrence in the pelvis (circled on the left). Concurrent transaxial CT scan through the pelvis shows no abnormality (a), but 6 months later (b) CT does demonstrate a morphological abnormality.

6.4 Comparison of FDG-PET and CT for evaluating local recurrence and extrahepatic colorectal metastases

6.4.1 Results

Patient details

15 patients were recruited with a median age of 68 years and 8 months (range 44years, 10 months to 77 years, 6 months). There were 8 males and 7 females. Follow up was for a mean of 15.5 months and diagnosis was confirmed histologically in 4 cases. In the remaining patients diagnosis was confirmed by means of clinical and radiological follow up. This data is summarised from table C8 (appendix C)

In the 15 patients who had recurrence confirmed, eight had additional metastatic lesions. The overall sensitivity of FDG-PET for detecting metastatic disease in patients with a confirmed extrahepatic recurrence was 100 per cent compared to 75 per cent with CT. Specificity for FDG-PET was 86 per cent and 100 per cent for CT (table 6.3). In all eight patients FDG-PET correctly diagnosed the site of metastases, but CT was correct in only six (figure 6.3). The single false positive FDG-PET scan was in a patient who had confirmed local pelvic recurrence with an additional FDG avid lesion in the apex of the right lung (figure 6.4). This was diagnosed as a tuberculous granuloma and treated as such.

	TP	FN	TN	FP	PPV (%)	NPV (%)	Sensitivity %	Specificity %
PET	8	0	6	1	89	100	100	86
CT	6	2	7	0	100	78	75	100

Table 6.3 Results of FDG-PET and CT for detecting metastatic lesions in patients with confirmed local recurrence or extrahepatic metastatic CRC. (n=15). Abbreviations used : True positive (TP), false negative (FN), true negative (TN), false positive (FP), positive predictive value (PPV), negative predictive value (NPV). All results confirmed by histopathology and/or clinical and radiological follow up.

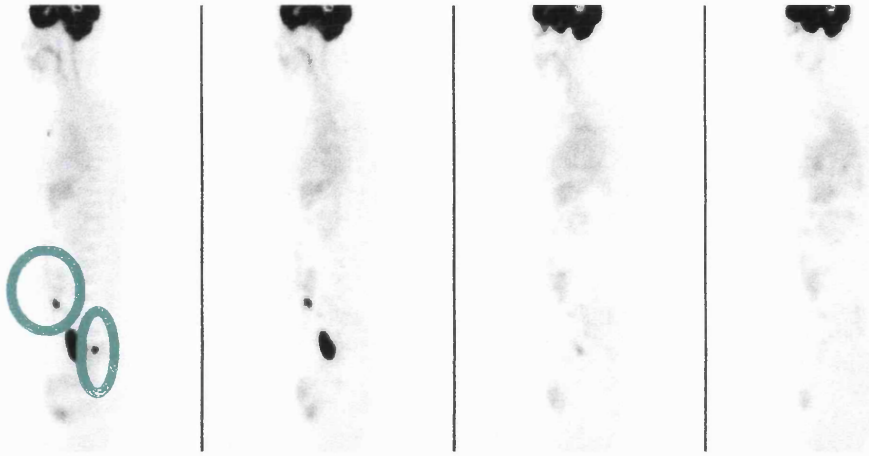


Figure 6.3 Sagittal FDG-PET scan in a patient with multiple additional metastatic lesions (circled)

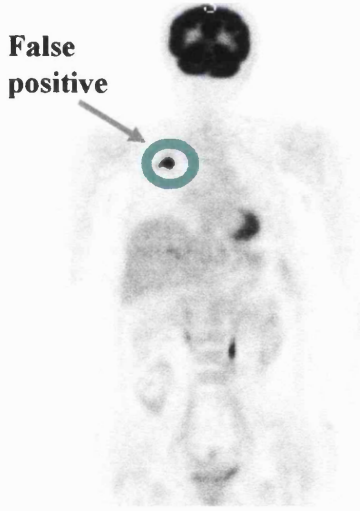


Figure 6.4 Coronal FDG-PET of a patient demonstrating a false positive region of FDG-uptake. This was in fact due to a tuberculous granuloma

Altered clinical management

In both patients who had FDG-PET positive, but CT negative metastatic lesions management was altered. In these patients consideration of surgical intervention was abandoned. In the first patient a locoregional recurrence was present in the pelvis as well as an hepatic metastasis. In the second patient extensive pulmonary metastatic disease was discovered in addition to a locoregional recurrence in the peritoneal cavity.

6.5 Discussion

In section 1.1.3 I discussed the general principles of treatment for CLM. The most important aspect of treatment is the fact that the surgeon is able to offer the opportunity of cure by performing a suitable resection. Current anatomical imaging modalities tend to be inaccurate for both detecting the presence of hepatic metastases as well as the number of lobes involved [Steele, Jr. et al., 1991]. Significantly, these failings also apply to the detection of additional metastatic lesions. If the extent of metastatic disease is accurately delineated, the 5-10% of patients who would truly benefit from surgical intervention can be selected and the remaining patients spared the morbidity and mortality associated with hepatic resection.

CLM are common, but experience suggests that local recurrence and pulmonary metastases pose equally awkward questions of the clinician. The pattern of recurrence is well documented with relapse after surgery occurring within two years [Galandiuk et al., 1992; Sagar and Pemberton, 1996]. The question of how best to treat these individuals is difficult, but data suggests that surgical resection of recurrent/metastatic disease does offer the hope of cure in 20% to 30% of cases [Barr et al., 1992; Wanebo et al., 1987]. These results indicate that a large proportion of patients are subjected to unnecessary surgical morbidity, as the intervention has no effect on survival.

Selecting those with truly isolated disease would spare those with "occult" disseminated disease and consequently a limited outcome, the morbidity of surgery as well as reduced financial cost. Alternative non-surgical strategies may be more appropriate in this group and emphasis on improved palliation could be planned from the outset. At the same time patients who would benefit most may have surgery. In

the case of recurrent rectal cancer as many as 30% of cases may occur in isolation [Turk, 1993] and therefore be suitable for curative resection. Similarly, in the case of pulmonary metastases, if disease is localised and slow growing then one would be justified in offering resection.

The accurate delineation of recurrent and/or metastatic disease is esential to the optimal treatment of individuals with CRC. This chapter clearly demonstrates the superiority of FDG-PET over CT for this task. It should be noted that the utility of FDG-PET for evaluating additional metastatic disease is most benficial for patients with CLM. This is primarily because a greater proportion of these are suitable for resection and cure. Usually, locoregional recurrences and extrahepatic metastases are discovered at an advanced stage when surgical intervention is not appropriate. Thus the clinical impact of FDG-PET on CLM is far greater as accurate detection of additional metastatic lesions may contraindicate liver resection, a costly procedure with morbidity even when carried out in the specialised centres.

The benefits of FDG-PET over CT for evaluating CLM and specifically for detecting synchronous CLM are clear, but it must be noted that the gold standard technique for assesing CLM is contrast enhanced MR. At present CT is more commonly and widely used to evaluate CLM and while it is desirable to compare FDG-PET with MR, the reported work has focused on CT.

It is interesting how many pulmonary metastatic lesions were discovered in patients with CLM. Many of these would not have been evident on CT protocol at the study hospital as full CT thorax was not mandatory. This policy has changed in the light of FDG-PET findings. It may be that I have overestimated the sensitivity of both modalities as I do not have 100% confirmation that CT and PET negative studies were infact negative other than the extent of follow up.

With regard to locoregional recurrence and extrahepatic metastases two important changes in the coming years must be considered when assessing the potential use of FDG-PET. Firstly, management of recurrent CRC is becoming the responsibility of nominated specialised centres with appropriate imaging and support infrastructure. It is, therefore, conceivable that a PET scanner could become part of this infrastructure

as the number of specialised centres will be far fewer than the number of UK hospitals. As a cost issue this is significant.

Secondly, the approach to aggressive management of recurrent/metastatic CRC is set to change because of the specialisation and consequent expertise available to deal with demanding surgical procedures. Possibly more important, however, is the fact that FDG-PET may demonstrate recurrent/metastatic CRC at an earlier stage than previously. More patients may then be suitable for surgical salvage and the selection of patients for operative intervention may a crucial.

The false positive FDG-PET study reported in this chapter indicates that the modality has weaknesses and must in the first instance be see as a complementary investigation.

In summary this chapter has demonstrated the accuracy of FDG-PET over CT for evaluating the extent of CLM as well as local recurrence and extrahepatic metastatic CRC. The clinical impact of these findings was more substantial for CLM, but this may balance out over time as more patients are potentially suitable for resection of locoregional recurrence or metastatic deposits.

CHAPTER 7

Investigation of a new PET radiotracer

7. A comparison of F18-Fluorothymidine (FLT) and FDG for PET imaging in colorectal cancer

7.1 Overview

The limitations of FDG as a tracer have been discussed throughout this thesis. I now look at a novel tracer, FLT, with a view to exploring its' potential as an agent with which to study CRC. This study is a direct comparison FLT with FDG for PET imaging in CRC.

Investigation of FLT as a clinical PET tracer necessitates characterisation of tracer dynamics as well as the study of FLT uptake in CRC tissue. FLT may also be developed for monitoring therapy response, an application that I have not attempted to cover in this work. Currently, therapy monitoring is performed using clinical examination and anatomical imaging techniques in order to measure change in tumour volume. It is accepted that changes in tumour size may take weeks to months to occur, contribute very little to predicting therapy and is only a crude means of monitoring toxic treatments.

I propose to briefly review the state of knowledge regarding FLT before setting out the objectives of this chapter. FLT is a fluorinated analogue of thymidine, which is a substrate for the synthesis of DNA; therefore, the positron labelled analogue can be used as a marker of DNA synthesis, a surrogate measure of cellular proliferation. Thymidine analogues have been successfully labelled with carbon-11[van Eijkeren et al., 1996], but the kinetics of these compounds in the body are erratic. This is because in addition to having a very short half-life (20 minutes), ^{11}C thymidine is rapidly degraded in vivo. The result is that modelling tracer uptake, distribution and washout may be inaccurate [Shields et al., 1998].

Recent progress has been made in the biosynthesis of stable fluorinated thymidine by Grierson and colleagues [Grierson et al., 1997]. The process has advanced to such an extent that the tracer FLT is now commercially available, but the available data is inconsistent especially with respect to CRC imaging [Shields et al., 2001]. Much

work remains to be done in the realm of characterising the biological activity of FLT as well as application of the tracer to clinical imaging.

Fluorothymidine

FLT (3'-deoxy-3'-fluorothymidine) is an anti-viral compound that has been investigated in the treatment of patients with human immunodeficiency virus (HIV) [Flexner et al., 1994]. This compound is rapidly incorporated into newly synthesized DNA. The metabolic pathway followed has parallels with the uptake and trapping of FDG. Initially FLT is transported into the cell and then phosphorylated by TK, specifically TK1, into FLT monophosphate (FLT-P) (Figure 7.1) [Kong et al., 1992]. The FLT becomes trapped and decays by positron emission, thus the detected activity is proportional to the activity of TK1. This in turn is related to the rate of DNA synthesis and therefore cellular proliferation. The tracer is excreted through the kidneys.

It is evident that the kinetics studied are not a direct measure of actual cellular proliferation, rather a surrogate marker of proliferation. These assumptions can be made only as a result of clear evidence of the close link between cellular proliferation and TK activity. Studies have demonstrated an approximate ten-fold increase in TK activity when cells enter the DNA synthetic phase [Sherley and Kelly, 1988]. FLT has several advantages over ^{11}C thymidine; these include an increased half-life (^{18}F has a half-life of 109 minutes) as well as being a stable compound in vivo. Metabolic modelling and characterisation are, therefore, more straightforward.

The biological characteristics of FLT

There is very little validated data on FLT for tumour imaging and there are methodological criticisms of the data that is available. There are several areas of weakness when one analyses the published data on FLT. These areas include:

1. Lack of comprehensive data for uptake, distribution and excretion of FLT against time.
2. Possible flaws in the validity for the derived SUV's in patients imaged with FLT.

3. Inability to formulate a non-invasive methodology.
4. Lack of extensive experience with FLT-PET in CRC and particularly with colorectal liver metastases.

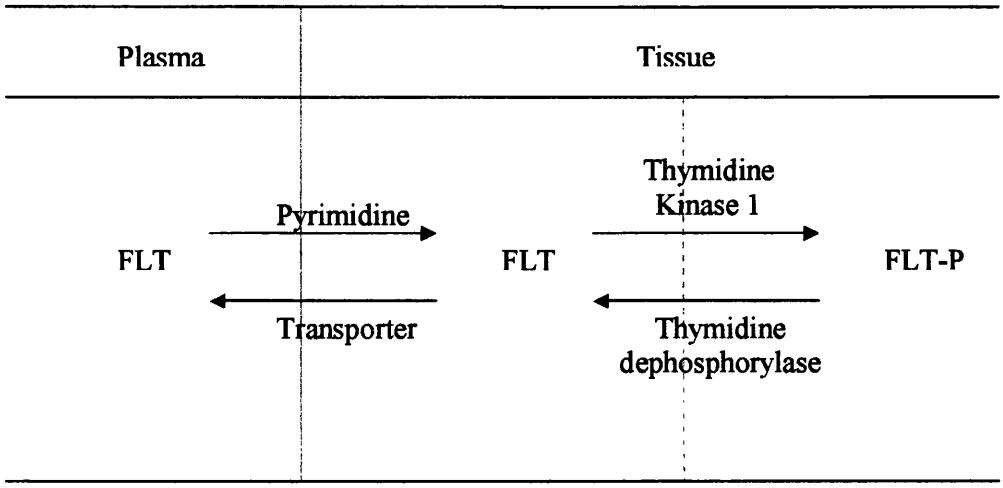


Figure 7.1 Schematic diagram showing the intracellular metabolic trapping of FLT. FLT is trasported into the cell by a pyrimidine transporter and phosphorylated by TK1 into FLT-P. FLT-P becomes metabolically trapped in a similar fashion to FDG-6-P and proceeds to decay by positron emission.

7.2 Aims

The objectives of this chapter are:

1 To characterise the uptake of FLT in CRC tissue with respect to time. This will enable FLT-PET scans to be taken at the correct time after injection so as to enable maximal differential uptake in normal and malignant tissues.

2 To correlate image derived SUV with blood derived SUV so as to establish an input function for FLT so that a non-invasive methodology can be derived for calculation of the SUV. This will mean that a validated non-invasive method of calculating SUV can be derived, which will be related accurately to tumour metabolism.

3 To establish accurate protocols for FLT-PET so that comparison of FLT-PET images with FDG-PET is valid.

4 To establish experience with FLT-PET in CRC as solid tumour model

7.3 Methods

Tracer injection and scanning protocol

Patients with CRC lesions identified by CT were recruited to the study after giving written informed consent. FDG scans were performed according to the protocol detailed below and then 2 days later FLT scans were performed. All patients gave informed consent and studies were approved by the Hospital Ethics Committee and ARSAC.

1. **Patient preparation:**

For both tracers, patients were asked to starve for 4 hours prior to the injection of tracer. Patients attended the PET suite where on arrival baseline parameters were noted. These included height, total body weight and blood glucose for FDG imaging. Patients were then cannulated using a suitable forearm vein and the appropriate tracer was injeced with documentation of the time.

The average injected dose was approximately 375 MBq for FDG and 360 MBq for FLT. FDG supply was obtained from the sources detailed in chapter 2. FLT was synthesised exclusively at the MRC cyclotron at the Hammersmith Hospital (MRC Cyclotron Unit, Hammersmith Hospital, Ducane Road, London W12 0NN). They both had a radiochemical purity of >98%. Delivery of tracer was made mid morning and calibration of the dose took place as described in chapter 2.

2. **Scanning protocol:**

Image and data acquisition was performed on the GE Advance PET scanner as previously described and was the same for both tracers. Data was acqiured in the 2D

mode. A 60 minute dynamic acquisition was performed over a single field of view of interest as identified by CT and commenced immediately after bolus injection of tracer. The location was such that multiple wherever possible lesions were included in the field of view. The dynamic acquisitions comprised of the following frame durations: 15×5s, 3×15s, 6×20s, 11×60s, 9×300s. Folowing the end of the dynamic acquisition a whole body emission scan was performed with emission frames of 5 minutes per bed position. Acquisition was carried out for 3 hours p.i. of FGD and 5 hours p.i. for FLT.

In addition whole body scans were perfomed at 60 minutes p.i. for FDG and at 60, 180 and 300 minutes p.i. for FLT.

3. Blood sampling:

Arterial and venous blood sampling was performed during FLT scanning and concentration of radioactivity in blood was measured throughout the FLT study. An arterial line was sited in the radial artery using a standard technique. The line was connected to an automated system which allowed withdrawal of a sample at precise times. Similarly, the venous cannula was connected up to the automated system; both cannulae were located in the opposite arm from tracer injection site. A series of manual discrete blood samples were taken from the radial artery and an antecubital fossa vein.Venous and arterial blood samples were collected using the following frequency: 12x8s, 4x30s, 6x60s, 4x300s, 9x600s. A portion of each sample was centrifuged and the activity concentration in blood and plasma for both arterial and venous samples was measured using a well counter which had been previously cross-calibrated with the scanner.

At certain time points larger volumes of blood were withdrawn since part of them were used for metabolite analysis. These time points were at 5min, 15min, 30min, 60min and 90min p.i.Using these samples metabolite analysis was performed using liquid chromatography.

4. Image reconstruction:

All acquired images were reconstructed using OSEM and segmented attenuation correction. All emission datasets were corrected for attenuation using data acquired with two rotating 68Ga/68Ge rod sources. The time of transmission acquisition was 3 minutes per axial field of view. Transmission data were corrected for post-injection emission contamination and processed using an unsupervised segmentation algorithm prior to its utilization for the attenuation correction of the emission data. Transaxial emission images of 4.3x4.3x4.25mm^3 (matrix size 128x128, 35 slices per axial field of view) were reconstructed using OSEM with 2 iterations and 28 subsets. All images were decay corrected to the time of the first frame of the dynamic series and both scatter and random corrections were applied.

5. Data analysis

Time activity curves (TAC's) for all the lesions as well as for a number of normal organs were derived by image ROI analysis. Image based input functions were obtained by abdominal aorta ROI's. SUV's were derived as detailed in chapter 2.

In the case of the tumours, ROIs were drawn over all identified lesions in the images. For each of the ROIs five consecutive slices were used. The slices selected were comprised from the one with the maximum count density over each volume of interest and the four immediately adjacent slices. ROIs were identified in an image created from the sum of the last three frames of the dynamic acquisition series and then were placed over the complete series. In both the FDG and FLT scans, TACs were also obtained for the liver and the bone marrow which have been identified in the past as high physiological uptake organs with FLT. In the liver, ten 20mm diameter regions were drawn in the late summed image and projected to the whole of the dynamic series. The mean of these ten average activity concentrations was subsequently calculated for each image in order to yield the normal liver TAC. For the bone marrow, three ROIs were placed in consecutive slices over the same vertebra.

The validity of using an image derived input function for FDG quantitation has been previously investigated in a number of studies, although similar work was never carried out in

the case of FLT. In both the FLT and FDG series, circular ROIs were placed over the abdominal or the thoracic aorta (AA and TA), depending on the body location where the dynamic images were acquired. These ROIs were drawn over six consecutive transaxial slices on the summed image of the frames acquired between 30s and 60s post injection. These same ROIs were then projected onto the complete dynamic datasets and TACs were subsequently derived.

7.4 Results

The data obtained for a comparison between FDG and FLT in CRC can be best represented graphically (figures 7.3 and 7.4). Coronal PET images of the patient under investigation to which the graphs of tracer uptake against time post injection (p.i.) are shown also. Eight lesions have been analysed in two patients.

Metabolites:

The metabolites measured from these patients were ^{18}F and glucuronide. Similar levels of of both metabolites were recorded in both arterial and venous samples. Approximately 80% of the parent compound was present 30 minutes p.i.. This proportion dropped to 65% at 90 minutes p.i. (figure 7.2).

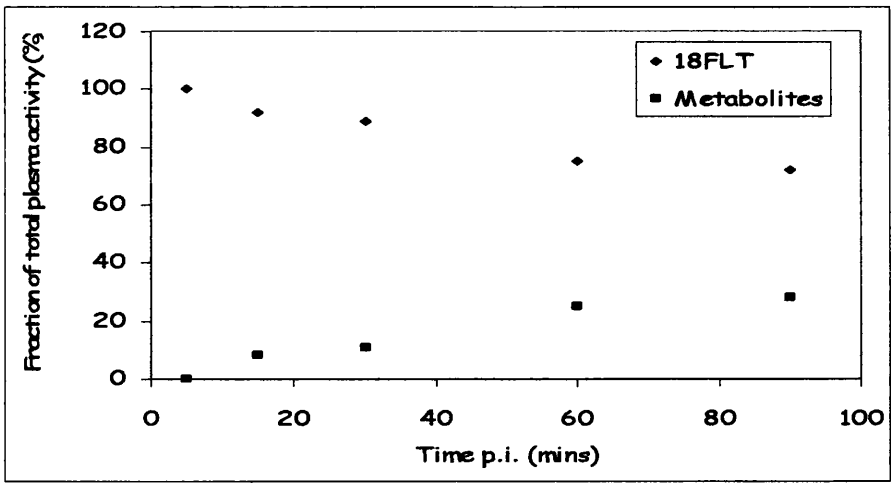


Figure 7.2 Plot representing the proportion of total plasma activity of both parent compound (FLT) and metabolites in patient with CRC undergoing FLT-PET imaging.

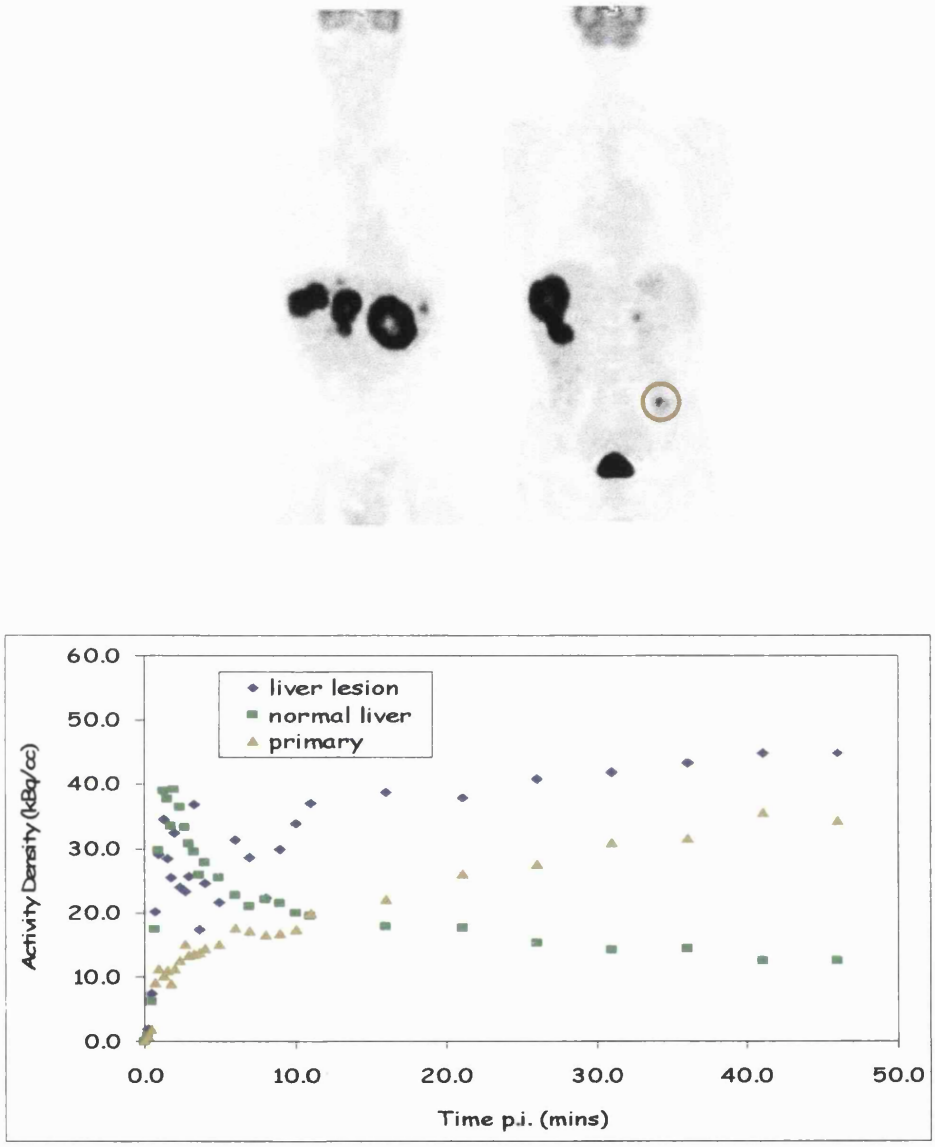
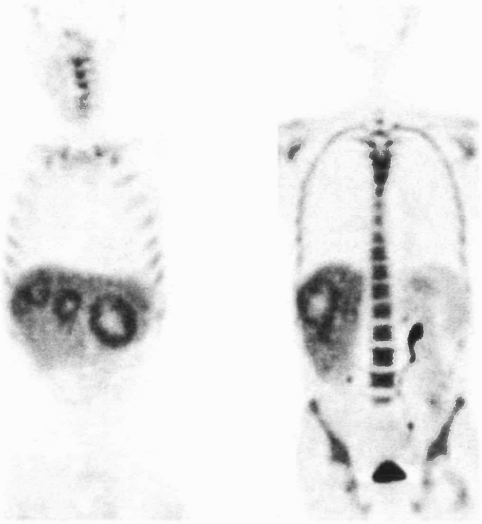


Figure 7.3 Coronal FDG-PET scan in a patient with a colonic primary (circled) and CLM (above). Below is the plot of FDG-uptake in the liver lesion (CLM), normal liver and the primary CRC.



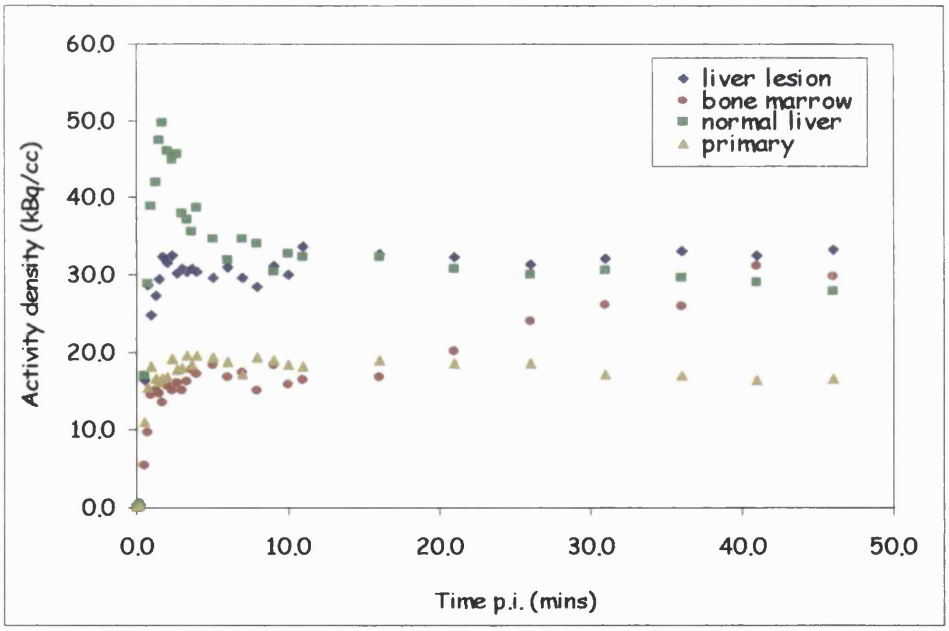


Figure 7.4 Coronal FLT-PET scan in the same patient as in figure 7.2 with a colonic primary and CLM (above). Below is the plot of FLT-uptake in the liver lesion (CLM), bone marrow, normal liver and the primary CRC.

Uptake (TAC's):

There was a rapid accumulation of FLT in all eight lesions investigated. These values are tabulated in table 7.1. Interestingly the SUV reached a maximum at 15-20 minutes p.i. for FLT compared to 40 minutes p.i. with FDG. All lesions demonstrated uniformly higher SUV for FDG. When these SUV's were analysed at 60 minutes p.i. there was a clear cut increase in SUV for FDG compared to FLT by a factor of 3-4 fold.

time(mins)	Liver lesion	Liver (normal)	Primary lesion
0	0.003933623	0.00408	0.003626667
0.25	0.257547171	0.10268	0.105173333
0.5	1.010319067	0.8364	0.249786667
0.75	2.727028278	2.3698	1.239866667
1	3.944	4.02356	1.526373333
1.25	4.712991493	5.31692	1.386746667
1.5	3.861654443	5.13128	1.485573333
1.75	3.446337651	4.55872	1.200426667
2	4.403101683	5.3312	1.515493333
2.333333333	3.247877888	4.95584	1.700453333
2.666666667	3.162623062	4.51656	2.03864
3	3.476305891	4.17928	1.817413333
3.333333333	5.002840719	4.01404	1.834186667
3.666666667	2.35473951	3.5054	1.869546667
4	3.34419884	3.77604	1.9652
5	2.936078905	3.45916	2.04816
6	4.257359571	3.08448	2.3868
7	3.899744034	2.86824	2.333306667
8	3.038692527	3.00628	2.240373333
9	4.069825478	2.9172	2.279813333
10	4.600129298	2.71252	2.35144
11	5.032	2.64792	2.717733333
16	5.2632	2.43576	2.995626667
21	5.4	2.3902	3.53872
26	5.8	2.0774	3.74272
31	6.1	1.94072	4.21736
36	6.3	1.95024	4.308026667
41	6.5	1.71156	4.854746667
46	6.7	1.6966	4.662533333

Table 7.1 (a) Uptake values for FDG against time (plotted in figure 7.3)

time(mins)	bone marrow	Liver (normal)	Liver lesion
0	0	0.001941624	0.003883249
0.25	0.08153734	0.057601523	0.044010152
0.5	0.22754508	2.214746193	2.119606599
0.75	0.34989488	3.736979695	3.715621827
1	0.758828679	5.047576142	3.194619289
1.25	2.094567655	5.426840102	3.531814721
1.5	2.07940968	6.129060914	3.80428934
1.75	1.985006821	6.434543147	4.192614213
2	2.62538662	5.968553299	4.091002538
2.333333333	1.872302895	5.811928934	4.19714467
2.666666667	1.881341374	5.90965736	3.91819797
3	2.104017896	4.905837563	3.989390863
3.333333333	2.066630867	4.815228426	3.940850254
3.666666667	1.990140617	4.619771574	3.982918782
4	2.980648921	5.022982234	3.935025381
5	3.42994884	4.481916244	3.828883249
6	3.0167577	4.132423858	4.008159898
7	3.570862773	4.492271574	3.841180203
8	3.461577053	4.416548223	3.676142132
9	4.11509959	3.940850254	4.044403553
10	4.731844984	4.234682741	3.889720812
11	5.238713676	4.180964467	4.363477157
16	5.513765594	4.190672589	4.232093909
21	5.871994042	3.975799492	4.182906091
26	7.206376845	3.885190355	4.048286802
31	7.39139516	3.969327411	4.168020305
36	8.004977909	3.839885787	4.292931472
41	8.689482789	3.751218274	4.217208122
46	9.04755197	3.597182741	4.318172589
51	9.850051272	3.5	4.4
56	10.71929825	3.3	4.5

Table 7.1 (b): Uptake values for FLT against time (plotted in figure 7.4)

Non-invasive quantitation

FDG uptake measured in the blood was correlated with uptake in the aorta as delineated on the FLT-PET scan. This is done so that a method of predicting FLT uptake without having to perform arterial blood sampling could be derived. The prelinary data presented here (figure 7.5) suggests that non-invasive quantitative methodology can be derived in order to accurately measure FLT utilisation in tissues.

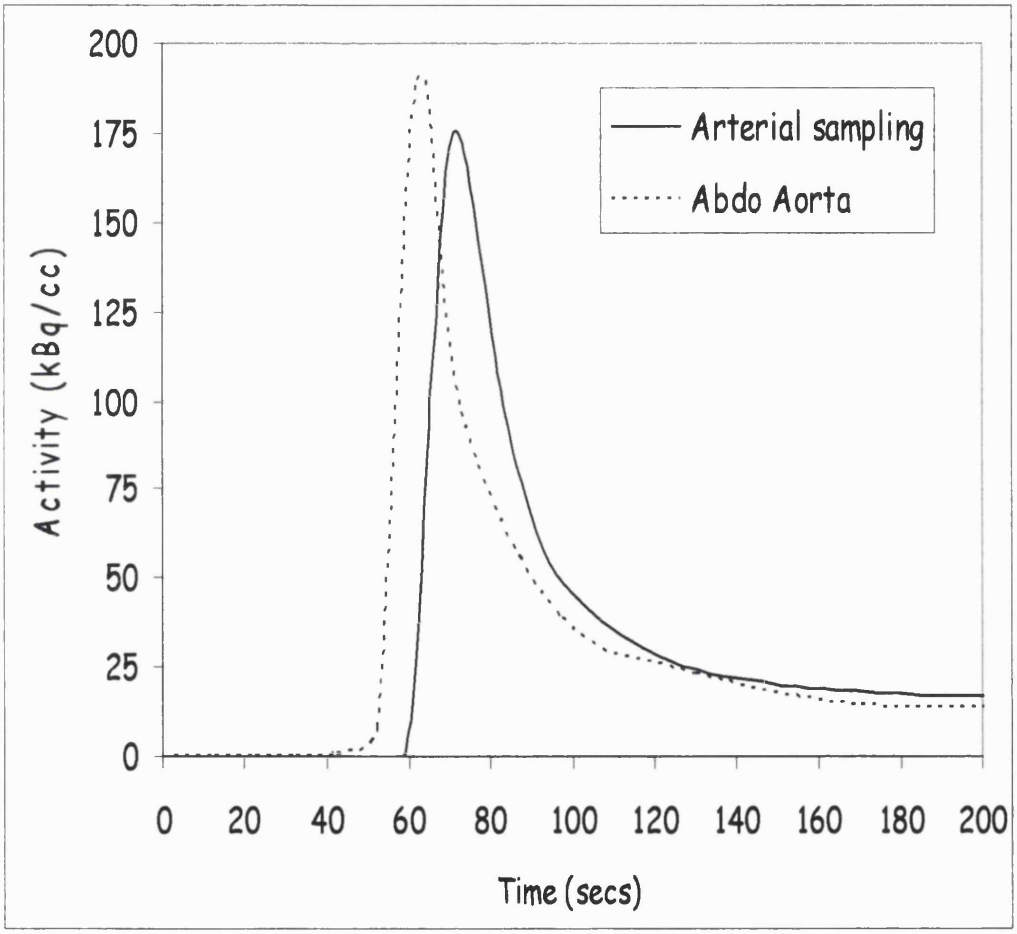


Figure 7.5 Image derived and blood sampling derived activity concentration plotted against time for FLT-PET in human subject

7.5 Discussion

Development of PET as an imaging modality relies on increasing the understanding of currently used tracers in parallel with the development of novel agents. FDG is widely used in oncological imaging and has consistently been shown to be sensitive and specific for a variety of solid tumours [Bomanji JB et al., 2001] including CRC [Huebner et al., 2000]. The information that is obtained from FDG-PET relates to the differential consumption of glucose between normal and malignant tissue. The model for FDG-PET as described in the introduction (chapter 1.3) is widely accepted, but is an oversimplification of the complex metabolism of glucose. In addition, there are other factors that have an important bearing on FDG uptake and these include tissue oxygenation and glucose utilisation, regional blood flow and the inflammatory reaction surrounding the tumour [Clavo and Wahl, 1996;Lindholm et al., 1993;Yao et al., 1995].

The fact that inflammatory lesions take up FDG may often lead to misinterpretation of FDG-PET scans as has already been described [Kubota et al., 1992;Yamada et al., 1998;Lindholm et al., 1993]. This is confirmed by the results presented in chapter five of this thesis, which demonstrates that the signal recorded from FDG may be a composite area and interfere with the specificity of FDG-PET for malignant tissue [Yao et al., 1995]. In this study, which compared FDG-PET with CT for detecting recurrence there were difficulties in differentiating tumour from active inflammation in the pelvis. This is because the FDG uptake reflects the metabolic activity of a tissue [Strauss et al., 1989] and in areas of active inflammation we know that activated macrophages will be present. These cells avidly consume glucose [Delbeke et al., 1997;Schlag et al., 1989;Strauss et al., 1989]. All the studies undertaken as part of this thesis demonstrate extremely high sensitivity for malignant tissue, but specificity is disappointing. Although, the specificity for the studies recorded here are lower than most others published [Huebner et al., 2000] it is an aspect of this technique that needs to be addressed.

Simple measures, such as increasing the experience of the reporting physician may have improve matters. This is difficult to control for, as all PET centres will go through a learning curve phase. In this chapter I have adopted a different approach by examining a new tracer, FLT.

Shields and colleagues have extensive experience with FLT and have published data on studies of one human subject with a non-small cell carcinoma of the lung and canine tumour models [Shields et al., 1998]. There is no data that demonstrates any relationship that derived SUVs will have to actual tracer dynamics. This suggests that the SUVs one derives may not relate in any meaningful way to the actual tracer metabolism in the tumour. The use of blood sampling does allow characterisation of the tracer uptake in particular tumours. I have demonstrated the relationship between SUV for FLT and FDG and this appears to be a fair reflection of tracer uptake.

Sheilds' paper sets out time activity curves for FLT in bone marrow with acquisitions up to 60 minutes. From the graphical data presented it appears that FLT uptake is still rising at 60 minutes. This suggests that the washout phase has not begun (ie equilibrium has not been reached). This washout phase will most certainly vary between different normal tissues and tumours. In humans with CRC I have demonstrated that the optimum timing for scanning is 20 minutes p.i. The use of arterial and venous blood sampling was an essential component of this study.
It is equally important to demonstrate and characterise possible metabolites in the blood contributing to the radioactivity signal. There appears to be a significant amount of parent compound at both 30 and 90 minutes.

Another important observation in Shields' paper is the high uptake of FLT in the liver (7.6 at 64 minutes). There may be significant limitations for the use of FLT in treatment monitoring of CRC. Upto 50% of CRC patients develop hepatic metastases. One of the areas that needed to be clarified is whether delayed imaging may result in high tumour to normal liver contrast. It is possible to use FLT-PET for liver imaging in patients with CRC. This study does demonstrate that the differential uptake of tracer is most marked for FDG. FDG has an approximately 3-fold increase in uptake compared to FLT. This does suggest that FDG may be a more accurate tracer for detecting CLM.

The recent interest in FLT can be gauged by analysing FLT related abstracts in the Proceedings of the 48th Annual Meeting of the Society of Nuclear Medicine (Toronto, June, 2001). There are several pertinent abstracts, none of which answer questions

that would allow a non-invasive methodology to be developed. In fact, there appears to be a need for characterisation of FLT dynamics in CRC tissue.

Vesselle and colleagues [Vesselle et al., 2001] describe a methodology for NSCLC using Patlak analysis. This was more accurate than SUV analysis for correlation with cell proliferation rate as assessed immunohistochemically with Ki-67. Dohmen [Dohmen et al., 2001b] describes studies of FLT in breast cancer with blood sampling to measure clearance and metabolites. There is a suggestion for optimal timing of imaging, but this may be quite different for CRC. The same group [Shields et al., 2001] also looked at FLT-PET imaging in a variety of gastrointestinal tumours including the colon. SUV's varied between 1.5 and 13 in colon cancer patients, which suggests SUV's will be difficult to interpret without correlation to blood measurements of FLT. Also uptake in the liver was significant, raising the question whether late imaging of the liver may be the optimal means of demonstrating metastases. However, there were no timings mentioned. This is of particular relevance for a subpopulation of patients we intend to study. Dohmen et al [Dohmen et al., 2001a] indicates that there are no FLT metabolites and there is a suggestion that equilibrium is reached at 60 minutes or so. This investigation, however, has not been carried out on CRC.

The published data suggests that invasive monitoring of arterial and venous blood is necessary. It is however, possible to derive a non-invasive input function using the thoracic aorta or heart. The difficulty with this technique is that simultaneous imaging of a distant site, for example a rectal tumour in the pelvis, and obtaining data from the chest is not possible with current PET technology. In the case of imaging CRC metastasis in close proximity to the heart, the dynamic data collected can be used to validate the use of data collection from the heart to derive an arterial input function.

In conclusion, this preliminary study with FLT in CRC shows that it can be used as a clinical PET tracer but there are limitations when compared to FDG. The tracer has a much lower uptake compared to FDG and proliferating tissues such as bone marrow show confounding uptake. This study does show that non-invasive input function for FLT can be derived and that SUV's can be related to actual tracer uptake. This study contributes to the knowledge of biological characterisation of FLT dynamics in patients with CRC.

CHAPTER 8

Conclusions of thesis

8.1 Summary of findings

Although several authors have studied the role of PET in CRC, there is little data available comparing PET with advanced spiral or multislice CT. In addition, very little has been published in the literature on the UK experience of PET in CRC. In the UK, CT is one of the most frequently used staging and surveillance investigations for CRC and it is against this background that this thesis was undertaken.

i) Primary CRC

1. FDG-PET is clearly extremely accurate for the detection of primary CRC in symptomatic individuals. FDG-PET demonstrated 100% of the CRC's in 12 patients studied. However, it is well recognised that conventional imaging modalities such as Ba enema, colonoscopy and more recently CTC are equally accurate, cheaper and more available alternatives.

2. In CRC lesions the SUV's calculated from images that were iteratively reconstructed with segmented attenuation correction and corrected for total body weight correlated with those corrected for body surface area and blood glucose. SUV_W was therefore used throughout this study.

3. The theoretical additional benefit of a metabolic imaging technique such as FDG-PET was the ability to correlate tracer uptake values to histological grade so as to predict outcome and help rationalise adjuvant therapy. The spread of data was unfortunately, not sufficient. Even in the small number of cases in this pilot study SUV's varied widely amongst the moderately differentiated adenocarcinomas.

4. Although, in theory FDG-PET should be ideal for assessing malignant lymphadenopathy in the peritoneal cavity results were disappointing. This was very much the case for the N_1 nodes, but not for N_2 nodes. In three patients out of 13 studied FDG-PET failed to detect local N_1 nodes. This can be explained by the fact that the proximity of the primary tumour and FDG-uptake in this region affected the ability to practically differentiate

lymph nodes from primary tumour. Both modalities were equally poor for staging primary disease, particularly malignant lymphadenopathy.

5. This was certainly not the case when assessing the liver for CLM. Overall, the sensitivity of FDG-PET for detecting additional metastatic lesions compared favourably with CT (67% vs 29%). Specificity for both modalities was similar if not slightly better with CT (75% with FDG-PET and 88% with CT). In 2 patients CLM were detected by FDG-PET, but not CT. This is an important consideration when trying to offer definitive and curative therapy to a patient with CRC. The benefits of CLM detection are at odds with the poor detection of malignant lymphadenopathy in the peritoneal cavity. A clear answer as to whether this technique adds significantly to the clinicians diagnostic power is not clarified.

6. The issue of asymptomatic CRC and the ability of FDG-PET to screen for occult CRC was not directly tackled in this thesis. Published literature [Yasuda et al., 2000] suggests that this technique has significant weaknesses for untargetted screening. However, it is possible to detect colonic adenomas [Yasuda et al., 2001] and intriguingly we were able to demonstrate this phenomenon.

ii) Recurrent and matastatic CRC

7. The ability of FDG-PET to detect both recurrent and/or metastatic disease combined with accurate assessment of any additional metastatic disease is clearly shown. Sensitivity and specificity for detection of recurrence are 93% and 58% with FDG-PET compared to 73% and 75% with CT. Sensitivity and specificity for detection of additional metastatic lesions with FDG-PET were 100% and 100% for CLM and 100% and 86% for extrahepatic disease. The figures for CT were 45% and 100% for CLM and 75% and 100% for extrahepatic disease. What is interesting is that the diagnoses tend to be made earlier and extent of disease is accurately delineated. This means that patients who are suitable for surgical re-intervention may be offered this treatment. Equally if not more important is the ability of FDG-PET to direct the clinician away from inappropriate

laparotomy and this benefit is particulary seen for the substantial number of patients who develop CLM.

8. The findings in chapters 5 and 6 must be considered against disappointing specificity for FDG-PET. This could be accounted for by the misinterpretation of a signal emanating from a metabolic active, but benign source. The commonest cause for this is inflammatory tissue.

9. Another interesting finding was the fact that FDG-PET, when used as the routine follow-up investigation for treated CRC patients, did not miss the recurrences that did develop, but also confirmed the diagnosis significantly sooner in one patient (one year). There were 2 false positives, however. This finding begs the question should clinicians be looking for recurrence using a metabolic signal rather than morphological imaging and/or tumour markers. It seems reasonable for FDG-PET to be used to direct morphological imaging once an abnormal signal is detected.

iii) FLT

10. There are weaknesses with FDG that have been discussed. The study to evaluate a novel tracer aimed to establish a body of data so that these two tracers could be compared directly in CRC. The data in chapter 7 illustrates the process involved for studying a new tracer. Time activity curves for both FDG and FLT show that tracer uptake is maximal at 15-20 minutes post injection for FLT compared with 40 minutes post injection for FDG.

11. The tissue characteristics for FLT metabolites (^{18}F and glucuronide) have been studied. Upto 75-80% of the parent compound was present 30 minutes post injection and 65% at 90 minutes post injection.

12. There was correlation between image derived uptake values and those from arterial blood. This data suggets that it would be possible to calculate a non-invasive input function, which may be invaluable for future clinical studies. All FLT data is pilot data and part of an ongoing project that will

establish the characteristics of FLT in patients with CRC with primary, recurrent and metastatic lesions. The data obtained and presented in this thesis forms the basis for this project.

8.2 Implications of findings

- There does not appear to be a role for the routine use of FDG-PET in assessment of patients with primary CRC. The data presented here along with the current published literature would suggest that this is, however, an area that requires further investigation. The specific aspects of this clinical problem that need clarifying are whether FDG-PET does, in fact, correlate with histological features and clinical stage of the primary CRC. To answer this question a large, multi-institution study with extended follow-up would be required. The second aspect of FDG-PET in primary CRC that needs to be assessed is its' potential use as a screening modality.

- The role of FDG-PET in recurrent CRC now has a substantial basis and FDG-PET is able to confer many benfits to the patient and clinician through altered clinical management. The next step would be to incorporate this modality into clinical management algorithms and study the effect on survival. The studies described in Renehan's recent systematic review and meta-analysis [Renehan et al., 2002] assess the value of various investigations (including CT) and protocols and their impact on survival for treated CRC patients. A study should now be conducted comparing FDG-PET and other follow up protocols in CRC patients who have been treated. A specific aspect of this subject should address the question whether FDG-PET should be the primary investigation for follow up. Earlier diagnosis by FDG-PET may lead to the administration of a treatment (medical or surgical) at a stage that was not previously possible. Actual impact on survival, both of the findings of FDG-PET and the subsequent intervention, as well as lead time biases can be studied.

- The study of FLT is limited to two patients and this data should form the basis for gathering data on a significant number of patients with CRC. This will help clarify the role of this tracer in CRC imaging.

8.3 Ongoing developments and future perspectives

i) Experimental research

1. As with any radionuclide tracer technique, PET will evolve as the tracers available develop. A number of new tracers with clinical potential will and are being developed. One or more of the ^{18}F labelled thymidines presently being developed offers such promise.

2. The subject of subclinical treatment response for chemotherapy and radiotherapy is not addressed in this thesis because the focus of this study is PET for detection and staging of CRC. The use of PET for treatment monitoring should form the basis of an investigation in its own right. The major impact on clinical practice will be that those who may not respond or who start treatment and are not benefiting in terms of tumour regression can be switched to alternative treatments or be spared the morbidity.

3. The study of new pharmacological agents may now be studied in vivo using animal micro-PET cameras. This has particularly important implications for novel oncological agents especially those directed at cell signalling pathways or gene therapy. The prospect of molecular imaging is therefore a practical reality.

ii) Clinical issues

4. PET is an expensive modality with high start up costs needed to establish tracer production and distribution, purchase hardware and software and train staff. There are approximately 200 PET systems in clinical use in the United States where state-of-the-art PET systems cost $800,000 to $2.5 million. In

the UK, PET systems cost between £1-1.5 million. The overall cost of a whole body FDG-PET is approximately £800 per study, of which £350 is spent on a single dose of FDG. The cost of a spiral CT of the abdomen and pelvis is £350. There is a body of evidence established for the use of FDG-PET in the assessment of recurrent CRC mainly because FDG-PET leads to alteration in clinical management [Lai et al., 1996;Delbeke et al., 1997;Valk et al., 1999], for example surgery can be avoided due to the identification of non-resectable tumour. Valk et al [Valk et al., 1996] studied patients with lung cancer (99 patients), recurrent CRC (57), melanoma (36), and head and neck cancer (29) and found that the savings from contraindicated surgical procedures exceed the cost of PET by ratios of 2:1 to 4:1 depending on the indication. This same group also studied 115 patients with recurrent CRC and showed that the potential saving from the demonstration of non-resectable tumour by PET was approximately $3000 per preoperative study [Valk et al., 1999;Valk et al., 1996]. These studies demonstrate significant cost savings similar to those seen for FDG-PET used to assess solitary lung nodules [Gambhir et al., 1998] and must be considered when looking at the true cost of PET. Analytical cost modelling is now essential if clinical implementaion of PET is to take place.

5. Significant progress is to be expected with PET and other cross-sectional imaging modalities. Instrumentation is developing and multimodality imaging, using a single instrument, is a reality with CT and/or MR combined PET scanners and PET capable gamma cameras coming onto the market. The aim is to increase the accuracy of image registration, between cross-sectional imaging modalities, which offer detailed anatomical information (CT/MR) and functional imaging techniques (PET), which offer metabolic information.

   The quality of this detector technology comes at a price. The production cost is approximately 50% of the total cost and efforts by the manufacturers are concentrated on lowering these. By removing two thirds of the detector ring, the cost is reduced by 50%, but the sensitivity is also reduced to around to 80%. These rotating partial ring BGO PET detectors are practical alternatives to the full ring, multicrystal BGO PET.

6. Another development that is a compromise of the best that BGO PET has to offer is a change in detector design. Photo-multiplier-quadrant sharing and a convertible geometry combine to give a system which is flexible. There are gaps in the BGO detector ring, which reduces cost at the expense of overall sensitivity. However, when applied to image small objects the field of view can be shrunk using the convertible geometry, thus bringing the detectors together. This camera now acts as a full ring system and has increased detection sensitivity. This property is conversely lost when imaging bigger objects. Resolution of a prototype camera is around 3mm.

7. Advances in detector materials continue also. A combined SPECT/PET camera has been developed using lutetium orthosilicate (LSO) crystals for coincidence imaging that are positioned behind NaI (T1) crystals for SPECT. This combined detector has a much higher sensitivity for 511KeV photons and it combines features of the photomultiplier quadrant sharing technology, which further reduces cost. In addition LSO can count six times faster than NaI (T1).

These developments illustrate the drive from industry as well as clinicians to improve the instrumentation available. A realistic target for practical image resolution is 3mm and this is achievable. Experimental cameras designed for animal imaging have demonstrated resolution of 1.5 to 2mm using ^{18}F tracers.

From the outset the primary objective has been to evaluate functional imaging against morphological techniques in CRC. The findings suggest that even though some drawbacks exist with PET, there is a case for incorporating this modality in certain applications for imaging CRC. This applies to the technology currently available to the clinician and the prospect of future developments heralds a most formidable clinical imaging tool. The major philosophical shift for the oncologist, both surgical and medical is to incorporate metabolic data from the CRC being studied to other clinical and imaging parameters. FDG-PET augments the information from conventional modalities and can be applied in practical terms for the benefit of patients.

Appendices

Appendix A

Guidelines issued by the Department of Health (England and Wales) for urgent referral of patients with symptoms of CRC

Incidence: About 30,000 cases per year

Age: 99% aged >40 years
85% aged >60 years

Primary symptoms:

- Rectal bleeding persistently without anal symptoms
- Change in bowel habit – most commonly increased frequency and/or looser stools persistently for at least 6 weeks

Secondary effects

- A significant iron deficiency anaemia
- Clear signs of intestinal obstruction

Clinical examination

- A definite right sided abdominal mass
- A definite rectal (not pelvic) mass

The criteria for urgent referral set out in the following section should identify 90% of patients with bowel cancer

Colorectal cancer: Guidelines for urgent referral

It is recommended that these symptom and sign combinations WHEN OCCURING FOR THE FIRST TIME should be used to identify patients for urgent referral under the two week standard.

	Age threshold
• Rectal bleeding with a change in bowel habit to Looser stools and/or increased frequency of defaecation persistent for 6 weeks.	All ages
• A definite palpable right-sided abdominal mass.	All ages
• A definite palpable rectal (not pelvic) mass.	All ages
• Rectal bleeding persistently WITHOUT anal symptoms*.	Over 60 years†

- Change in bowel habit to looser stools and/or increased frequency of defaecation, WITHOUT rectal bleeding and persistently for six weeks. Over 60 years[†]

- Iron deficiency anaemia WITHOUT an obvious cause (HB < 11g/dl in men or < 10 g/dl in postmenopausal women

NB. Patients with the following symptoms and no abdominal or rectal mass, are very low risk of cancer:

- Rectal bleeding with anal symptoms*.

- Change in bowel habit to decreased frequency of defaecation and harder stools.

- Abdominal pain without clear evidence of intestinal obstruction.

*Anal symptoms include soreness, discomfort, itching, lumps and prolapse as well as pain.

[†] Age 60 years is considered to be the maximum age threshold. Local Cancer Networks may elect to set a lower age threshold (eg 55 years or 50 years).

Appendix B

Protocols, Patient information sheets and consent forms

1. Protocols

The role of Positron Emission Tomography (PET) in the Pre operative Assessment of Colorectal Cancer

Research Protocol:

Pre operative assessment in patients with primary colorectal cancer

The objective is to determine whether pre operative investigation using FDG-PET (2-F18-fluoro-2-deoxy-D-glucose) gives superior information regarding extent of primary disease and distant spread when compared to spiral CT. If PET is shown to be superior in detecting micrometastasis then surgical management as well as pre and post operative adjuvant therapeutic strategies will be influenced.

Patients will be studied over a two year period and be recruited from the pool of patients referred to the Department of Surgery for treatment of colorectal cancer. We aim to recruit 40 patients over the period of the study.

Inclusion criteria:

Confirmed diagnosis of cancer of the colon or rectum
Cancer suitable for curative resection
Informed consent

Exclusion criteria:

Patients who are unable to give informed consent
Patients who are unable to undergo PET scan

Each patient will undergo the following investigations:

i) Spiral CT scan (abdomen & pelvis)
ii) FDG-PET scan (whole body)

Patients will have a spiral CT scan as part of their routine investigation prior to admission to hospital for surgery and not more than four weeks previously. It is routine practice to perform spiral CT of the abdomen and pelvis as well as a chest x-ray. If a liver metastasis is found then spiral CT of the chest is performed. Patients are admitted to hospital two days before surgery so that they can undergo pre anaesthetic assessment and bowel preparation. On the day before surgery patients will starve for a period of four hours (and must not have intravenous glucose in any form). They will then be taken to the institute of Nuclear Medicine where they will be given an intravenous injection of radiolabelled glucose (FDG) through a cannula sited in an

arm vein prior to scanning. Following the injection of FDG the patient will lie on a platform in the PET scanner. The scan information is acquired over the course of an hour. The patient will then return to the ward and prepare for and proceed to surgery in the usual way. Full details of history and examination will be available for documentation as well as serum tumour markers, however, CT and PET scans will be reported blind and double read.

Information required from the CT scan and PET scan:

i) The position of the tumour
ii) The size of the tumour
iii) The extent of spread of the tumour -with particular note made of
a) liver abnormalities
b) suspected lymphadenopathy

CT's will give the radiological TNM stage. Please refer to the two algorithms attached. Treatment given will be routinely directed by the clinical findings and spiral CT. If an abnormality is found on PET and not on CT then in all cases a policy of observation will be adopted unless there is concurrence at laparotomy (for example, the detection of liver lesions) when appropriate biopsies and treatment will be initiated as standard practice in the Department of Surgery.

At Operation:

The operating surgeon will perform a thorough laparotomy and note the following:

i) The position of the tumour
ii) The size of the tumour
iii) The extent of spread of the tumour -with particular note made of
a) liver abnormalities
b) suspected lymphadenopathy

Surgery will be directed at the primary tumour and draining lymph nodes. If unexpected liver lesions are discovered appropriate biopsies and treatment will be initiated post operatively, once histology is available. The resected specimen will then have a fragment removed from the main cancer as well as from surrounding normal tissue (greater than 5cm away). The main specimen will be processed by the Histopathology Department.

Post operative surveillance:

Patients will be followed up as per the protocol in the Department of Surgery. Over the period of the study and for at least two years note will be made of survival and recurrence rate.

Analysis:

Correlate: 1. Spiral CT and PET with each other and with operative findings.

These results will then be related to the following.

1. Histological stage and grade
2. Tumour markers
3. Survival and recurrence

The role of Positron Emission Tomography (PET) in the follow up of patients with a history of colorectal carcinoma

Research Protocol:

The objective is to assess whether FDG-PET (2-F18-fluoro-2-deoxy-D-glucose) is a more specific and sensitive method of following up patients who have been treated surgically for colorectal cancer than the methods currently available.

Patients will be studied over a period of two years from those treated surgically for colorectal cancer in the Department of Surgery. We aim to recruit 40 patients over two years.

Inclusion criteria:
Patients previously diagnosed with colorectal who have undergone operative treatment.
Full informed consent.

Exclusion criteria:

Patients who are unable to give informed consent
Patients who are unable to undergo PET scan

Each patient will undergo the following investigations:

i) Spiral CT scan every 6 months (abdomen)
ii) FDG-PET scan every 6 months (whole body)
iii) Serum carcinoembryonic antigen (CEA) level measurement (every 3 months).

Patients who have undergone operative treatment for colorectal cancer will be followed up as per the Department of Surgery protocol (i & iii). In addition they will have an FDG-PET scan every 6 months over a two year period.
Full details of history and examination will be available for documentation as well as serum tumour markers, however, CT and PET scans will be reported blind and also double read.

If an abnormality is discovered on spiral CT or PET scan the patient will follow the algorithms attached. Treatment will be directed by clinical findings and CT scans. If there is an abnormality detected on PET but not on spiral CT a policy of observation with CT and PET will be followed. If PET is positive and CT equivocal then an alternative to imaging follow up will be a biopsy. Recurrences in the pelvis will be investigated by MRI if detected by PET or CT. If the recurrent cancer is amenable to operative treatment the patient will proceed to surgery and the steps outlined below will be followed. These cases should be in the minority. If an elevation is noted on routine CEA measurement the patient will undergo spiral CT and PET scan. They will then follow the algorithm for each imaging modality.
In some patients a biopsy may be offered if CT is equivocal and PET positive or if indicated under the normal policy of the Department of Surgery on clinical grounds. If a patient declines a biopsy or is unable to have a biopsy performed then the patient will be treated on clinical grounds as determined by the multidisciplinary team as well as being followed up with 6 monthly spiral CT and FDG-PET.

Information required from spiral CT and FDG-PET:

i) The position of the recurrence
ii) The size of the recurrence
iii) The extent of spread of the tumour -with particular note made of
a) liver abnormalities
b) suspected lymphadenopathy

CT criteria for metastases are : Typical appearance
Growth on CT
Concordance

If a patient does proceed to surgery they will undergo the following steps:

At Operation:

The operating surgeon will perform a thorough laparotomy and note the following:

i) The position of the tumour
ii) The size of the tumour
iii) The extent of spread of the tumour -with particular note made of
a) liver abnormalities
b) local spread

The resected specimen will then have a fragment removed from the main cancer as well as from surrounding normal tissue (greater than 5cm away). The main specimen will be processed by the Histopathology Department.

Post operative surveillance:

Patients will be followed up as per the protocol in the Department of Surgery. Over the period of the study and for at least two years note will be made of survival and recurrence rate.

Analysis:

Correlate:

1. Spiral CT and PET with each other
2. CT and PET with levels of CEA.
3. The above with survival and recurrence

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Patient Information Sheet

The Role of Positron Emission Tomography (PET) in the Pre operative Assessment of Patients with Colorectal Cancer

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Other Investigators:

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Mr. T.H.A. Arulampalam	**Department of Surgery**
Ms. B. Lovett	**Department of Surgery**
Dr. D.C. Costa	**Institute of Nuclear Medicine**
Dr. J. Bomanji	**Institute of Nuclear Medicine**
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Dr. A. Gillams	**Department of Radiology**

If you have any queries regarding this information sheet, please contact the Mr. T.H.A.Arulampalam in the Department of Surgery on **0207-679-9312**

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Patient Information Sheet

The Role of Positron Emission Tomography (PET) in the Pre operative Assessment of Patients with Colorectal Cancer

You are invited to take part in a research project. You do not have to take part in this study if you do not want to. If you do decide to take part you may withdraw at any time without having to give any reason. Your decision whether to take part or not will not affect your care and management in any way. All proposals for research using human subjects are reviewed by an ethics committee before they can proceed. This proposal was reviewed by the joint UCL/UCLH Committees on Ethics of Human Research.

1. This study aims to establish if positron emission tomography (PET) scans are better than conventional computerised tomography (CT) scans at detecting the extent of spread of bowel cancer.

2. It is routine practice to perform a CT scan and blood tests prior to surgical treatment of bowel cancer. These tests aim to detect the extent of spread of cancer cells from the main tumour in the bowel. The information from these tests and laboratory analysis of the tumour after it is removed gives doctors the necessary information with regard to microscopic spread. This will allow the most appropriate treatment to deal with an individual patients cancer to be chosen. The information, therefore, influences the extent of surgery performed and possibly the use of other treatments such as chemotherapy or radiotherapy.

3. Some patients may develop a recurrence of the cancer due to the presence and spread of microscopic cancer cells. If PET scans are shown to detect microscopic spread earlier than current tests the treatment chosen may be altered accordingly This may result in fewer patients developing a recurrent cancer. Patients who take part in this study will have a PET scan (described below) in addition to normal treatment. This will not directly affect the treatment for your cancer.

Description of the research study:

Prior to your admission to hospital for surgery you will undergo a CT scan and blood test (to measure a marker of your cancer in the blood called carcinoembryonic antigen (CEA)). These tests are part of the normal preparation for surgery. You will be admitted to hospital two days prior to your operation in order to prepare your bowel for surgery. On the day before your surgery you will have a PET scan in the Institute of Nuclear Medicine in the Middlesex hospital. The procedure will entail you having to fast for a period of four hours (so that glucose that you consume in your diet will not interfere with the PET scan). Once you are in the Institute of Nuclear Medicine you will be given an injection of glucose which has been labelled with a radioactive substance, through a cannula (plastic tube) in a vein. You would need a cannula in one of your veins (usually forearm) for your surgery in any case. The radioactivity lasts approximately 90 minutes, therefore you do not have to wait for the scan. You will have to lie on a platform which moves you into the scanner. The scan takes one hour and you will need to lie still. Once the scan is complete you will return to your ward and prepare for your surgery on the following day as explained to you by your doctors. At the operation the surgeon will make a thorough examination and document the findings. A tiny fragment of the cancer and surrounding tissue will be taken for examination by one of the doctors involved in the study. Cancers need growth promoting agents as well as a blood supply therefore particular attention will be paid to the presence of these factors. The main part of the tissue which is removed will be sent for analysis by a pathologist as is the usual practise. A comparison will be made between the CT scan and PET scan findings to see if there is in fact any difference. Both scan findings will then be related to the analysis of the tissue removed. You will be looked after in your ward by your doctors and recovery will be as explained to you by them.

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Consent Form

STUDY TITLE: **The role of Positron Emission Tomography (PET) in the pre operative assessment of patients with colorectal cancer**

PATIENT NAME:

HOSPITAL NUMBER:

WARD/ ADDRESS:

By signing this form I agree that:

1. I have read the patients information sheet and the procedure has been fully explained to me.

2. I have had the opportunity to ask questions and I did receive satisfactory answers.

3. I have been given a copy of the information sheet and the consent form to keep.

4. I understand that I am participating in a research study and I understand the risks and benefits involved. I freely give my consent to participate in the research study outlined in the patient information sheet.

5. I understand that I may withdraw from this research study at any time without giving a reason for withdrawing and such a decision would not affect the standard of care that I receive in any way.

Signature of participant..... Date...../...../.....

Name of participant (Block Capitals).....

Investigator Statement

I have carefully explained to the above named patient the nature of the research protocol. I hereby certify that to the best of my knowledge the subject signing this form understands the nature, demands, risks and benefits involved in participating in this study.

Signature of investigator.....
Name of investigator (Block Capitals).....

Date...../...../.....

Signature of witness.....
Name of witness (Block Capitals).....

Date...../...../.....

Principal investigator : Prof. I. Taylor (tel: **0207-504-9312)**

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Patient Information Sheet

The Role of Positron Emission Tomography (PET) in the Follow up of Patients with Colorectal Cancer

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Other Investigators:

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Ms. B. Lovett	**Department of Surgery**
Dr. D.C. Costa	**Institute of Nuclear Medicine**
Dr. J. Bomanji	**Institute of Nuclear Medicine**
Dr. E. Prvulovich	**Institute of Nuclear Medicine**
Prof. W.R. Lees	**Department of Radiology**
Dr. A. Gillams	**Department of Radiology**

If you have any queries regarding this information sheet, please contact the Mr. T.H.A.Arulampalam in the Department of Surgery on **0207-679-9312**

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Patient Information Sheet

The Role of Positron Emission Tomography (PET) in the Follow up of Patients with Colorectal Cancer

You are invited to take part in a research project. You do not have to take part in this study if you do not want to. If you do decide to take part you may withdraw at any time without having to give any reason. Your decision whether to take part or not will not affect your care and management in any way. All proposals for research using human subjects are reviewed by an ethics committee before they can proceed. This proposal was reviewed by the joint UCL/UCLH Committees on Ethics of Human Research.

1. This study aims to establish if PET scans are better than conventional methods, such as computerised tomography (CT) scans and measurement of carcinoembryonic antigen (CEA) in the blood, at detecting recurrence of cancer of the large bowel. CEA is a substance found in the blood and which may be elevated when bowel cancer is present.

2. After operative treatment for large bowel cancer some patients develop recurrent cancer. If this is detected early further surgery, chemotherapy or radiotherapy may result in an improved chance of cure. It is routine practice to perform CT scans (every 6 months) and blood tests for CEA (every 3 months) following operative treatment of bowel cancer in order to detect and treat these patients who may develop a recurrence. If an abnormality is detected in a CT scan or the CEA is elevated then patients are offered a series of tests in order to confirm the diagnosis and start appropriate treatment. These tests may involve further scans or a biopsy if there is any doubt.

3. PET scanners detect radioactive substances. A small amount of radioactive glucose, which is so small as to be safe for the purpose of diagnostic testing, is injected into one of your veins. If recurrent cancer is present the glucose injected is concentrated here. The PET scanner will therefore detect recurrent cancer by detecting areas of high concentration of radioactive glucose. In this study you will have a PET scan every 6 months for 2 years. If an abnormality is detected you may require further scans or possibly a biopsy if there is any doubt.

Description of Research Study

Patients who have been treated for cancer of the large bowel will be followed up in the surgical outpatient department in the normal way. This will involve CT scans every six months and blood tests for CEA every three months (abnormal results will trigger investigation for recurrent cancer). Those patients taking part in the research study will also have a PET scan as an outpatient every six months for a two year period. If abnormalities are found on PET scans then investigation for recurrence will be initiated as routinely with the other two tests. In some cases biopsies are necessary to confirm or refute the diagnosis of recurrence. If biopsies are taken they will be analysed (as is routine practice) for recurrence. In addition a fragment of tissue will be examined for receptors to cancer growth factors. At the end of the study PET and CT will be compared to see if PET is better, the same as or worse than CT for detecting recurrence and whether this diagnosis can be made with more certainty. These results will be then compared to the pathological findings and endothelin receptor status in those patients who undergo a biopsy. The ultimate aim is to devise a way of detecting recurrence early and possibly developing a marker in the tissue which indicates the risk of recurrence from a particular individual cancer. This information will allow appropriate and early treatment of recurrence with better information on eventual outcome.

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CONSENT FORM

STUDY TITLE: **The role of Positron Emission Tomography (PET) in the follow up of patients with a history of colorectal cancer**

PATIENT NAME:

HOSPITAL NUMBER:

WARD/ ADDRESS:

By signing this form I agree that:

6. I have read the patients information sheet and the procedure has been fully explained to me.

7. I have had the opportunity to ask questions and I did receive satisfactory answers.

8. I have been given a copy of the information sheet and the consent form to keep.

9. I understand that I am participating in a research study and I understand the risks and benefits involved. I freely give my consent to participate in the research study outlined in the patient information sheet.

10. I understand that I may withdraw from this research study at any time without giving a reason for withdrawing and such a decision would not affect the standard of care that I receive in any way.

Signature of participant..... Date...../...../.....

Name of participant (Block Capitals).....

Investigator Statement

I have carefully explained to the above named patient the nature of the research protocol. I hereby certify that to the best of my knowledge the subject signing this form understands the nature, demands, risks and benefits involved in participating in this study.

Signature of investigator..... Name of investigator (Block Capitals).....

Date...../...../.....

Signature of witness..... Name of witness (Block Capitals).....

Date...../...../..... Principal Investigator: Professor I. Taylor (tel: **0207-504-9312**)

Appendix C

Clinical data and investigations of patients studied

Patient	Age (years)	Sex	Follow Up (months)	Diagnosis	Confirmatory test	PET result
1	61.83	M	18	Descending Colon Cancer	CT	+ve
2	53.08	M	13	Rectal Cancer	Sigmoidoscopy	+ve
3	77.67	F	9	Transverse Colon Cancer	Colonoscopy	+ve
4	74.67	F	14	Caecal Cancer	CT/colonoscopy	+ve
5	76.42	M	7	Rectal Cancer	CTC/colonoscopy	+ve
6	80.08	M	6	Ascending Colon Cancer	CTC/colonoscopy	+ve
7	86.75	F	22	Rectal Cancer	Sigmoidoscopy	+ve
8	76	M	11	Rectal Cancer	CTC	+ve
9	81.33	F	10	Rectal Cancer	CTC/colonoscopy	+ve
10	56	M	15	Rectal Cancer	Sigmoidoscopy	+ve
11	65.08	M	9	Sigmoid Colon Cancer	Colonoscopy	+ve
12	74.92	M	7	Rectal Cancer	CTC/colonoscopy	+ve
13	77.92	M	3	Rectal Cancer	CTC/colonoscopy	+ve
	Median **76**		**Mean** **11**			

Table C1 Patient details, diagnosis, confirmatory test and FDG-PET result for patients studied in chapter 3 and 4.

Patient	Height (cm)	Weight (Kg)	Blood glucose (mmol/l)	Injected activity (MBq)	Residual activity (MBq)
1	163	101	3.8	368	4.2
2	176	73	4.9	266	0.7
3	147	51	5.6	327	11.3
4	159	64	5.1	290	9
5	168	73	5.4	340	3.7
6	174	106	6.3	360	5.1
7	148	49	3.7	351	8.2
8	170	78	7.8	298	3.2
9	157	89	10.9	410	6.91
10	165	63	4.7	365	1.2
11	181	95	9.9	330	5.4
12	179	89	6	327	1.2
13	172	83	5.2	386	5.2

Table C2 Physical parameters measured in patients undergoing FDG-PET to evaluate primay CRC (chapters 3 and 4).

PATIENT	SUV_W Av	SUV_W Max	SUV_{BSA} Av	SUV_{BSA} Max	Slice
1	16.822	19.156	24.678	28.102	272
2	14.994	16.932	73.092	82.54	148.5
3	7.534	8.701	31.56	39.787	280.5
4	27.207	33.858	132.894	165.381	289
5	16.764	19.31	79.012	91.01	93.5
6	19.831	25.684	77.367	100.905	204
7	*	*	*	*	*
8	8.866	10.484	40.57	47.974	114.75
9	18.125	38.769	72.573	155.231	136
10	2.982	3.505	15.16	17.816	51
11	2.45	2.653	10.476	11.342	293.25
12	19.379	25.004	85.335	110.1	127.5
13	10.612	12.285	47.257	54.7	144.5
Mean	**13.797**	**18.028**	**57.498**	**75.407**	
sd	**7.416**	**11.347**	**35.589**	**51.100**	

Table C3 SUV variants (average and maximum) for patients evaluated in chapter 3

Patient	Histological diagnosis	Grade of differentiation	Perineural invasion	Lymphatic invasion	Vascular invasion
1	Dukes B	Moderate	No	N/A	No
2	Dukes C_2	Moderate	N/A	N/A	Yes
3	Dukes B	Moderate	N/A	N/A	N/A
4	Dukes B	Mucinous	N/A	N/A	No
5	Dukes B	Well to Moderate	Yes	No	No
6	Dukes B	Moderate	Yes	N/A	N/A
7	*	Moderate	N/A	N/A	No
8	Dukes B	Moderate	N/A	N/A	N/A
9	Dukes A	Moderate	N/A	N/A	N/A
10	*	Moderate	N/A	N/A	N/A
11	Dukes C_1	Moderate	N/A	No	No
12	Dukes C_1				
13	Dukes C_1	Moderate	N/A	N/A	Yes

Table C4 Histopathological evaluation of CRC's sent for analysis from patients studied in chapters 3 and 4.

**** Unable to assign a Dukes stage as patient 7 underwent local resection and patient 10 underwent biopsy and primary chemotherapy only.***

Patient	Age (Years)	Sex	Follow up (months)	PET	CT	Diagnosis	Diagnosis confirmation
1	68	M	12	FP	TN	No disease	H
2	69.17	F	16	FN	TP	LR (pelvis)	H
3	67.33	M	19	TP	FN	LR (pelvis)	H
4	74.92	F	14	FP	TN	No disease	C/R
5	62.83	M	20	TN	TN	No disease	C/R
6	51.42	M	16	FP	TN	No disease	H
7	71.08	M	20	TN	TN	No disease	C/R
8	69.08	M	15	TN	FP	No disease	C/R
9	74.08	F	13	TP	FN	LR (abdomen)	H
10	70.33	M	20	FP	TN	No disease	C/R
11	70.83	F	20	TP	FN	Metastasis (P)	H
12	82.58	M	17	TN	TN	No disease	C/R
13	68.5	M	12	TN	TN	No disease	C/R
14	71.83	M	19	TP	TP	LR (pelvis)	C/R
15	61.17	M	16	TP	TP	Metastasis (P)	C/R
16	59.5	F	21	TP	FN	LR (abdomen)	C/R
17	75.92	F	13	TP	FN	LR (abdomen)	H
18	77.5	M	10	TP	FN	LR (pelvis)	H
19	62.08	F	15	TP	FN	LR (abdomen)	H
20	62.92	M	20	TN	FP	No disease	C/R
21	44.83	F	23	TN	FP	No disease	C/R
22	85.5	M	14	FP	TN	No disease	C/R
23	73.58	F	17	TP	FN	LR (pelvis)	H
24	68.67	M	3	TP	TP	LR (abdomen)	H
25	56.92	M	16	TP	TP	Metastasis (P)	H
26	69.67	F	11	TP	TP	Metastasis (P)	C/R
27	63.75	M	17	TP	TP	Metastasis (D)	C/R
28	77.83	M	8	TP	TP	Metastasis (L)	C/R
29	66.58	F	18	TP	TP	Metastasis (L)	H
30	62	M	22	TP	TP	Metastasis (L)	H
31	66.67	F	16	TP	TP	Metastasis (L)	C/R
32	56.92	F	17	FN	TP	Metastasis (L)	H
33	72.08	M	17	TP	TP	Metastasis (L)	C/R
34	74.08	M	22	TP	TP	Metastasis (L)	H
35	47.67	M	11	TP	TP	Metastasis (L)	C/R
36	70.67	F	17	TP	TP	Metastasis (L)	C/R
37	71.83	M	11	TP	TP	Metastasis (L)	C/R
38	40.83	F	21	TP	TP	Metastasis (L)	C/R
39	74.5	F	12	TP	TP	Metastasis (L)	C/R
40	41.58	F	14	TP	TP	Metastasis (L)	C/R
41	70.67	F	14	TP	TP	Metastasis (L)	H
42	64.83	F	22	TP	TP	Metastasis (L)	C/R

Table C5 Patient details, imaging results, diagnosis and mode of confirmation for patients suspected of recurrent/metastatic CRC (chapter 5).

Patient	Age	Sex	Follow-up	PETs	Recurrence or Progression
1	62.52	M	12	2	No
2	66.92	M	16	3	Yes
3	61.83	M	18	4	No
4	74.67	F	14	3	No
5	73.25	F	10	2	No
6	56	M	15	2	No
7	53.83	F	17	3	Yes
8	71.67	M	12	2	No
9	86	M	16	3	No

Table C6 Follow up of patients with treated primary CRC

Patient	Age	Sex	Follow up (months)	PET	CT	Diagnosis	Diagnosis confirmation
1	77.83	M	8	TP	TP	Lung metastasis	C/R
2	66.58	F	18	TP	FN	Multiple CLM	C/R
3	62	M	22	TP	FN	Extraperitoneal metastasis	H
4	66.67	F	16	TP	FN	Multiple CLM	C/R
5	56.92	F	17	TN	TN	Solitary CLM	C/R
6	72.08	M	17	TN	TN	Solitary CLM	C/R
7	74.08	M	22	TN	TN	Solitary CLM	C/R
8	47.67	M	11	TP	TP	Multiple metastases	C/R
9	70.67	F	17	TP	FN	Multiple CLM	C/R
10	71.83	M	11	TN	TN	Solitary CLM	C/R
11	40.83	F	21	TP	TP	Lung metastasis	C/R
12	74.5	F	12	TP	FN	Extraperitoneal metastasis	C/R
13	41.58	F	14	TP	TP	Multiple CLM	C/R
14	70.67	F	14	TP	TP	Multiple CLM	C/R
15	64.83	F	22	TP	FN	Multiple CLM	C/R
	median 66.67		**mean** 16.13				

Table C7 Details of patients studied in chapter 6 (those with CLM)

Patient	Age	Sex	Follow up (months)	PET	CT	Diagnosis	Diagnosis confirmation
2	69.17	F	16	TN	TN	No metastatic lesions	C/R
3	67.33	M	19	FP	TN	No metastatic lesions	C/R
9	74.08	F	13	TN	TN	No metastatic lesions	C/R
11	70.83	F	20	TP	TP	Metastases (P)	H
14	71.83	M	19	TN	TN	No metastatic lesions	C/R
15	61.17	M	16	TP	TP	Metastases (P)	C/R
16	59.5	F	21	TP	FN	Metastases (P)	C/R
17	75.92	F	13	TN	TN	No metastatic lesions	C/R
18	77.5	M	10	TP	FN	Locoregional metastasis	H
19	62.08	F	15	TP	TP	Locoregional metastasis	H
23	33.58	F	17	TN	TN	No metastatic lesions	C/R
24	68.67	M	3	TN	TN	No metastatic lesions	C/R
25	56.92	M	16	TP	TP	Metastasis (P)	H
26	69.67	F	11	TP	TP	Metastasis (P)	C/R
27	63.75	M	17	TP	TP	Metastasis (D)	C/R
	Median 68.67		**Mean** 15.47				

Table C8 Details of patients with locoregional recurrence or extahepatic metastases studied in chapter 6

Appendix D

Institute of Nuclear Medicine protocols for tracer dose measurement

(a)

SOP:		TITLE:	SOP for measuring FDG upon arrival in the PET Suite		
Rev:		Date:	4/6/2001	Review:	W.Waddington
Group:		Author:	C.E.Townsend	Authorised:	

OVERVIEW

This SOP addresses the checks which must be performed on each consignment of 18F-FDG *before* it may be used to dispense patient dose preparations that day.

RELEVANT STAFF

INM practitioners and operators working in the PET Suite.

BACKGROUND

The PET Unit obtains 18-F FDG from three centres :

- Addenbrooke's Hospital, Cambridge (Wolfson Brain Imaging Centre)
- Hammersmith Hospital (MRC Cyclotron Unit)
- St Thomas' Hospital (PET Centre)

Before any FDG may be injected into a patient there must be notification from the producing cyclotron that it has passed its QC.

- Cambridge dispatches the FDG and will then fax to confirm if the consignment has passed the QC. The fax will be sent to the fax machine in the PET Suite.
- St Thomas' Hospital do the same.
- Hammersmith Hospital perform QC testing before the FDG leaves them, and confirmation that the FDG has passed its QC is on the delivery note.

PROCEDURE

Pre-Dispensing Checks to be done daily :

- Daily QC testing must be performed on the Dose Calibrator before the FDG consignment can be assayed. Refer to the SOP for Dose Calibrator QC in PET.
- The FDG will arrive in a lead shielded container. (Take care when lifting it, as it is heavy.)
- Display a sign at the door of the dispensing lab - 'Please do not enter: Dose dispensing in progress. Radioactive sources in use'. Ensure that you are wearing a white coat, film badge, and finger dose TLDs.
- Take a new Radiopharmaceutical Holding Record Sheet. (See Appendix). Indicate on the record sheet that you have received confirmation that the consignment of FDG has passed its QC. From the delivery note mark the volume of liquid dispensed into the FDG vial, the time at which the FDG was measured prior to despatch, and the assayed activity.
- Remove the glass vial containing the FDG from the lead shielded container using the tongs provided; check that it has a label on saying FDG. Place in the dose calibrator.
- Check that the dose calibrator is set to the correct radioisotope setting (18-F). Measure the activity and note this, together with the time at it was measured.
- Using the 18F decay chart displayed on the wall, check that the activity that was dispatched matches the activity that has arrived to within ± 10%. If it does circle the appropriate box on the sheet, and initial this.

- Put the FDG vial in the lead shielded dispensing station and screw on the top.
- File the delivery notes and the QC confirmation notes in the file in the dispensing suite.

APPENDIX

INM PET Facility - Record Sheet of Current Radiopharmaceutical Holdings

Date : _____ **Radiopharmaceutical Form :** _____ **Radiopharmaceutical QA Status (circle and initial) :** **Pass** **Fail**

Consignor (tick) : **University of Cambridge** **UMDS (Guy's and St. Thomas')** **MRC Cyclotron Unit, Hammersmith**

Activity Assay - Entire Shipment

	Stock Volume (mls)	Time of Assay	Assayed Activity (MBq)	Two Assays in Agreement ?
Consignor Activity Assay				(i.e. both agree within ± 10%)
Decay-Corrected Consignor Assay	_____	_____		circle below as appropriate
INM PET Unit Activity Assay				Yes / No

Activity Assay - Sub-dispensed Preparations

Time of Assay	Operator Initials	Stock Volume Diluted ?	Volume Removed (mls)	Assayed Activity (MBq)	Volume Remaining (mls)	Activity Remaining	Purpose

Consignment of Current Holdings to Waste

Time	Operator Initials	Volume Remaining (mls)	Estimated Max. Remaining Activity (MBq)	Purpose
				WASTE
				WASTE

(b)

SOP:		TITLE:	SOP for DOSE CALIBRATOR QC in PET		
Rev:		Date:	4/6/2001	Review:	WWaddington
Group:		Author:	C.E.Townsend	Authorised:	

OVERVIEW

The dose calibrator in the PET Suite needs to be calibrated every day that doses are measured in the calibrator. The calibration needs to be done before any doses are measured.

RELEVANT STAFF

INM practitioners and operators working in the PET Suite.

BACKGROUND

This SOP details how to perform daily QC testing on the PET Unit Veenstra VDC–404 Radioisotope Dose Calibrator. For further information regarding the calibrators' correct operation, refer to the Owner's Manual (copies are kept in the Dose Calibrator QC record file in the PET Unit and in the Physics Office).

The tests are designed to a) check the operation of the calibrator and b) its response to a standard ^{137}Cs source to eliminate the possibility of sudden equipment failure and incorrect readings. Additionally, as each radioisotope setting links to specific software and/or electronic circuitry, a reading must be obtained for the ^{137}Cs source for each radioisotope setting to be used that day. This policy is in line with current guidelines for the daily testing of dose calibrators, developed by the NPL and IPEM. The following tests must be performed each day for each calibrator to be used to assay dose preparations, and must be performed *before* that calibrator is used for the first time that day.

PROCEDURE

- Ensure that the LCD shows 'BGD On'. With no activity in the chamber or in the vicinity select **MODE** and then select **ZERO ADJUST.** Press **ENTER,** wait while the cycle completes (about 30-60 seconds) and then hit **ENTER** to continue.

- Select **BATTERY TEST**. Press **ENTER,** wait while the cycle completes (about 10 seconds).
  Check that the reading is greater than 135 volts, and enter this reading on the record sheet for Daily QC and Consistency Checking (see Appendix).
  NB If the battery reading is less than 135 volts it must be replaced.

- Hit **ENTER** to continue, and select **MODE** to return to the measurement screen.

- Now use the Cs-137 standard source to record the activity measured in the Cs-137 channel and the F-18 channel. The source is kept in the locked isotope safe store, with the key is kept under the calibrator control panel. Remove the standard source and place it centrally in the dipper.

- To select the 137-Cs channel, hit the **SELECT ISOTOPE** key and use the arrow keys to locate CS-137. Press **ENTER** to measure. To select 18-F, locate F-18 using the arrows.

- Note the measured activity for both channels on the record sheet for Daily QC and Consistency Checking. **If the measured activity for either channel is outside the printed ± 5% limits shown on the record sheet, notify the Duty Physicist immediately.**

- Return the Cs-137 source to the safe and lock it.

NB Do not forget to select F-18 prior to measuring the patient's dose.

GLOSSARY

APPENDIX

Institute of Nuclear Medicine, UCL Hospitals NHS Trust

PET Unit Veenstra VDC - 404 Dose Calibrator

Daily QC Check for Correct Operation and Consistency of Response

^{137}Caesium Dose Calibrator Standard Reference Source : **Month beginning : Nov-01**

Calibration Data 8.77 MBq on 23 Aug 2001

Serial No. HT 778

Manufacturer AEA Technology / QSA GmbH

				^{137}Caesium Setting				^{18}Flourine Setting			
	Operator	Bkg Activity	Ion Chamber		Calculated		Measured		Calculated		Measured
Date	Initials	(MBq)	Voltage (V)	-5%	Activity	+5%	Activity	-5%	Activity	+5%	Activity
01-Nov-01				8.295	8.731	9.168		4.956	5.217	5.478	
02-Nov-01				8.294	8.731	9.167		4.956	5.216	5.477	
03-Nov-01				8.294	8.730	9.167		4.955	5.216	5.477	
04-Nov-01				8.293	8.730	9.166		4.955	5.216	5.477	
05-Nov-01				8.293	8.729	9.165		4.955	5.216	5.476	
06-Nov-01				8.292	8.728	9.165		4.954	5.215	5.476	
07-Nov-01				8.292	8.728	9.164		4.954	5.215	5.476	
08-Nov-01				8.291	8.727	9.164		4.954	5.215	5.476	
09-Nov-01				8.290	8.727	9.163		4.953	5.214	5.475	
10-Nov-01				8.290	8.726	9.163		4.953	5.214	5.475	
11-Nov-01				8.289	8.726	9.162		4.953	5.214	5.474	
12-Nov-01				8.289	8.725	9.161		4.953	5.213	5.474	
13-Nov-01				8.288	8.725	9.161		4.952	5.213	5.474	
14-Nov-01				8.288	8.724	9.160		4.952	5.213	5.473	
15-Nov-01				8.287	8.724	9.160		4.952	5.212	5.473	
16-Nov-01				8.287	8.723	9.159		4.951	5.212	5.472	
17-Nov-01				8.286	8.722	9.159		4.951	5.212	5.472	
18-Nov-01				8.286	8.722	9.158		4.951	5.211	5.472	
19-Nov-01				8.285	8.721	9.157		4.950	5.211	5.471	
20-Nov-01				8.285	8.721	9.157		4.950	5.211	5.471	
21-Nov-01				8.284	8.720	9.156		4.950	5.210	5.471	
22-Nov-01				8.284	8.720	9.156		4.949	5.210	5.470	
23-Nov-01				8.283	8.719	9.155		4.949	5.210	5.470	
24-Nov-01				8.283	8.719	9.154		4.949	5.209	5.470	
25-Nov-01				8.282	8.718	9.154		4.948	5.209	5.469	
26-Nov-01				8.282	8.717	9.153		4.948	5.209	5.469	
27-Nov-01				8.281	8.717	9.153		4.948	5.208	5.469	
28-Nov-01				8.281	8.716	9.152		4.948	5.208	5.468	
29-Nov-01				8.280	8.716	9.152		4.947	5.208	5.468	
30-Nov-01				8.279	8.715	9.151		4.947	5.207	5.468	
01-Dec-01				8.279	8.715	9.150		4.947	5.207	5.467	

(c)

SOP:		TITLE:	SOP for measuring FDG doses in the PET Suite		
Rev:		Date:	11/09/2001	Review:	
Group:		Author:	C.E.Townsend	Authorised:	

OVERVIEW

This SOP describes the drawing up of a dose of FDG for a patient. The adult dose of FDG is 400MBq.

RELEVANT STAFF

INM practitioners and operators working in the PET Suite.

BACKGROUND

The PET Unit obtains 18-F FDG from three centres :

- Addenbrooke's Hospital, Cambridge (Wolfson Brain Imaging Centre)
- Hammersmith Hospital (MRC Cyclotron Unit)
- St Thomas' Hospital (PET Centre)

Before any FDG may be injected into a patient there must be notification from the producing cyclotron that it has passed its QC.

- Cambridge dispatches the FDG and will then fax to confirm if the consignment has passed the QC. The fax will be sent to the fax machine in the PET Suite.
- St Thomas' Hospital do the same.
- Hammersmith Hospital perform QC testing before the FDG leaves them, and confirmation that the FDG has passed its QC is on the delivery note.
- The FDG must have been measured and its activity checked against the delivery note. SOP-

PROCEDURE

Pre-Dispensing Checks to be done daily :

- Daily QC testing must be performed on the Dose Calibrator before the FDG dose may be measured. Refer to the SOP for Dose Calibrator QC in PET.

- Display a sign at the door of the dispensing lab - 'Please do not enter: Dose dispensing in progress. Radioactive sources in use'. Ensure that you are wearing a white coat, film badge, and finger dose TLDs.
- From the Radiopharmaceutical Holding Record Sheet (See Appendix) and the decay chart work out the activity needed and the volume in which it should be dispensed.
- Operator should be wearing white coat, film badge and finger TLDs. Using a blue needle and a 5ml syringe in the syringe holder draw up the appropriate volume.
- Check that the dose calibrator is set to the correct radioisotope setting (18-F). Measure the activity and note this, together with the time at it was measured on the record sheet and the patient's clerking sheet. The clock in the dispensing lab should be set to match the clock of the Advance.
- Note the time of the injection on clerking sheet, along with the residual activity and the time that was measured.

GLOSSARY

Appendix E

Publications arising from thesis

Papers:

1. **Glucose utilisation and cell proliferation in colorectal cancer**
   Visvikis D, Francis DL, Costa DC, Mulligan R, Townsend C, Arulampalam THA, Islam MS, Taylor I, Ell PJ
   European Journal Nuclear Medicine 2002;**29**:280

2. **The impact of FDG-PET on the management algorithm for recurrent** colorectal cancer
   Arulampalam THA, Costa DC, Visvikis D, Boulos PB, Taylor I, Ell PJ
   European Journal Nuclear Medicine 2002;**28**:1758-1765

3. **The clinical application of PET to the management of colorectal cancer**
   Arulampalam THA, Costa DC, Bomanji J, Ell PJ
   Quarterly Journal Nuclear Medicine 2001;**45**:215-230

4. **Evaluating an asymptomatic patient with a rising CEA**
   Arulampalam THA, Ledermann J, Costa DC
   Lancet Oncology 2001;**2**:172

5. **Positron emission tomography and colorectal cancer**
   Arulampalam THA, Costa DC, Loizidou M, Visvikis D, Taylor I, Ell PJ
   British Journal of Surgery 2001:**88**:176-189

Abstracts:

1. **Whole Body FDG-PET for Staging Colorectal Liver Metastases**
   Francis DL, **Arulampalam THA**, Costa DC, Loizidou M, Ell PJ, Taylor I.
   Br. J. Surg. 2002;**89**:*58*

2. **Positron Emission Tomography for the Evaluation of Colorectal Liver Metastases**
   Arulampalam THA, Costa DC, Loizidou M, Ell PJ, Taylor I.
   Eur. J. Surg. Oncol. 2001;**27**:779-780

3. **The Use of PET for the Evaluation of Recurrent or Metastatic Colorectal Cancer**
   Arulampalam THA, Costa DC, Loizidou M, Boulos PB, Ell PJ, Taylor I.
   Br. J. Surg. 2001;**88**:56

4. **Does PET Have a Role Staging Colorectal Cancer**
   Arulampalam THA, Costa DC, Loizidou M, Vaizey CJ, Boulos PB, Ell PJ, Taylor I.
   Colorectal Disease 2001;**3**:50

5. **PET for the Evaluation of Recurrent or Metastatic Colorectal Cancer**
   Arulampalam THA, Costa DC, J Bomanji, Loizidou M, Boulos PB, Ell PJ, Taylor I.
   Colorectal Disease 2001;**3**:30
   Six of the Best Research Papers of the Year at the Meeting of the Association of Coloproctology of Great Britain and Ireland (Harrogate 2001)

6. **The Utility of PET for Assessing Patients with Colorectal Liver Metastases**
   Arulampalam THA, Costa DC, Bomanji J, Loizidou M, Ell PJ, Taylor I.
   Colorectal Disease 2001;**3**:50

7. **The Role of PET in Colorectal Cancer Management**
   Arulampalam THA, Costa DC, J Bomanji, Loizidou M, Taylor I, Ell PJ.
   Nuclear Medicine Communications 2001;**22**:453-454
   3rd Prize Best Scientific paper at The British Nuclear Medicine Society Meeting (Brighton 2001)

8. **The role of positron emission tomography in the management of recurrent colorectal cancer.**
   Arulampalam THA, Lovett B, Loizidou M, Costa DC, Boulos PB, Ell PJ, Taylor I.
   Eur. J. Surg. Oncol. 2000;**26**:837

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Abe Y, Matsuzawa T, Fujiwara T, Fukuda H, Itoh M, Yamada K, Yamaguchi K, Sato T, Ido T (1986) Assessment of radiotherapeutic effects on experimental tumors using 18F- 2-fluoro-2-deoxy-D-glucose. *Eur J Nucl Med* 12: 325-328

Advanced Colorectal Cancer Meta-Analysis Project (1992) Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. *J Clin Oncol* 6: 896-903

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The clinical application of positron emission tomography to colorectal cancer management

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The clinical application of positron emission tomography to colorectal cancer management

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Colorectal cancer (CRC) is the second commonest cancer in the Western World. Successful treatment relies significantly on accurate detection and staging of primary disease as well as the early identification of the presence and extent of recurrence. Morphological imaging techniques, particularly computed tomography (CT), are well established and widely available to carry out these tasks in addition to predicting and monitoring response to therapy. This review analyses the current inadequacies for imaging CRC and critically assesses the potential role of functional imaging with positron emission tomography (PET). We review the current literature, use our experience from the first 1000 PET studies carried out at our Institution and the perspective of surgical colleagues. We find little evidence for the use of 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG)-PET for screening asymptomatic individuals and current modalities appear better suited for detection of symptomatic primary CRC. There is evidence of increased accuracy for FDG-PET in staging primary disease, but this area remains controversial and larger studies are necessary. The situation is quite the reverse with respect to imaging suspected recurrent disease with FDG-PET being more sensitive and specific than conventional techniques. This benefit manifests itself through alteration in patient management and results in cost savings. PET also appears to have a specific place in the evaluation of patients undergoing radiotherapy and chemotherapy, a role that will expand. The evidence suggests that PET will ultimately become routinely incorporated into CRC patient management algorithms. Technological advances coupled with novel tracer research will facilitate this.

KEY WORDS: Colorectal neoplasms, radionuclide imaging - Tomography, emission computed - Fluorodeoxyglucose F18, diagnostic use - Neoplasm staging - Colorectal neoplasms, diagnosis - Colorectal neoplasms, therapy.

Colorectal cancer (CRC) remains a major diagnostic and therapeutic challenge today. CRC, the second commonest cancer in mainland Europe,[1] the UK [2] and the United States,[3] is considered to be poorly imaged by conventional anatomical methods.[4] There are particular circumstances where computed tomography (CT) and other anatomical modalities such as magnetic resonance imaging (MR) and ultrasound (USS) have significant disadvantages.

Approximately 70% of patients who present to the surgeon with a primary CRC are suitable for a so called "curative" resection, but 30-40% of these patients go on to develop a recurrence, usually within 18-24 months of initial surgery.[5] So, although awareness of the disease has increased and successful detection of primary CRC is possible, there appears to be difficulty staging primary disease accurately. This may result in patients receiving inappropriate treatment, for example not being considered for liver resection when hepatic metastases are present or not receiving

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TABLE I.—*Reported sites of recurrence/metastasis from colorectal cancer (two studies).*

Sites	Incidence[5] (%)	Incidence[10] (%)
Liver	33	13
Lung	22	3
Locoregional	21	—
Intra-abdominal	18	—
Retroperitoneal	10	—
Intraluminal	6	6
Brain	—	0.7
Bone	—	0.9

adjuvant therapy again due to inaccurate assessment of disease load. The resultant compromise in therapy may contribute to high recurrence rates.

Detecting recurrence is problematic. Commonly patients undergo clinical examination, colonoscopy, CT and measurement of serum tumour markers such as carcinoembryonic antigen (CEA).[6] All these modalities have been shown to be inadequate for surveillance for various reasons. Clinical examination tends to pick up advanced recurrence. Although colonoscopy detects interval polyps that may have developed, the number of intraluminal recurrent CRC's is relatively small (Table I). CEA is not sufficiently sensitive (59%) or specific (84%) despite being frequently used for surveillance in many surgical units.[7] CT does detect intra abdominal and pelvic abnormalities, but there are substantial difficulties differentiating benign fibrosis [postoperative and/or postradiotherapy (RT)] from malignant recurrence.[8]

Furthermore, colorectal liver metastases occur in nearly half of all patients and the only hope of cure is surgical resection.[9] Selecting those with truly isolated liver metastases, therefore those that are most likely to benefit from resection, is inaccurate with conventional anatomic imaging modalities.[10, 11] Those patients with CRC who receive chemotherapy or RT often suffer significant morbidity with no guarantee that they will respond prior to commencing treatment. During treatment, CT is used to monitor morphological response on a lesion by lesion basis, but this does not take into account non-viable tumour that will be detected or the radiological changes that lag behind actual change in a lesion. Therefore, a very crude evaluation of therapy response is obtained.

The optimal management of patients with CRC relies on accurate imaging to detect and stage both primary and recurrent disease as well as to evaluate patient response to therapy. Positron emission tomography (PET) has moved from the sphere of pure research into every day clinical practice. The fastest growing application of clinical PET is oncological imaging,[12] but the utilisation of this technique varies throughout the world. There are approximately 260 diagnostic PET centres in the United States, 100 in continental Europe and very few in the UK.[13] This situation is set to change over the coming years as the clinical efficacy of PET is established and resources are streamed into national PET programmes.[14]

CT in particular is widely used to image CRC at present, but current evidence suggests that it may not achieve the required accuracy.[4, 8] It is against this background that we review here the use of PET in CRC management.

A review of the literature was undertaken by performing an online search of Pubmed and Medline for the period 1980 to 2001. Keywords used: PET; positron emission tomography; colorectal cancer; treatment evaluation; staging; computerised tomography. Articles retrieved were manually cross-referenced and only those references that were of relevance or contained validated new information were included. Comprehensive inclusion of all references identified was not attempted.

We also give examples from our experience of the first 1000 PET patients investigated and the first 100 CRC patients imaged using FDG-PET at our Institution since April 1999. All FDG-PET scans were performed with a GE Advance full ring, dedicated PET scanner (General Electric Medical Systems, Milwaukee, USA) and CT scans were performed in a Somatom Plus 4 or Somatom Plus 4 Volume Zoom (Siemens AG Medical Engineering Group, Forchheim, Germany).

The gold standard PET camera is the dedicated bismuth germanate oxide (BGO) PET assembly. Unlike other cameras described this assembly consists of several thousand small BGO crystal detectors,[15] which are constructed into a ring that surrounds the patient. This system has two advantages. Firstly, the crystals are better suited to 511KeV photons produced by positron decay because of their higher density compared to sodium iodide (NaI), so increasing sensitivity. The multicrystal layout lets the operator work with much higher count rates so that the injected dose of tracer can be increased, which in turn improves image quality. In addition, eliminating the rotation of

the detector ring means that the quality of studies using short-lived isotopes such as oxygen-15 [^{15}O] and nitrogen-13 [^{13}N] is improved. Overall, these improvements in hardware mean that the practical spatial resolution of these cameras is far superior to the majority in clinical use and is currently reported at between 4.5 and 6 mm. Ultimately, the resolution of BGO PET detectors for cancer lesions depends very much on the differential uptake of tracer between tumour and normal tissue. The current view is that malignant lesions of 6-10 mm can be accurately detected although smaller, very glucose avid lesions can also be seen.

PET tracers

A detailed description of oncological PET tracers can be found elsewhere.[13] This technology is evolving very rapidly, but we mention here the important tracers related to CRC imaging.

The tracer most frequently used for oncological applications of PET is the fluorinated glucose analogue 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG). The use of FDG in cancer imaging with PET is based on Warburg's now well documented observations that malignant cells have an increased rate of glucose consumption.[17] More recently the cellular mechanisms for this have been clarified by the findings that cancer cells have an increase in the number of both cell membrane glucose transporter proteins (mainly GLUT 1 and GLUT 3)[17, 18] and glycolytic enzymes (hexokinase, phosphofructokinase, pyruvate dehydrogenase).[19] When injected intravenously, FDG, like unlabelled glucose is preferentially transported into the cancer cell compared to normal cells, but the tracer becomes metabolically trapped as previously described.[20] FDG decays by positron emission and the PET assembly detects emitted coincident gamma ray pairs. Images are reconstructed using appropriate computer software and displayed in the coronal, sagittal and transaxial orientations.

FDG-PET is described in detail for CRC imaging and many studies demonstrate its high sensitivity and specificity,[21] although the latter can be a problem due to false positive FDG uptake in highly metabolic benign lesions, most notably inflammatory tissue (Fig. 1). Other tracers such as [^{18}F]Fluorouracil ([^{18}F]FU) are available to predict and monitor treatment response. This tracer is an analogue of 5-Fluorouracil (5-FU), a chemotherapy agent used in the treatment of metastatic CRC. The field of tracer development in CRC imaging continues to expand and we speculate that one of the fluorinated thymidine analogues may prove to be of great value in this respect.

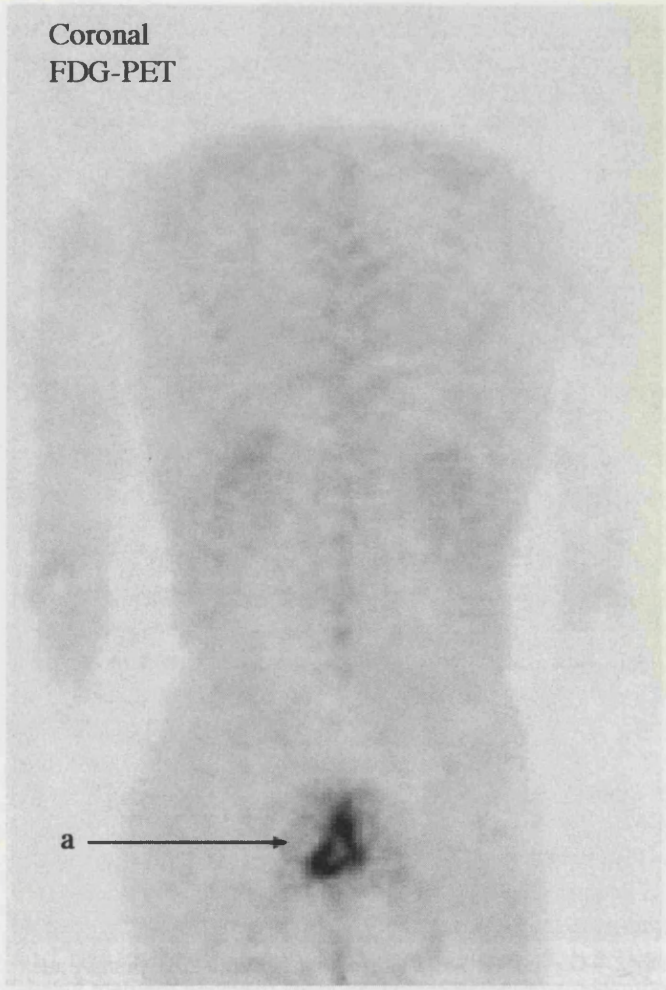


Fig. 1.—Coronal FDG-PET in a patient who underwent anterior resection of the rectum for adenocarcinoma. FDG uptake was demonstrated behind the bladder (a), but flexible sigmoidoscopy and biopsy revealed inflammatory tissue only.

PET in colorectal cancer imaging

FDG-PET is a minimally invasive whole body imaging modality that offers the clinician accurate metabolic information, which complements CT, MRI and USS. We discuss each stage of CRC management in detail below.

Screening and diagnosis of primary colorectal cancer.—There is no substantial published data for

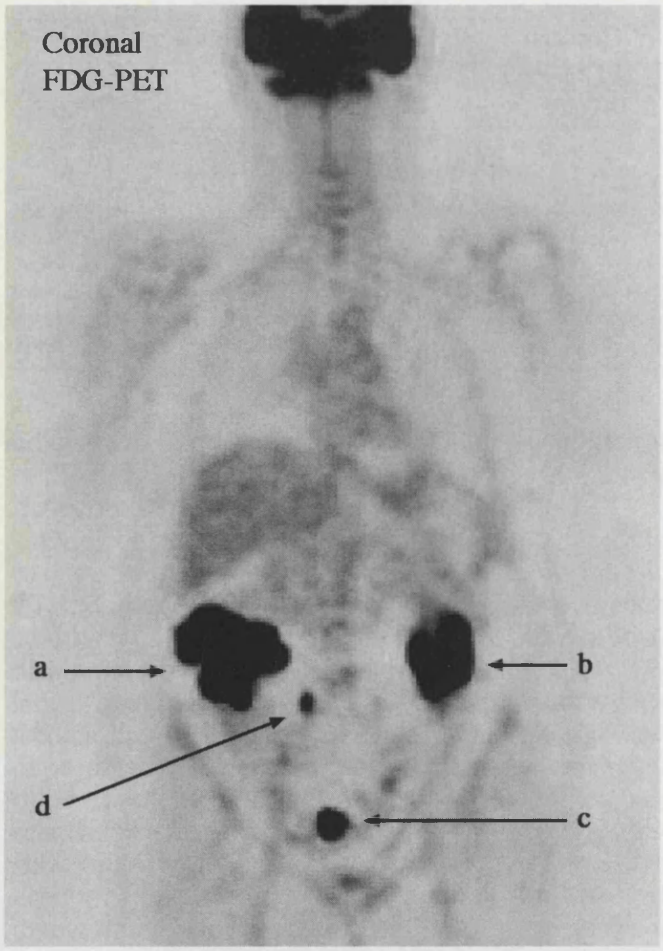


Fig. 2.—Coronal FDG-PET scan demonstrating a large primary adenocarcinoma of the ascending colon (a) overlying the right kidney. Also visualised are large jejunal (b), terminal ileal (c) and peritoneal lymph node (d) metastases. All lesions were confirmed at surgery.

the use of FDG-PET in screening for asymptomatic CRC. The availability of PET and the cost (a PET study currently costs approximately twice that of a CT of the abdomen and pelvis at our Institution and this seems consistent with other reports [22]) are two important contributory factors. Furthermore, the inclusion of patients with low disease probability increases the likelihood of false positive PET scans, therefore this technique is unsuitable for unselected screening programmes.

The situation is, to a certain extent, similar for diagnosis of CRC in symptomatic individuals. Published data is scarce compared to that on recurrent CRC, but it is possible to detect primary lesions in symptomatic patients with PET.[23, 24] Ruhlmann,[25] Takeuchi,[24] and Mukai [23] identified patients with primary CRC and (Fig. 2) illustrates the type of images obtained using FDG-PET in a patient with a primary adenocarcinoma of the colon.

There are, however, several factors that make FDG-PET less attractive than other imaging techniques. Currently endoscopy and barium enema detect over 90% of CRC's.[26] These investigations are more readily available and cheaper than PET. CT pneumocolon is gaining popularity and is cost effective because the technique is not only sensitive and specific for CRC, but is minimally invasive with a low morbidity.[27] The study by Harvey *et al.*[27] showed that in 52 patients 47 diagnostic studies were obtained and none of the malignant lesions were misdiagnosed. The application of three-dimensional CT reconstruction allows a "virtual" colonoscopy viewing the colonic mucosa from anus to caecum,[28] but further refinement is needed.[29] Finally, hydrocolonic sonography, which is highly accurate (97% sensitivity), is also becoming available and has the potential to become a valuable diagnostic tool.[30] The accuracy, reliability and availability of current imaging modalities mean that PET is unlikely to play a significant role in diagnosing primary CRC, although its use as a targeted screening investigation in high risk groups is yet to be fully evaluated.

Staging of primary colorectal cancer.—Preoperative staging investigations for patients with CRC aim to identify the extent of local infiltration, involvement of lymph nodes, and metastases to the liver. This allows all foci of cancer to be treated by an appropriate combination of surgical excision, chemotherapy and radiotherapy so as to minimise the chance of recurrence. CRC's were histologically staged according to the modified Dukes' classification [31] (Dukes "A" being carcinomas confined to the bowel wall; "B" those through the wall but not involving lymph nodes; "C" those through the wall and involving draining lymph nodes and "D" for metastases to distant sites) and many centres still continue this practice. In order to standardise histopathological staging, however, the UICC Tumour, Node and Metastasis (TNM) classification is now established.[32] A cancer of the colon or rectum can now be specifically classified according to the TNM status, which makes comparison between centres more standardised.

1) *Local infiltration.* Accurate delineation of the extent of local infiltration allows planning of resection by allowing the surgeon to assess if a tumour is

resectable and which procedure is of maximum oncological benefit. This information is also necessary to assess the need for additional treatments such as neoadjuvant radiotherapy.[33] CT is widely used to stage primary CRC and is an accurate method of assessing local infiltration especially in advanced tumours (sensitivity range 55-70% [34-36]). The accuracy of CT for low stage tumours (Dukes A and B/T_{0-2}) can be poor, but the overall detection and characterisation of transmural penetration is deemed acceptable. The development of sophisticated endoluminal MR coils will augment CT in this respect.[36] Endoanal USS provides useful clinical evaluation of the depth of invasion of rectal cancers with a sensitivity of 96% and specificity of 89% for T_{1-3} rectal tumours.[37-39] This is a substantial improvement on transabdominal USS. However, as with transabdominal USS the information is only targeted to one region and complementary imaging is also required.

2) *Involvement of lymph nodes and extrahepatic intra-abdominal spread.* Standard evaluation of lymph nodes and extrahepatic, intra-abdominal spread with CT and MR is inadequate.[35, 40-42] This is primarily because judging a lymph node to be malignant on size criteria alone is misleading since nodes less than one centimetre (the usual CT criterion for malignancy) can be malignant and this stage migration effect is well described in small lymph nodes retrieved at resection of gastric cancers.[43] Reported accuracy for CT range between 25-73% (overall sensitivity is 45% [4]) with a 40% sensitivity for MR. Laparoscopy with or without USS may further improve staging accuracy, [37, 44] but this must be weighed against its invasive nature. Also information that could alter treatment is not available prior to definitive surgery. Immunoscintigraphy has been shown to be significantly more sensitive for pelvic (74%) and intra-abdominal disease (66%) disease when compared to CT (57% and 34%, respectively),[45] however, other reports have questioned this accuracy.[46] Recently emerging evidence suggests that this technique has potentially useful clinical applications.[47]

3) *Metastases to the liver.* Detection of liver metastases and additional metastatic foci is an essential part of the preoperative staging process. Liver metastases are found in 10-25% of patients at the time of operation for their primary CRC and 25% are candidates for resection.[48] The sensitivity of transabdominal USS is too low to exclude small lesions in the liver.[49] Intraoperative USS has been shown to be a sensitive investigation and is possible laparoscopically,[50] but its use is not universal. CT is the imaging modality most frequently used in the staging of primary CRC and has a reported sensitivity of 72% and specificity of 99% with MR having similar results.[35, 51] However, published data also shows that CT failed to demonstrate lesions in 7% and underestimated the number of lobes involved in 33% of cases.[10, 11] Immunoscintigraphy using Indium-111-labelled anti-CEA antibodies has shown promise,[52] but specificity and poor spatial resolution can be a problem when compared to FDG-PET.

4) *Staging primary CRC with PET.* Studies by Falk,[22] Abdel-Nabi,[53] Ogunbiyi [54] and Mukai [23] all report varying degrees of superiority for FDG-PET in the staging of primary CRC when compared to CT. It should also be noted that synchronous tumours can be detected when FDG-PET is used [55] and this can potentially influence the extent of surgical resection. FDG-PET does not give accurate information regarding local infiltration unless image fusion with CT or MR is performed. Falk's study showed that in a cohort of 16 patients with 15 foci of CRC FDG-PET was superior to CT for staging [positive predictive value (PPV) 93% and negative predictive value (NPV) 50% for FDG-PET *versus* PPV of 100% and NPV of 27% for CT]. However, the group contained patients with primary and recurrent CRC and it should be noted that one liver (2-3 mm in size) and one mesenteric metastasis were missed by FDG-PET. More recently Abdel-Nabi *et al.*[53] investigated 48 patients with CRC (44 with biopsy proven CRC and 4 who were highly suspicious). FDG-PET had a PPV of 90% and NPV of 100%, but sensitivity for lymph node metastases was only 29% and similar to that of CT. Detection of liver metastases by FDG-PET was superior to CT (sensitivities of 88 *versus* 38%). This study was not controlled and PET reporters were not blinded to CT reports. Mukai *et al.*[23] report sensitivity of 22.2% (2/9) for lymph nodes with specificity of 86.7% (13/15) which possibly raise further questions about the precise role of PET in a contentious area of CRC management. Figures 2 and 3 demonstrate the value of FDG-PET staging information in the context of primary CRC.

Thus, there appears to be a place for the use of FDG-PET in staging primary CRC, especially with respect to detection of colorectal liver metastases (Fig. 3). PET has the advantage of studying the whole body and

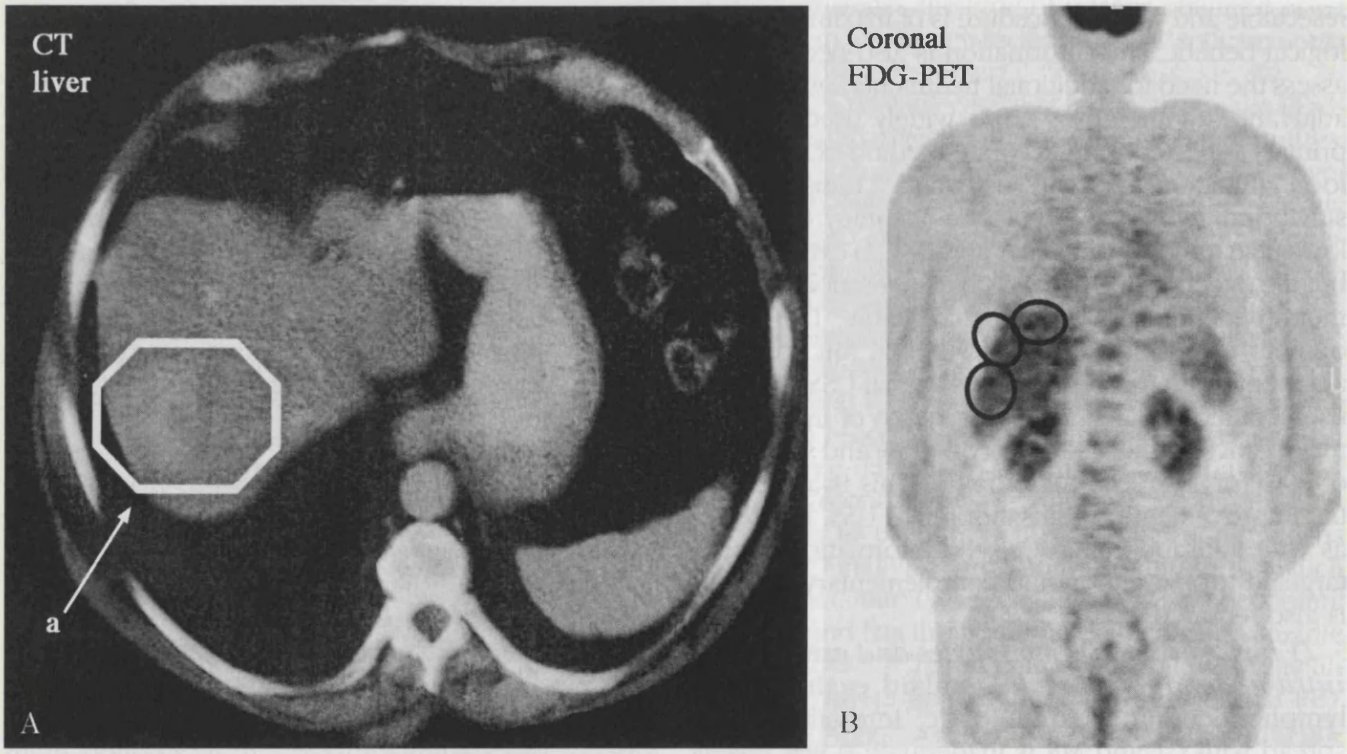
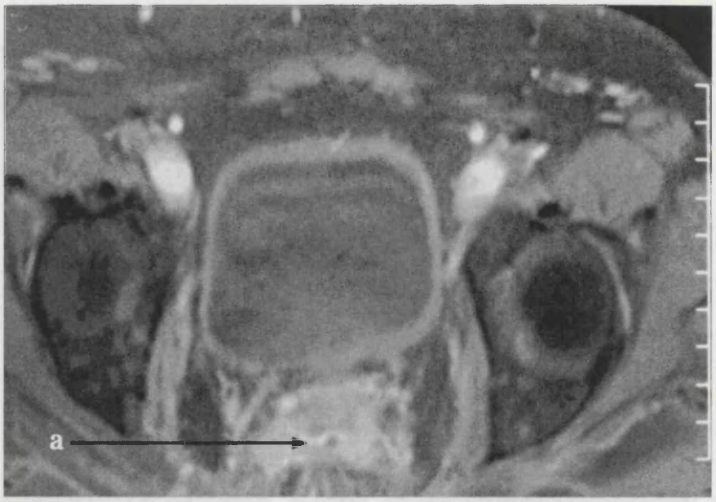


Fig. 3.—A, B) Coronal FDG-PET demonstrating at least three liver metastases from a sigmoid colon adenocarcinoma. CT scan was reported as showing a "vascular blush" (a), but no definitive diagnosis was made.

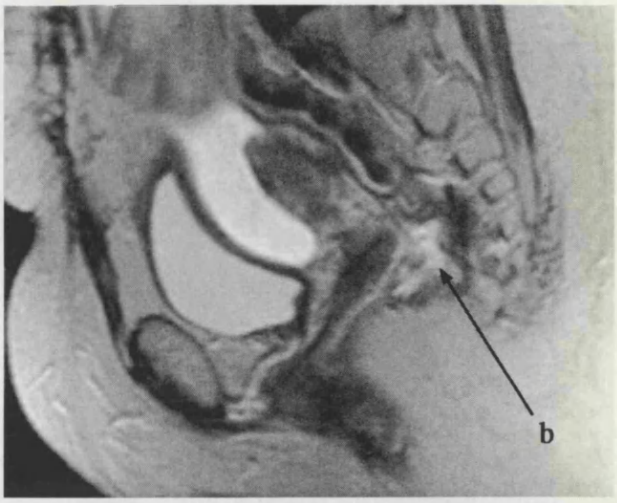
therefore only submitting the patient to one staging investigation. However, further evaluation of PET in primary CRC is required in order to quantify benefits to the patient, in terms of decreased rate of recurrence, increased disease free survival and decreased mortality. Rigorous cost analysis is also needed in order to justify the cost/benefit to the healthcare system. Staging primary CRC remains controversial and the effect on outcome for all modalities needs to be re-evaluated, especially with the advent of fast, high resolution, thin slice CT. PET, however, will be invaluable for the diagnosis of equivocal lesions both in the peritoneal cavity and within the liver.

Surveillance for recurrent colorectal cancer.—Following treatment of primary CRC patients undergo surveillance of varying intensity in order to detect recurrence. Approximately a third of patients who undergo curative surgery for CRC develop recurrence within 24 months.[5] In up to 30% of these cases the recurrence is localised and therefore suitable for curative resection.[56] If recurrence is detected early it is reported that survival may be improved especially if radical surgery is performed.[57] In order to avoid unnecessary morbidity and mortality appropriate selection of patients is essential as only 20-30% of these particular cancers are curable.[58, 59]

We have briefly discussed some of the clinical issues that pose the greatest problems for the attendant clinician managing a patient suspected of recurrent CRC. Some of the imaging dilemmas have been partially addressed by the use of high signal T2 weighted MR especially for imaging the pelvis.[60, 61] There are reports questioning the ability of MR to distinguish recurrent tumour from benign changes,[62] but this modality remains the optimum morphological imaging solution at present. Immunoscintigraphy with 111-Indium labelled B72.3 (sensitivity 74%),[63] for example, heralded another potential candidate for detecting recurrent CRC and this technique has been shown to be superior than CT for differentiating scar from tumour in the pelvis.[64] These findings have been confirmed by Lunniss *et al.*[65] who used ^{99m}Tc labelled PR1A3 antibody for detecting recurrent CRC (sensitivity 96%, specificity 50%, PPV 73%, NPV 89%). Although curative surgical strategies could not be offered to all patients in whom recurrence was detected, manage-



Transaxial CT pelvis



Sagittal MR pelvis

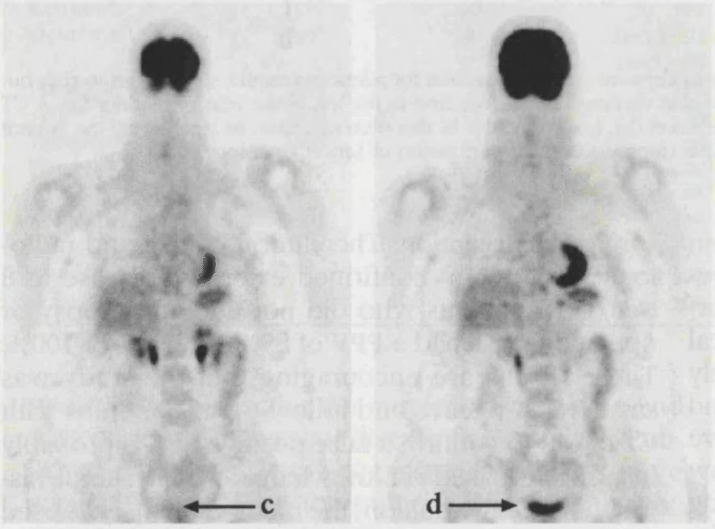


Fig. 4.—CT and MRI in a patient who previously underwent anterior resection of the rectum. Both investigations were highly suggestive of anastomotic recurrence of rectal cancer (a and b) FDG-PET shows no uptake of tracer (c) behind the bladder (d), therefore refuting the diagnosis.

ment was altered in more than a third of patients with the small subgroup who had operable disease benefiting most from early, accurate detection. The results also demonstrate that this technique has its own problems with a specificity of only 50%.

Another frequent problem that arises is the patient who presents with an isolated elevation of CEA with minimal symptoms and normal imaging. A policy of observation that may lead to missing the opportunity to resect a curable recurrence must be weighed up against aggressive investigation with its attendant psychological and physical morbidity and cost. In this context tissue biopsy has been shown to have a false negative rate due to sampling error even with CT guidance.[66, 67] Second look laparotomy can lead to a definite diagnosis in 90% of cases, yet up to 60% of these patients are unsuitable for resection.[68] These findings contribute to the on going debate regarding the actual need for and benefits of aggressive follow-up for detecting recurrence following treatment for CRC.[69]

1) *Detecting recurrent CRC with PET.* Very early in the development of FDG-PET several authors.[70-73] confirmed its value when trying to differentiate scar from local recurrence (Figs. 4 and 5). In Schiepers' study [70, 76] patients with confirmed or suspected recurrence were evaluated with PET against conventional imaging (CT, USS, plain radiograph). Accuracy for disease in the pelvis was 95% with FDG-PET against 65% with CT. Takeuchi *et al.*[24] also reported the accu-

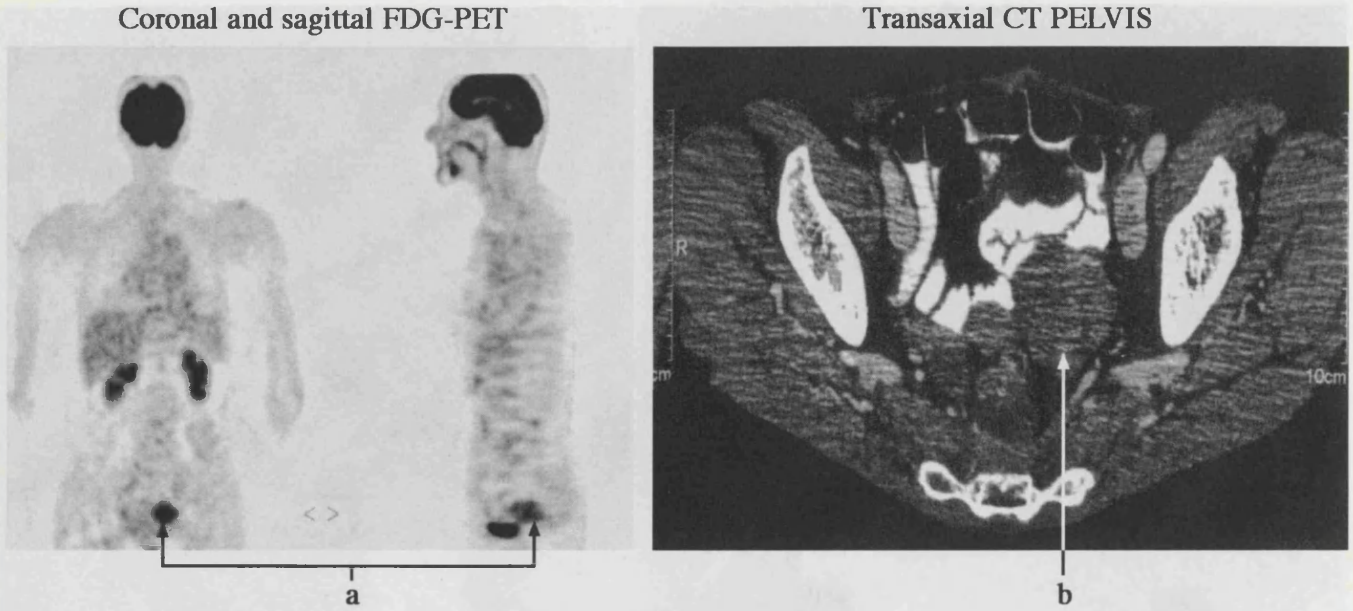


Fig. 5.—Coronal and sagittal FDG-PET in a patient who previously underwent anterior resection for adenocarcinoma. CEA began to rise, but all imaging and colonoscopy was reported as normal. FDG uptake was demonstrated above and to the left of the urinary bladder (a). A CT scan reported in the light of the FDG-PET scan did demonstrate a lesion (b), but the nature of this was uncertain. At laparotomy the patient was found to have an isolated recurrence of a rectal adenocarcinoma (reproduced with permission of Lancet Oncology).[91]

racy of PET for diagnosis of pelvic recurrence when compared to CT and MR. Fifteen out of 16 histologically proven pelvic recurrences were identified correctly by FDG-PET, 4 of these patients had equivocal CT or MR. The authors stated that by retrospectively analysing the standardised uptake values (SUV's) and clinical findings an SUV cut off of 2.8 would have made diagnoses with 100% accuracy. There are now several reports of the efficacy of FDG-PET for detecting and staging recurrent CRC (Table II).[24 25 54 70 74-89] Not all of these made comparison of FDG-PET with CT, therefore, comparison between studies may be difficult primarily because of the heterogeneous methods of conventional imaging used. Perhaps the most notable recent studies are those of Flamen [74] and Valk.[75] Valk *et al.*, in fact demonstrated sensitivity and specificity of 93 and 98% respectively with FDG-PET compared to 69 and 96% in the 115 patients with available CT's. This led to a cost saving of approximately US$ 3000 through avoiding surgical intervention.

Flanagan *et al.*[76] assessed the potential role of FDG-PET in patients with unexplained elevation in CEA and normal CT scans. In 17 out of 22 patients PET was abnormal and recurrence was confirmed by tissue sampling and/or follow-up. Biopsy was performed in seven patients of whom four underwent curative surgical intervention. The clinical course and radiological follow-up confirmed extensive disease in 8 out of 10 patients who did not undergo biopsy or operation. PET had a PPV of 89% and NPV of 100%. These results are encouraging, but the study was small, retrospective and follow-up of 6 months with CT or MR to confirm a false positive PET is probably insufficient based on knowledge of the natural history of CRC. In addition, the method of analysis used to calculate FDG accumulation has been criticised and a more rigorous calculation of actual glucose metabolism suggested.[90] The superior accuracy of PET over CEA for the detection of recurrent CRC has also been discussed by other authors.[24, 70, 87] and we have reported on such a case (Fig. 5).[91]

Evaluation of the extent of recurrent colorectal cancer.—The evaluation of patients with suspected recurrent CRC aims to confirm the diagnosis and to differentiate isolated resectable disease from disseminated metastases. Reported sites most commonly affected by metastases from CRC vary (Table I).[5, 10] Current staging investigations for recurrent CRC are not sufficiently sensitive enough to achieve this goal. As already mentioned the accurate, early identification of patients with localised disease allows appro-

TABLE II.—*Studies on the application of FDG-PET for the detection and staging of recurrent CRC.*

Authors	Date	No. of patients	Sensitivity PET (%)	Sensitivity CT (%)	Specificity PET (%)	Specificity CT (%)
Yonekura[77]	1982	3	100		100	
Strauss[71]	1989	29	100		100	
Gupta[78]	1991	18	100	70	86	43
Ito[79]	1992	15	100		100	
Gupta[80]	1993	16	90	60	66	100
Multicentre[81]	1994	59	93		78	
Beets[81]	1994	35	Local 64		33	
Pounds[83]	1995	57	95		87	
Schiepers[70]	1995	76	Local 94	60	97	72
			Liver 94	85	100	n/a
Daenen[84]	1996	19	95		67	
Lai[85]	1996	34	Liver 93	100	57	14
			(Non liver 100%)		—	
Vitola[86]	1996	24	90	86	100	100
Delbeke[87]	1997	52	93	79	89	58
Ruhlmann[25]	1997	59	100		67	
Keogan[88]	1997	18	92		80	
Ogunbiyi[54]	1997	40	Local 91	52	100	80
			Liver 95	74	100	85
Flanagan[76]	1998	22	100		71	
Valk[75]	1999	115	93	69	98	96
Takeucki[24]	1999	23	94		100	
Flamen[74]	1999	103	Local 94		100	
			Liver 98		100	
Arulampalam[89]	2001	42	93	73	58	73
			Staging:			
			Local 100	75	86	100
			Liver 100	55	100	100

priate patient selection for surgical intervention and the chance of increasing disease free survival. Published data consistently suggests FDG-PET is more accurate than CT for the purpose of evaluating the extent of recurrent CRC.[54, 92]

1) *Hepatic metastases.* In the United States approximately 14,000 patients per year present with isolated liver metastases at their first recurrence [93] and about 20% of these patients die with metastases exclusively to the liver. Beets *et al.*[82] demonstrated the value of whole body PET for detecting CRC metastases to the liver. Schiepers' study confirmed a higher sensitivity and accuracy with FDG PET (94 and 98%, respectively) compared to CT/USS (85 and 93%) for the detection of hepatic metastases.[70] In the latter study there were no false positives for PET and 1 for CT/USS). There were also two false negative FDG-PET scans for two nodules discovered in the liver at surgery. In each of the two patients the nodule was less than 1 cm and not detected by CT.

Delbeke [87] compared FDG-PET with CT and CT portagram. Fifty-two patients presented on 61 occasions (CT portagram was not performed on those with known extrahepatic disease and not undergoing surgery) and final diagnosis was made by histopathology (n=44) and clinical/radiological follow-up (n=17). FDG-PET had an accuracy of 92% compared with CT/CT portagram 78 and 80% respectively for hepatic disease and 92 and 71% for extrahepatic disease. Ogunbiyi [54] looked at 40 patients with recurrent CRC and reported a sensitivity of 95% and specificity of 100% for FDG-PET compared to CT (74% and 85%, respectively) for detection of hepatic metastases and a higher accuracy than CT for delineating multiple liver lesions. More recent studies have systematically confirmed the benefits of FDG-PET for the detection of both hepatic and extrahepatic metastases from CRC.[94, 95] The available evidence suggests that optimal evaluation of patients with colorectal liver metastases should include FDG-PET and Topal *et al.*[84] demonstrate this in a large series of 91 consecutive patients. In this study FDG-PET provided additional

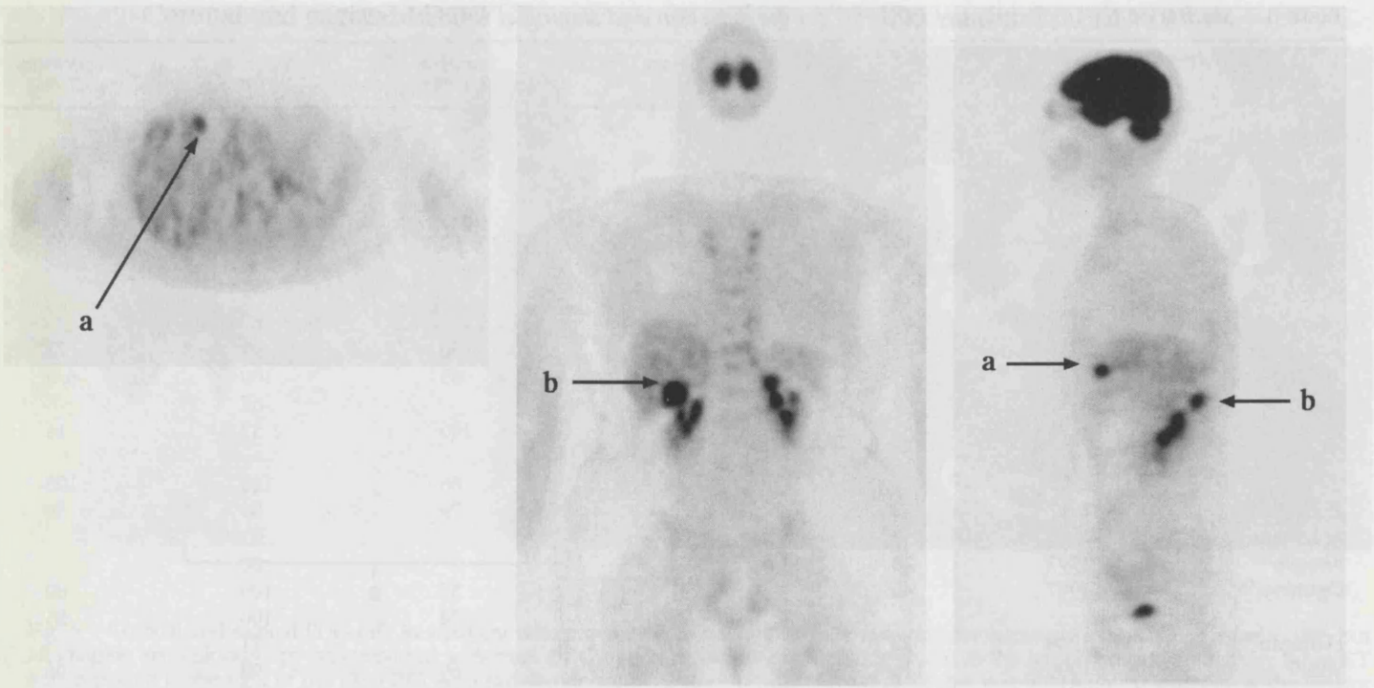


Fig. 6.—A-C) FDG-PET study in a patient who was diagnosed on CT as having a solitary colorectal liver metastasis that was deemed operable. This study, however, demonstrates two liver lesions (a) and (b).

information in 11% of patients. This could be the difference between a curative resection being attempted or therapies such as radiofrequency thermoablation and chemotherapy being initiated. In this context the impact not only for the patient, but for healthcare resource management is significant (Fig. 6).

2) *Extrahepatic metastases.* Lai *et al.*[85] compared FDG-PET with conventional imaging in 34 patients and found unsuspected extrahepatic disease in 11 (32%) patients. Clinical management was affected in 10 patients directly as a result of PET (Fig. 7). Schiepers [91] also reported that a significant number of unexpected extrahepatic metastases could be demonstrated using FDG-PET. Even more accurate delineation of these lesions is possible with image fusion and careful patient selection so that false positive PET studies in the latter study may be further reduced.

The crucial advantage that FDG-PET must confer to patient management in order to become an acceptable clinical tool is that it should alter clinical management for the benefit of the patient. This may be by avoiding surgery, early commencement of non-surgical treatments or selecting patients suitable for surgical re-intervention. FDG- PET is highly sensitive and accurate for the diagnosing and staging recurrent CRC as demonstrated by Huebner *et al.*[21] The meta-analysis of 11 studies showed a sensitivity of 97%, specificity of 76% and impact on clinical management in 29% of cases (Table III). Detection of unsuspected metastases by FDG-PET ranges from 13-32%.[70, 75, 82] A multicentre study by the Institute of Clinical PET (ICP) examined the cost effectiveness of 14 PET centres (reviewing 267 CRC patient records). The conclusion was that a potentially large saving could be made if PET was incorporated into the routine management algorithm for recurrent CRC on the basis of a reduction in unnecessary laparotomies (from 20 to 10%) and the increased number of resections with curative intent.[81] These results add still more weight to Huebner's [21] analysis, which supports the incorporation of FDG-PET in the routine clinical algorithm for patients with recurrent CRC.

Evaluating subclinical treatment response.—Accurate information regarding the response to radiotherapy and/or chemotherapy in patients being treated for CRC would provide useful guidance in predicting, planning and revising ongoing adjuvant therapy. This is particularly important when considered in the context of the unwanted side effects that some of these

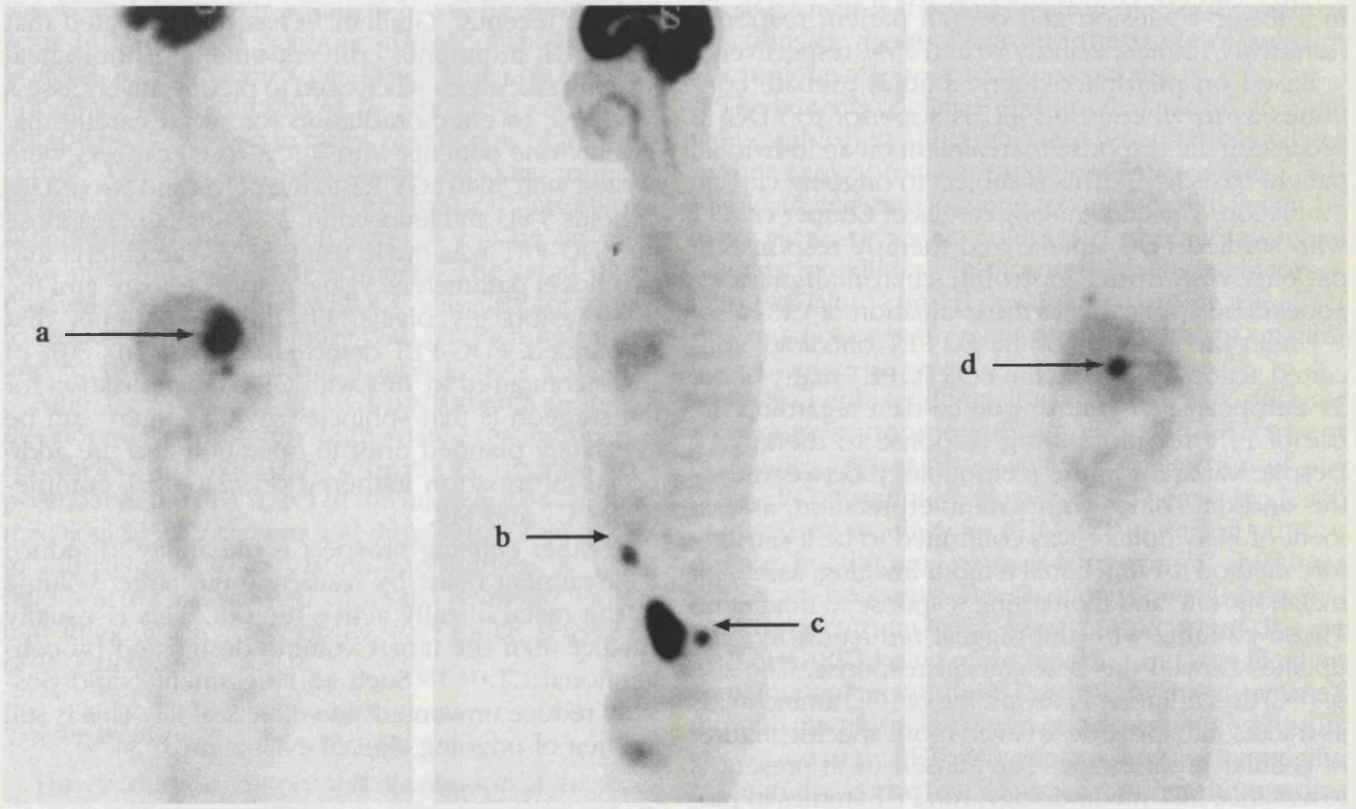


Fig. 7.—A-C) Sagittal FDG-PET study in a patient referred for assessment of a solitary liver metastasis. FDG-PET, however, demonstrated lesions in the liver (a and d) as well as pelvic (c), and anterior abdominal wall (b) disease. This is an extreme example, but in certain patients with local recurrence, the detection of additional metastatic lesions suggests disseminated disease, poor prognosis and therefore contraindicates surgical resection.

treatments have. Nagata [96] has shown a correlation between FDG uptake and tumour response in patients with primary or metastatic liver lesions who had received arterial embolization, hyperthermia and radiotherapy. Studies assessing the uptake of FDG measured by PET and correlation with the anti-tumour effects of chemotherapy have been reported for certain tumour types including CRC.[97-100]

1) *Response to chemotherapy.* The potential use of FDG-PET for monitoring chemotherapy in advanced CRC appears very promising. The available data suggests highest concentration of [18F]FU in responsive tumours.[101] Strauss [102] demonstrated that lesions with low [18F]FU uptake had a significant increase in volume and no response to treatment. Findlay *et al.*[97] evaluated the metabolism of CRC liver metastases using FDG-PET before and at intervals after treatment. The findings were compared with tumour outcome conventionally assessed using change in size on CT. Twenty patients were studied of whom 18 had assessable liver metastases. The results were expressed as a ratio of FDG uptake in tumour and normal liver (T:L). Pretreatment T:L ratio did not correlate with response. The T:L ratio 4-5 weeks after treatment was able to discriminate response from non response both

TABLE III.—*Studies demonstrating FDG-PET directed change in management as reported by Huebner*[21].

Authors	No. of patients	Change in management (%) (n)
Beets[82]	35	40 (14/35)
Vitola[92]	24	25 (6/24)
Lai[85]	34	29 (10/34)
Delbeke[87]	52	33 (17/52)
Ogunbiyi[54]	23	44 (10/23)
Valk[75]	78	31 (24/78)
Flamen[74]	103	20 (21/103)
Pooled change in management	349	29 (102/349)
95% confidence interval		25-34%

in a lesion-by-lesion and overall patient response (sensitivity 100%, specificity 90 and 75%, respectively).

Based on pharmacokinetic studies, debate continues as to whether [^{18}F]FU is superior to FDG in predicting the response to treatment on an individual patient basis.[103, 104] This is subject to ongoing clinical evaluation. The encouraging results of Couper *et al.*[105] who studied FDG uptake and therapy response in patients with upper gastrointestinal malignancies appears be applicable to the evaluation of CRC also.

Under the auspices of the EC PET oncology concerted action group and the EORTC PET many of the 31 European PET centres pooled data regarding the use of PET for monitoring response to therapy.[106] Despite variation in the methodology between centres and difficulties with data interpretation, assessment of FDG uptake was confirmed to be a satisfactory method for functional tumour imaging, assessing metabolic rate and monitoring response to treatment. Those patients with the biggest reduction in FDG uptake showed the best clinical response. The use of [^{11}C] thymidine, [^{18}F] thymidine or [^{11}C] amino acids as tracers may provide an even more specific marker of cellular proliferation. The consensus at present is to advance PET methodology, run PET studies in parallel with phase I/II clinical trials and collect more data regarding the application of PET to specific tumours. Because of the heterogeneous availability of PET both world-wide and nationally, PET remains a second choice for evaluating therapy response. The potential role of PET in this aspect of oncology and particularly in the management of CRC, however, suggests that practice will change.

2) *Response to radiotherapy.* Similar promise was thought to be present for PET in the evaluation of RT response. There are some problems, most notably demonstrated by Haberkorn [107] who evaluated FDG-PET in 21 patients (41 examinations) with recurrent CRC undergoing pelvic RT. A correlation was made between the palliative benefit and reduction in FDG uptake in 50% of patients (this was also more accurate than CEA). However, this figure was lower than the actual number of patients who responded, probably because the inflammatory response to RT may have caused an increase in FDG accumulation wrongly interpreted as residual tumour. An arbitrary delay in post-treatment FDG-PET evaluation of 6 months may increase the accuracy for assessing tumour response. The findings mirror the results of Abe *et al.*[108] and Engenhart *et al.*[109]

More recently, Guillem [110] has demonstrated that FDG-PET augments conventional morphological imaging modalities when used to preoperatively assess response to chemoradiation for rectal carcinoma. Twenty-one patients with T_3, N_1 rectal cancers were treated with 5040 cGY RT to the pelvis and two cycles of bolus 5-FU and leucovorin. Assessment of response on FDG-PET was made using SUV, size criteria and two novel parameters, visual response score and the total lesion glycolysis. Of the 15 patients that responded, FDG-PET detected response in 100% of cases compared to 78% with CT. The implication for the surgeon is that sphincter saving surgery can be accurately planned prior to operation and the additional information gathered on FDG-PET complements CT and MR.

Another enticing prospect is the ability to reduce RT treatment fields by restricting the target volume to the metabolically active tumour. This is usually smaller than the target volume designated by conventional CT.[111, 112] Such an assessment could possibly reduce unwanted side-effects of RT. This is still an area of ongoing clinical evaluation.

Future perspectives

PET is rapidly expanding. Technology is changing, not just in the instrumentation field but also in the area of tracer developments. Although, expensive to set up (4-5 million US dollars for to set up a scanner, cyclotron and radiochemistry laboratory), costs can be recouped by alteration in clinical management including avoidance of surgery (approximately US$ 3000 per patient in Valk's study [75]).

Instrumentation

The design of PET capable instrumentation is changing. Top of the range equipment is being expanded with the addition of whole body CT capability whilst a number of "intermediate" technical solutions are also in progress. The basic radiation detectors are undergoing a renewal [from BGO to lutetium orthosilicate (LSO) or other possible combinations such as NaI/LSO] and expectations are high in respect of both improved performance and lower costs.

Two main items will figure prominently in these developments. There is a clear need to speed the turnover of whole body imaging, the present scanning times are slow and inefficient. With optimal pro-

tocols and the newer scanners it will be possible to scan 2 to 3 patients per hour instead of the conventional 1 to 1.5 patients per hour. This will be very important both in terms of patient compliance and acceptability but also in terms of unit cost of the procedure. On the other hand, more accurate co-registration of PET data with anatomical landmarks obtained with high resolution CT will be on offer with new multi-modality scanners. The rapid transmission scans obtained with CT will also contribute to reduce the scanning times with CT/PET. Automatic and routine CT/PET image fusion is now available.

Animal PET/MRI or PET/CT instruments are being developed offering very high spatial resolution and sensitivity. This reflects the growing awareness of the potential of the PET tracer in the investigation of pharmacological interventions and drug distribution studies in animals prior to translation into humans. A "new" field is actively discussed under the *leitmotiv* "molecular imaging", in view of the 10^{-19} molar sensitivity of PET detection.

Tracer technology

The production, supply and distribution of the main clinical PET tracer (FDG) has now been solved, at least in part. Large geographical areas have been "covered" with distribution networks but large gaps remain. Since ^{18}F has a half-life of 2 hours, it has been possible to set up these distribution networks supplying tracer beyond the local supply of the hospital where the cyclotron producing PET radionuclide facility exists. It is clear that from a clinical utilisation point of view, other shorter half lived PET radionuclides will not be amenable to this type of distribution (^{11}C, ^{15}O). Hence new efforts are being made to develop ^{18}F based ligands and possibly expand the generator based PET radionuclide producing systems.

Of most promise is the advent of techniques to produce [^{18}F] thymidine (FLT).[113] This tracer is a marker of proliferation and may yield a means of improving tumour specific imaging without compromising sensitivity.[114]

Other ^{18}F labelled ligands under discussion include fluoroethyl tyrosine (an amino acid analogue), fluoro misonidazole (a hypoxia ligand), fluoro oestradiol (an oestrogen analogue). There is rapid progress in this field and new ligands are rapidly emerging. This will clearly expand the clinical indications for PET scanning beyond the simple staging or restaging of disease towards the investigation of specific cellular functions or metabolisms and the study of subclinical tumour response to interventions.

The benefits of clinical PET applied to CRC are now well established although there remain areas where further clinical trials are required. At present, FDG-PET is an accurate imaging technique, which can be used alone or as an adjunct to other anatomical imaging modalities. This forms the basis for incorporating PET into clinical practice and testing the effect PET has not only on management, but also on clinical outcome.

We find little evidence for the use of FDG-PET for screening asymptomatic individuals and current modalities appear better suited for detection of primary CRC in symptomatic patients. There is evidence of increased accuracy for FDG-PET in staging primary disease, but this area remains controversial and larger studies are necessary. The situation is quite the reverse with respect to imaging suspected recurrent disease with FDG-PET being more sensitive and specific than conventional techniques. This benefit manifests itself through alteration in patient management and results in cost savings. PET also appears to have a specific place in the evaluation of patients undergoing radiotherapy and chemotherapy, a role that will expand. Technology is advancing rapidly not only in terms of hardware and software, but also the positron labelled tracers that are available. The current evidence suggests that PET will expand further in oncological imaging, particularly for CRC and this will be facilitated by technological advances and novel tracer research.

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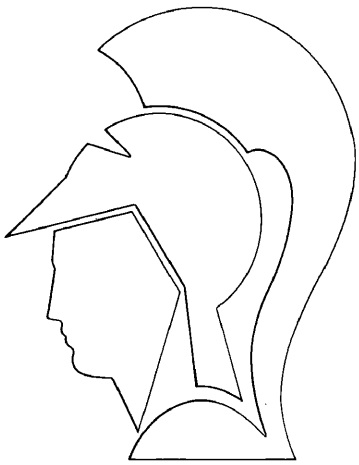

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The impact of FDG-PET on the management algorithm for recurrent colorectal cancer

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Abstract. Positron emission tomography (PET) has been successfully used to image colorectal cancer (CRC). This study evaluated the accuracy of 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG) PET for the detection and staging of recurrent CRC and the consequent impact on clinical management. Forty-two patients previously treated for CRC were investigated for suspected recurrence and, if recurrence was confirmed, the extent of disease was evaluated. All patients underwent whole-body FDG-PET and computed tomography (CT) scan and results were compared to assess sensitivity, specificity and diagnostic accuracy for each modality. We then assessed the FDG-PET directed alteration in clinical management from that planned on the basis of spiral CT results. FDG-PET was more sensitive (93%) than CT (73%) for detection of recurrence (specificity 58% and 75%, respectively). FDG-PET yielded a correct diagnosis in 35 (83%) out of 42 patients, while CT did so in 31 patients (74%). FDG-PET was more accurate than CT for staging local recurrence (sensitivity 100%, specificity 86% with FDG-PET vs 75% and 100%, respectively, with CT) and CRC liver metastases (sensitivity 100% vs 45%; specificity 100% for both). Overall, PET upstaged 8 out of 30 patients (27%) and altered patient management in 16 (38%) cases. This study confirms that FDG-PET is more sensitive than CT for the detection and staging of recurrent CRC. The results also indicate that FDG-PET is an accurate means of selecting appropriate patients for operative treatment. When applied to routine clinical practice, patient management is altered.

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Introduction

Positron emission tomography (PET), a metabolic imaging modality capable of identifying malignant tumours, is beginning to make an impact in the United Kingdom [1, 2]. The main advantage of 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG) PET over conventional imaging studies such as computed tomography (CT), magnetic resonance imaging (MRI) and ultrasound is that the deranged cellular biochemical activity detected by PET precedes the malignant structural changes detected by conventional methods [3].

The rationale for the use of PET in oncology is based on the finding that malignant tissue has an increased rate of glucose consumption [4] owing to an increase in both the rate of glycolysis [5] and the number of cell membrane glucose transporter molecules [6]. When injected intravenously, the glucose analogue tracer FDG preferentially concentrates in malignant tissue. Once within the cell, FDG is phosphorylated by hexokinase to FDG-6-phosphate and effectively becomes metabolically trapped as previously described [7]. Fluorine-18 decays by positron emission, which results in the production of a coincident gamma ray pair that can be detected by a PET scanner. The detected activity closely correlates with the amount of trapped FDG-6-phosphate. Using appropriate computer software, images of the detected activity can be reconstructed in the coronal, sagittal and transaxial orientations for visual interpretation. FDG is the most commonly used tracer in oncology and FDG-PET has been successfully applied to the study of a variety of cancers [8].

Colorectal cancer (CRC) is the second commonest cancer to occur in Western Europe [9] and the United

States [10]. Despite continuing advances in surgical and non-surgical therapeutic strategies, recurrence rates after initial treatment are estimated to be 30%–40%, and recurrence usually occurs within the first 2 years following surgery [11]. By implication, the problem of recurrence arises in part from weaknesses in the initial staging process and there is evidence that conventional methods for imaging patients with CRC, most commonly CT, are not sufficiently accurate [12, 13].

The purpose of this study was to investigate the advantages of FDG-PET in the context of a cohort of CRC patients for the detection and staging of recurrent CRC compared with the current practice of surveillance with spiral CT. We evaluated the impact of FDG-PET on clinical management by comparing the management plan directed by spiral CT results and the change in this management due to new or additional information obtained from FDG-PET.

Materials and methods

Study design

This study was conducted along similar guidelines to those published by Huebner et al. [14] for the evaluation and presentation of data from FDG-PET studies performed to investigate recurrent CRC. A prospective study was conducted between September 1999 and January 2001. This study was based at our institution, which is a tertiary referral centre with an interest in the treatment of recurrent CRC and particularly in multimodality therapy for CRC liver metastases. Patients were recruited from those with suspected or confirmed recurrent CRC who were referred to the hospital Multidisciplinary Colorectal Oncology Team (MCOT). All patients recruited to the study were subsequently included in the final data analysis.

Patient characteristics

Hospital Ethics Committee and Administration of Radioactive Substances Advisory Committee (ARSAC) approvals were obtained for the study. Forty-two patients, 23 male and 19 female, with a median age of 68.4 years (range 40.1–84.3 years) were recruited after informed consent had been obtained. Those with confirmed recurrence or metastatic lesions underwent further staging investigations as per protocol at this institution.

Technical specifications

Patients underwent investigation with both whole-body FDG-PET and concurrent spiral CT.

CT imaging. CT scans of the abdomen and pelvis were contrast enhanced with 100 ml intravenous Omnipaque 350 (Nycomed Amersham plc, Little Chalfont, Bucks.) and performed using either a Somatom Plus 4 or Somatom Plus 4 Volume Zoom (Siemens AG Medical Engineering Group, Forchheim, Germany). Abdominal and pelvis scans involved 5-mm and 3-mm contiguous slicing, respectively. For bi- or triphasic liver imaging, 5-mm slices were taken at 2.5-mm intervals with the Somatom Plus 4 and 3-mm slices at 1.5-mm intervals with the Plus 4 Volume Zoom

FDG-PET imaging. FDG-PET imaging was performed using a GE Advance dedicated PET scanner (General Electrics Medical Systems, Milwaukee, USA). FDG with a mean activity of 370 MBq (range 330–380 MBq) was administered intravenously along with 5 mg diazepam orally (Cox Pharmaceuticals, Barnstaple, Devon). Patients were not routinely catheterised or given frusemide. A whole-body emission scan was then taken (5 min per bed position), followed by a post-injection transmission scan using germanium sources (3 min per bed position). Transaxial images of 4.3×4.3×4.25 mm^3 (matrix size 128×128×35) were reconstructed using ordered subsets-expectation maximisation and segmented attenuation correction. Images were processed and reconstructed on a Sun Microsystems workstation (Palo Alto, Calif., USA) and displayed in three orthogonal projections for visual analysis. Standardised uptake values (SUVs) were calculated as follows:

$$\frac{[\text{Average tumour activity concentration } (\text{MBq/l}) \cdot}{[\text{Injected activity } (\text{MBq/l})]} \cdot \times \text{body weight (kg)}] \quad (1)$$

All FDG-PET studies were qualitatively analysed by at least two experienced nuclear medicine physicians of consultant grade and reports were based on the known biodistribution of FDG. CT scans were reported by radiologists of specialist registrar and consultant grade in addition to being presented to a consultant radiologist in the MCOT. Final diagnosis was confirmed either by clinical course and radiological follow-up or, where possible, by histological analysis. All cases were presented to the MCOT for consideration of the final management plan based on all the available information. In order to evaluate the clinical impact of FDG-PET, in each case management based on CT results was noted and compared with the management as directed by new or additional information obtained from FDG-PET.

Data and statistical analysis

For the purposes of presentation of data, patients were analysed in two groups: those assessed for detection of recurrence and those evaluated for extent of disease once recurrence had been confirmed. Findings were classified as true positive (TP), true negative (TN), false positive (FP) and false negative (FN). An assessment as to whether the additional information gathered from FDG-PET changed clinical management was based on the initial treatment plan using the CT report and then on any change as a result of the PET report. The difference in the ability of FDG-PET and CT to correctly direct clinical management was statistically evaluated using McNemar's test for matched pairs and considered significant when $P<0.05$.

Results

Forty-two patients were referred for detection of possible recurrence and, if recurrence was present, the patients underwent evaluation of the extent of confirmed recurrence. Follow-up to date has been for a mean of 15.6 months after PET scan or until death (two cases). The distribution of detected disease is listed in Table 1.

Table 1. Distribution of recurrent colorectal cancer in 42 patients studied with FDG-PET and CT. All results were confirmed by histopathology and/or clinical and radiological follow-up

Site	No.
No recurrence	12
Local recurrence only	7
Local recurrence and metastases	8
Hepatic metastases – solitary	4
Hepatic metastases – multiple	6
Hepatic metastases – plus extrahepatic lesions	5
Total	42

Detection of recurrence

Of the 42 patients investigated, 30 (71%) had a final diagnosis of local recurrence or metastatic disease which was confirmed by histological evidence in 16 cases and by the clinical course and follow-up radiology in the remainder.

FDG-PET yielded a correct diagnosis in 35 out of 42 patients (83%) compared to 31 (74%) with CT. FDG-PET had a sensitivity of 93% and a specificity of 58% compared with CT, which had a sensitivity of 73% and a specificity of 75% (Table 2). FDG-PET was of benefit for differentiating postoperative and/or post-radiotherapy scar from tumour recurrence (Fig. 1). This may only be possible with a metabolic signal.

In addition, one patient presented with an elevated CEA, but CT of the abdomen and pelvis was reported as normal other than showing the presence of either a bulky or fibroid uterus. Two years previously the patient had undergone anterior resection of the rectum followed by adjuvant chemotherapy. FDG-PET demonstrated an area of avid FDG uptake in the pelvis (Fig. 2) and at subsequent laparotomy an isolated recurrence of a rectal carcinoma was found to have invaded the left ovary. This use of FDG-PET has already been shown to be of clinical value when managing patients with a rising CEA but normal or equivocal imaging [15], and we have reported such a case included in this study [16].

Table 2. Results of FDG-PET and CT for the detection and staging of recurrent and metastatic colorectal cancer (n=42)

	TP	FN	TN	FP	PPV (%)	NPV (%)	Sensitivity %	Specificity %
Detection of recurrent and metastatic colorectal cancer (n=42):								
PET	28	2	7	5	85	78	93	58
CT	22	8	9	3	88	53	73	75
Staging of the extent of locally recurrent colorectal cancer (n=15):								
PET	8	0	6	1	89	100	100	86
CT	6	2	7	0	100	78	75	100
Staging of the extent of colorectal cancer liver metastases (n=15):								
PET	11	0	4	0	100	100	100	100
CT	5	6	4	0	100	40	45	100

TP, True positive; FN, false negative; TN, true negative; FP, false positive; PPV, positive predictive value; NPV, negative predictive value. All results confirmed by histopathology and/or clinical and radiological follow-up

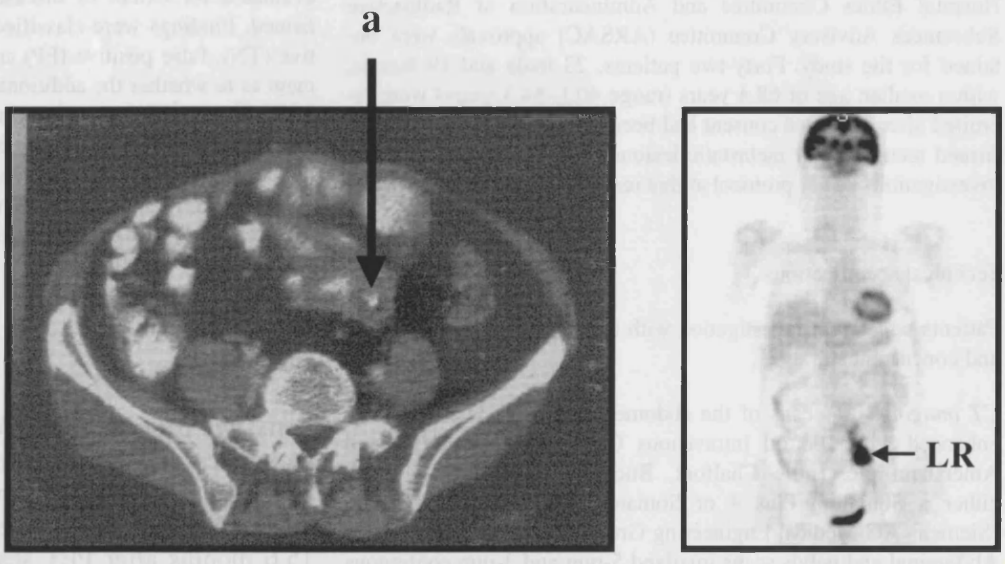

Fig. 1. Transaxial CT through the lower abdomen in a patient who had previously undergone resection and anastomosis for an adenocarcinoma of the sigmoid colon. This follow-up CT scan delineated an abnormal soft tissue mass at the anastomosis (*a*), which was thought to be benign. Coronal FDG-PET demonstrates avid FDG uptake in the left lower quadrant, which is indicative of a local recurrence (LR)

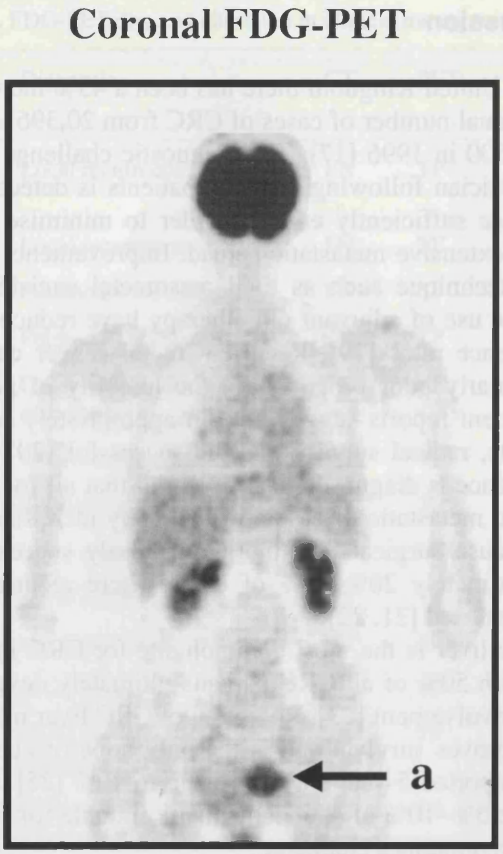

Fig. 2. Coronal FDG-PET study in a patient who previously underwent anterior resection of a rectal cancer. The tumour marker CEA began to rise 2 years postoperatively although the patient remained asymptomatic and no recurrence was identified on conventional imaging. FDG-PET detected a recurrent lesion (*a*) in the pelvis. This was successfully resected

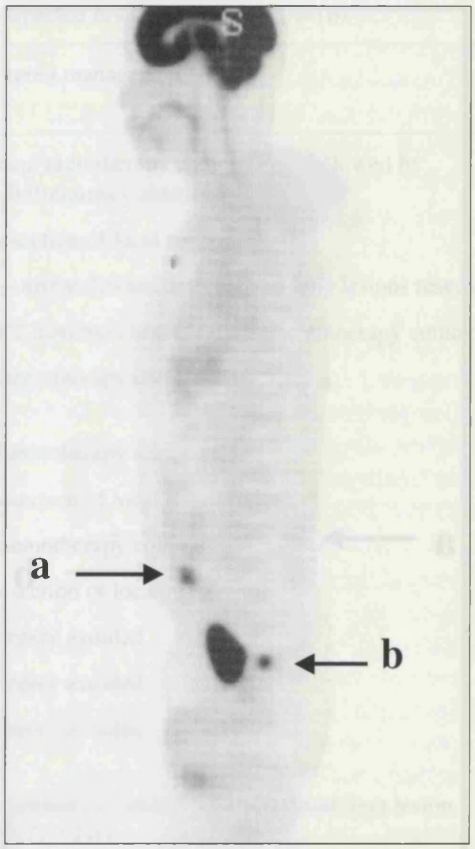

Fig. 3. Sagittal FDG-PET in a patient showing a recurrent pelvic tumour (*b*) as well as an abdominal wall recurrence (*a*)

Assessment of the extent of spread

Extent of spread from local recurrences. Of 15 patients who had recurrence confirmed, eight had metastatic disease (Fig. 3). The overall sensitivity of FDG-PET for the detection of metastatic disease in patients with a confirmed extrahepatic recurrence was 100% compared to 75% with CT. Specificity was 86% for FDG-PET and 100% for CT (Table 2). In all eight patients FDG-PET correctly diagnosed the site of metastases, but CT was correct in only six. The single false-positive FDG-PET scan was in a patient who had confirmed local pelvic recurrence with an additional FDG-avid lesion in the apex of the right lung. This was a tuberculous granuloma and was treated as such.

Liver metastases. In 15 patients with CRC liver metastases, FDG-PET had a sensitivity of 100% for the detection of additional disease, compared to 45% for CT. Both investigations had a specificity of 100% (Table 2). Four patients had truly solitary lesions, six had multiple liver metastases and five had extrahepatic metastases. FDG-PET and spiral CT both identified the four patients with solitary lesions. FDG-PET identified multiple and not solitary liver lesions in all six patients, whereas CT detected only two out of the six (Fig. 4). Spiral CT also failed to detect intra-abdominal, extrahepatic metastases that were present on FDG-PET in two patients. FDG-PET detected additional pulmonary lesions in three patients. This initiated further imaging of the thorax. In all cases CT of the chest subsequently demonstrated the pulmonary metastases. At our institution these lesions would have been missed had it not been for the FDG-PET scan because it is routine practice to perform CT scan of the liver and lung bases only when assessing liver metastases.

Altered clinical management

In total, eight patients (27%) were upstaged directly as a result of FDG-PET. FDG-PET also significantly altered clinical management ($P<0.01$) to the benefit of 14 patients (Table 3). In two other patients, FDG-PET led to invasive investigations, which ultimately did not benefit patient management. In both cases histological confirmation of the diagnosis was obtained. In 9 of the 14 patients, FDG-PET detected local recurrences; either these were resected or non-surgical treatments were commenced. This would not have occurred on the basis of

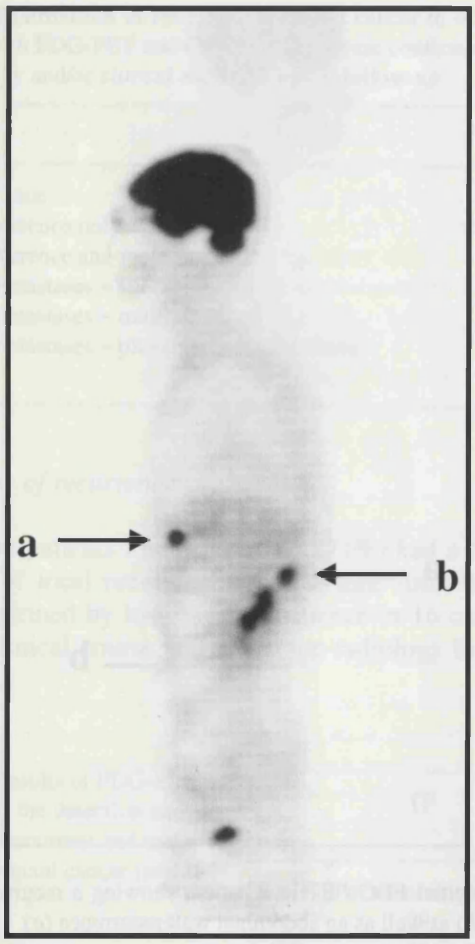

Fig. 4. Sagittal FDG-PET in a patient with two colorectal liver metastases (*a and b*). CT only identified a single "resectable" lesion

CT criteria alone. The final diagnosis was confirmed histologically in seven cases and clinically and radiologically in the remaining two. These nine patients included two in whom not only recurrence but also unsuspected distant metastases were detected.

The remaining five patients had CRC liver metastases. In two patients with multiple and not solitary liver metastases and another with additional extrahepatic metastases, hepatic resection was avoided. In all three cases, clinical course and follow-up radiology confirmed the diagnosis beyond doubt. In one patient, hepatic resection was carried out along with resection of an unexpected and histologically confirmed tumour recurrence in the appendix that was detected on FDG-PET alone. In the fifth patient, FDG-PET detected a second liver metastasis in addition to what was thought to be a solitary lesion on CT. The patient was put on a more intensive imaging follow-up schedule and the second lesion became apparent within 3 months. The patient then underwent successful radiofrequency thermoablation of this lesion.

Discussion

In the United Kingdom there has been a 45% increase in the annual number of cases of CRC from 20,396 in 1971 to 29,500 in 1996 [17]. The diagnostic challenge facing the clinician following up CRC patients is detecting recurrence sufficiently early in order to minimise subsequent extensive metastatic spread. Improvements in surgical technique such as total mesorectal excision [18] and the use of adjuvant radiotherapy have reduced local recurrence rates [19]. Recurrent rectal cancer carries a particularly poor prognosis in the majority of patients, but recent reports suggest that in appropriately selected patients, radical surgery may be successful [20]. When recurrence is diagnosed, it is essential that all foci of local and metastatic disease are accurately identified. This is because surgical re-exploration is only successful in approximately 20%–30% of cases where recurrence is truly isolated [21, 22].

The liver is the most common site for CRC metastasis, with 50% of all CRC patients ultimately developing liver involvement [23]. Resection of CRC liver metastases improves survival and is the only hope of cure [24], with reported 5-year survival of up to 40% [25]. Selecting the 5%–10% of patients who are suitable for such resection remains a challenge.

Current diagnosis of recurrence relies on a combination of regular clinical examination, CT scan, colonoscopy and usually measurement of tumour markers such as CEA [26]. It is estimated that only 6% of recurrences are intraluminal [11] and CEA has been reported not to be sufficiently sensitive (59%) or specific (84%) for surveillance [27]. CT has a better sensitivity, but there may be significant difficulties in differentiating tumour recurrence from benign postoperative and/or post-radiotherapy fibrosis [28]. T1- and T2-weighted MRI and endorectal coils may be slightly more accurate for this purpose, but examination time is considerable and the accuracy has been questioned [29]. Endo-anal ultrasound may also have a role to play, but imaging protocols need to be intensive and standardised. Diagnosis of recurrence in normal-sized lymph nodes would remain a problem with all these techniques. As regards imaging of the liver, one study has highlighted the inaccuracy of CT, showing that 7% of liver lesions had been missed and that the number of lobes involved had been underestimated in 33% of patients [30]. The application of PET to CRC dates back to 1982 [31] and offers the hope of improved clinical management.

Our results confirm the findings of others [14, 32, 33, 34] that FDG-PET is more accurate for detecting recurrence and making a correct diagnosis. More importantly, in 14 out of 16 patients management was altered to the benefit of the patient. The specificity of FDG-PET in our study remains a relative weakness of the technique when compared with spiral CT, although a recent meta-analysis suggests that FDG-PET has a specificity of 76% for

Table 3. FDG-PET-directed alteration in clinical management in patients with suspected or confirmed CRC (n=16)

Patient	Diagnosis	CT	PET	Diagnosis Confirmation	Altered management
1	Local recurrence	FN	TP	H	Local radiotherapy commenced, followed by radiofrequency ablation
2	Local recurrence	FN	TP	H	Resection of local recurrence
3	Pulmonary metastases	FN	TP	H	Recurrent disease detected and lung lesions resected
4	Pulmonary metastases	TP	TP	C	PET directed chest CT, then chemotherapy commenced
5	Local and pulmonary metastases	FN	TP	C	Chemotherapy commenced
6	Local recurrence	FN	TP	H	Chemotherapy commenced
7	Local recurrence	FN	TP	H	Resection of local recurrence
8	Local recurrence	FN	TP	H	Chemotherapy commenced
9	Local recurrence	FN	TP	H	Resection of local recurrence
10	Liver metastasis	FN	TP	C	Surgery avoided
11	Liver metastasis	FN	TP	C	Surgery avoided
12	Liver and distant metastasis	FN	TP	C	Surgery avoided
13	Liver metastasis and luminal recurrence	FN	TP	H	Resection of luminal recurrence and liver lesion
14	Multiple liver metastases	FN	TP	C	Resection of one lesion and radiofrequency ablation of second lesion
15	? Pelvic recurrence of rectal cancer	TN	FP	H	Sigmoidoscopy and biopsy were negative for tumour cells, but positive for inflammatory cells
16	? Recurrence in a pelvic lymph node	TN	FP	H	CT-guided biopsy

TP, True positive; FN, false negative; TN, true negative; FP, false positive; H, histological diagnosis; C, clinical and radiological confirmation of diagnosis

recurrent CRC [14]. FDG-PET is also more accurate than CT for staging locally recurrent CRC and metastases to the liver. As a result, inappropriate surgery was avoided in three patients. It is the alteration of clinical management demonstrated in our study that supports the routine use of PET in the imaging algorithm for patients with recurrent CRC.

These findings must be interpreted within the context of the limitations of both our study and FDG-PET as a clinical imaging modality. Tissue uptake of FDG is dependent on several factors, including tissue perfusion, oxygenation and the presence of inflammatory cells. In this study the presence of inflammatory cells caused a false-positive diagnosis of recurrence in six cases. In one case, clear evidence of infection was proven, while reactive pelvic lymph nodes were thought to be responsible for another two. In a further case, borderline FDG uptake in the lung was incorrectly interpreted as representing a pulmonary metastasis. In the remaining two patients, both with uptake in the lung and one with additional pelvic tracer accumulation, reactive lymphadenopathy was thought to be responsible. The reason for the increased tracer uptake in these cases is that inflammatory cells behave almost identically to cancer cells with respect to glucose metabolism.

There were two false-negative FDG-PET studies. In one of these the patient had a pelvic recurrence of rectal carcinoma, which was radiologically and histologically proven. FDG-PET showed high tracer uptake that was interpreted to be in the bladder or a bladder diverticulum. SUV for this lesion was 27.8 compared with a mean SUV of 6.4 (SD ±1.70) for confirmed recurrent lesions in the pelvis. In the other patient there was no FDG uptake in a known solitary CRC liver metastasis. Treatment was not altered and the patient underwent resection. The patient had completed chemotherapy 3 weeks previously and the liver lesion, which was metabolically silent on FDG-PET, was confirmed to be necrotic on histological analysis. There were no cases in which CRC was confirmed but FDG-PET was entirely normal.

Visual analysis could be criticised as often, normal tracer uptake is misinterpreted. The interpretation of FDG-PET scans is dependent on knowledge and experience of normal tracer biodistribution and use of the SUV is not always helpful. Interpretation may be extremely difficult when tracer uptake is borderline or inflammatory processes are present. In this study, as mentioned above, the mean SUV for recurrent pelvic lesions was 6.4 (SD ±1.70) compared with a mean SUV of 5.1 (SD ±1.73) for the four false-positive pelvic lesions. The mean SUV for pulmonary metastases was 5.3 (SD ±0.87) compared with a mean SUV of 5.0 (SD ±2.56) for the false-positive pulmonary lesions. In both instances there is the suggestion that a cut-off value could be applied for malignant lesions, but owing to an insufficient spread of data this cannot yet be statistically evaluated. An SUV of 3 has been suggested in the past, but in the gastrointestinal tract variable FDG uptake means that benign lesions can have SUVs of between 5 and 10 [35]. We corrected SUV for body surface area (data not presented) and showed a correlation with SUV corrected for total body weight. The use of SUV corrected for body surface area is, therefore, no more helpful than SUV corrected for body weight in deciding whether a lesion is malignant. It appears that at present, visual analysis remains the preferred method of assessment in this application of FDG-PET.

Other proposed solutions for improving on the poor specificity are firstly, the use of image co-registration (combining the CT and PET images) and secondly, the use of more specific tracers. Studies of the fluorinated thymidine analogue fluorothymidine are currently in progress. This tracer is a marker of deoxyribose nucleic acid synthesis and produces images based on cellular proliferation.

Our study is also limited by the low rate of histological confirmation of diagnosis. Histological evidence was obtained in 12 out of 27 patients with suspected local recurrence and 4 out of 15 patients with colorectal liver metastases. In all other cases diagnosis depended on intensive clinical follow-up and correlation with conventional imaging, using multiple modalities if FDG-PET was positive and CT negative. In certain cases it would have been unethical to investigate all PET-detected lesions by invasive means and chemotherapy was usually started based on criteria which are routinely used at our institution. Unequivocal clinical disease progression along with radiological evidence of CRC recurrence/metastasis was identified in 15 patients followed up in this way. In the remaining 11 patients, we have so far been unable to prove that there was no recurrent disease other than by the fact that radiological, endoscopic and clinical examinations have been negative. In five of these cases both FDG-PET and CT indicated that no disease was present. It may be that there were lesions that neither of the imaging modalities detected, resulting in overestimation of the true sensitivity of both PET and CT. In the six cases in which there was disagreement, if the opposite diagnosis to that used for our analysis were to be taken as the true diagnosis then the sensitivity and specificity of FDG-PET would be 86% and 66%, respectively, compared with 69% and 100% for CT.

We found that FDG-PET had a significant impact on clinical management (Table 3). Surgery to the liver, with its attendant morbidity, was avoided in three patients. This has important cost implications for the healthcare provider, offering the possibility of appropriate use of resources. Five patients underwent resection of recurrent disease as a result of early diagnosis using FDG-PET. Because FDG-PET provides the opportunity to perform this surgery, which may not have been undertaken in the past, data now have be collected regarding actual survival and disease-free interval in this group. Finally, non-surgical therapies, mainly chemotherapy, were commenced in six patients. It is thought that chemotherapy administered to patients with asymptomatic recurrent or metastatic CRC does have benefits. Again, the actual benefits of early commencement of therapy can now be tested if FDG-PET is incorporated into routine management.

FDG-PET is not widely available in the United Kingdom owing to a combination of a lack of trained staff and tracer production infrastructure and the cost of PET scanners. For PET to be successfully applied to clinical practice in the United Kingdom, substantial investment is required in these areas. Manufacturers continue to advance technology and devise solutions such as gamma camera PET and partial ring PET cameras, which reduce the cost of the hardware. However, these systems lead to reduced sensitivity compared with state-of-the-art PET scanners and their role is therefore disputed. Valk and colleagues estimate that in an oncological context, the cost savings from contraindicated operations exceed the cost of a PET scan by a ratio of between 2:1 and 4:1 [36].

In conclusion, we believe that our study confirms the important role FDG-PET has to play in the evaluation of patients with suspected recurrent CRC and CRC liver metastases. FDG-PET is a minimally invasive, whole-body imaging investigation with a high sensitivity for CRC. It alters patient management in that it enables appropriate selection of patients for different treatments based on accurate results regarding the presence and extent of recurrence. Even though the technique is evolving, with combined PET-CT machines now available and research into new tracers at an advanced stage, FDG-PET already has a great deal to offer patients with suspected or confirmed recurrent CRC.

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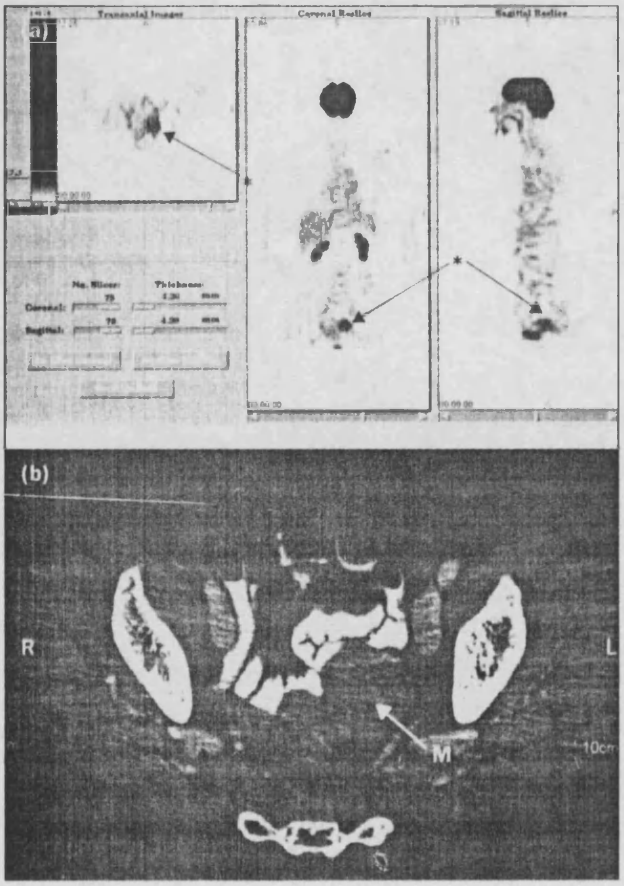
Clinical picture

Asymptomatic patient with an increasing concentration of CEA

We present here an example of how metabolic imaging using positron emission tomography (PET) can help resolve a difficult diagnostic dilemma. In January 2000, a 72-year old female presented with a sudden increase in carcinoembryonic antigen (CEA) to 11 μg/L (normal range 0–5 μg/L). She had previously had an anterior resection of the rectum followed by adjuvant chemotherapy with 5-fluorouracil and folinic acid for a moderately differentiated Dukes' B adenocarcinoma. At routine follow-up she had been asymptomatic with no focus of recurrence detected on radiological (6-monthly CT) or endoscopic investigation.



The management options were either to adopt a 'wait and see' policy or to evaluate the patient using a metabolic imaging technique, such as PET with the tracer fluorodeoxyglucose (FDG). The first option may lead to detection of recurrence at an inoperable stage. The second option uses a non-invasive imaging modality that is both sensitive and specific for recurrent colorectal cancer.

(a) The patient had a whole body FDG-PET, which showed considerable tracer uptake in the pelvis (*), reported as isolated colorectal cancer recurrence. (b) A concurrent spiral CT performed after the FDG-PET result was known then revealed a mass (M) in the pelvis, which was reported as a uterine fibroid.

At laparotomy, an isolated 8 x 6 x 4.5 cm mass corresponding to the lesion seen on FDG-PET and CT was identified, completely infiltrating the left ovary. The lesion was resected and histopathological examination confirmed a recurrent rectal adenocarcinoma.

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Review

Positron emission tomography and colorectal cancer

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Background: The oncological applications of positron emission tomography (PET) have gained widespread acceptance. This rapidly evolving technology has been applied successfully to colorectal cancer, but has not yet become part of routine clinical practice. This review considers (1) the biological basis for the use of PET in colorectal cancer, (2) the technical aspects of PET relevant to the referring clinician and (3) the application of PET to the management of primary and recurrent disease.

Methods: A Medline database search was performed for the period 1980–2000. Experience was also drawn from the first 40 patients with colorectal cancer investigated at this institution.

Results and conclusion: PET has a proven role, and is cost effective in the management of recurrent cancer and the monitoring of therapy. However, further evaluation is still required to justify its routine use for other indications in colorectal cancer. Development of new positron-labelled radiopharmaceuticals, in parallel with advances in detector technology and innovative models for tracer production and distribution, means that the availability of PET and its applications in the management of colorectal cancer will expand over the coming years.

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Introduction

Colorectal cancer is the second commonest cancer to occur both in the European Community[1] and in the USA[2,3]. The disease kills one in every two people affected. Despite the continuing advances in therapeutic strategies, both surgical and non-surgical, recurrence rates after initial treatment are estimated to be 30–40 per cent; recurrence usually occurs within the first 2 years of treatment[3–5]. There is weakness in the initial staging process and there is evidence that current methods of imaging patients with colorectal cancer are not sufficiently accurate[6]. Computed tomography (CT) forms part of the staging process for primary cancer, but it has a low staging sensitivity[7]. Intraoperative ultrasonography improves the detection of liver lesions, but this information cannot be provided before operation and so cannot contribute to preoperative patient management[8].

Detection of recurrence can also be difficult. Serial measurement of carcinoembryonic antigen (CEA) concentration in the blood is the most frequently used method for detection of asymptomatic recurrence[9], but both sensitivity (59 per cent) and specificity (84 per cent) are low[10]. The routine use of CT for postoperative surveillance is conventional, but it has not been shown to be either sensitive or specific[6,11,12]. Although magnetic resonance imaging (MRI) may augment CT in differentiating local recurrence from scar tissue in the pelvis[13,14], limitations still exist in terms of specificity and size of tumour detected[15]. Additionally, the dilemma remains of what course to take when the CEA level rises in association with minimal symptoms and normal imaging.

Positron emission tomography (PET) is beginning to make an impact in the UK. This technology couples picomolar sensitivity with high-resolution imaging. Positron emitting radiopharmaceuticals are used to target malignant or metabolically active tissue[16]. PET was considered a research tool when first applied to oncology by Di Chiro *et al.*[17] for the characterization of brain tumours. The application of PET to colorectal cancer dates back to 1982[18] and is based on the finding that the tracer 2-[^{18}F]fluoro-2-deoxy-D-glucose (F-18-FDG) concentrates in malignant tissue owing to an increase in glycolysis compared with normal tissue[19,20]. Conventional imaging studies, such as CT, MRI and ultrasonography, rely on structural change within the tissue and are reasonably good methods for assessing local infiltration in advanced tumours[12,21,22]. Functional imaging, such as PET and immunoscintigraphy, rely on abnormal cellular metabolic activity that usually precedes any structural change[23,24]. In the context of colorectal cancer, the areas of weakness

described for conventional imaging are the areas of strength for PET[25–27]. This article outlines the biological basis and technical considerations for the use of F-18-FDG PET in colorectal cancer, and examines the experience gained to date with F-18-FDG PET in colorectal cancer management.

Methods

A review of the literature was undertaken by searching the Medline database for the period 1980–2000. Keywords used were: 'PET', 'positron emission tomography', 'colorectal cancer', 'treatment evaluation', 'staging' and 'computed tomography'. Articles retrieved were checked manually and only those references that were of relevance or contained validated new information were included.

Rationale for the use of positron emission tomography in the management of colorectal cancer

Biological basis

The biological basis for PET centres on the observations made by Warburg[28,29] that cancer cells exhibit enhanced glycolysis. Glucose is preferentially concentrated in malignant cells owing to an increase in membrane glucose transporters[30,31] as well as an increase in some of the principal enzymes, such as hexokinase, phosphofructokinase and pyruvate dehydrogenase[31–33].

F-18-FDG, a radiolabelled analogue of glucose, decays by positron emission and is a commonly used tracer in PET imaging. Like unlabelled glucose, it concentrates in malignant cells. As it decays a positron is emitted which, after a very short path, collides with an electron. This leads to the release of two photons of 511-KeV energy, which travel at almost 180° to each other[16]. A PET scanner is designed to detect these photons and determine their point of origin, such that an image can be constructed based on detected activity. The mechanism by which F-18-FDG accumulates in human cancer cells is based on an increase in the expression of glucose transporter molecules on the cell surface[34–36]. Activation of the gene coding for the synthesis of the glucose transporter, *GLUT1*, is a major early marker of cellular malignant transformation[37]. Once transported into the cell, F-18-FDG is phosphorylated to F-18-FDG-6-phosphate by hexokinase, but takes no further part in the glycolytic or glycogen synthetic pathway. F-18-FDG-6-phosphate cannot diffuse out of the cell and becomes metabolically trapped as accessory metabolic pathways are too slow for the half-life of F-18-FDG. Therefore, the detected activity of fluorine-18 relates closely to the accumulated F-18-FDG-6-phosphate and the glycolytic activity for exogenous glucose[38,39]. *Fig. 1* illustrates this process schematically.

Although this model is widely accepted, there are certain important physiological factors that influence F-18-FDG uptake. These include tissue oxygenation, glucose utilization, regional blood flow and the inflammatory reaction surrounding the tumour[40–42]. The signal recorded from

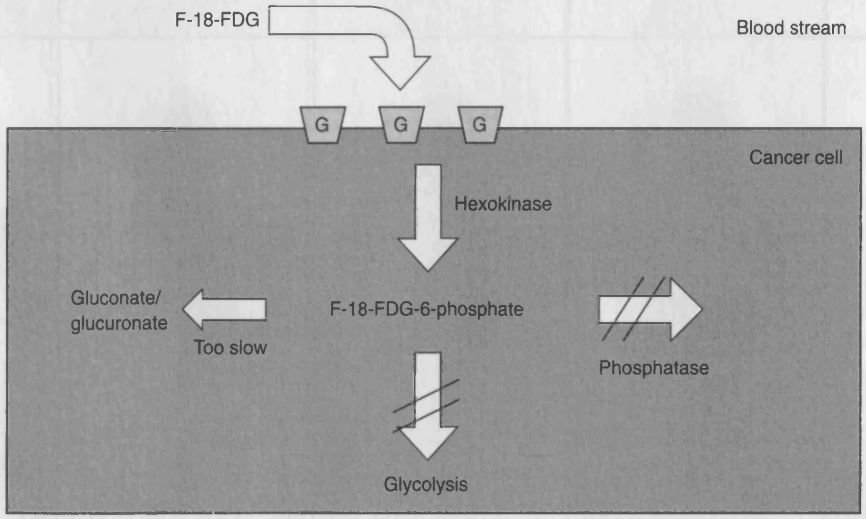


Fig. 1 2-[^{18}F]fluoro-2-deoxy-D-glucose (F-18-FDG) is transported into cancer cells as a result of upregulation of membrane glucose transporters (G). Once phosphorylated by hexokinase to F-18-FDG-6-phosphate, the fluorine-18 is metabolically trapped. F-18-FDG-6-phosphate takes no further part in glycolysis and there is little phosphatase activity. Alternative pathways to gluconate and glucuronate are too slow for the half-life of this compound and it cannot diffuse out of the cell

F-18-FDG may be from a composite area, interfering with the specificity of F-18-FDG PET for malignant tissue[41,42]. For example, there may be difficulty in differentiating tumour from active inflammation in the pelvis, as F-18-FDG uptake reflects the metabolic activity of a tissue[25,43,44].

Technical aspects

Instrumentation

The past 5 years have witnessed a significant expansion of the technology available for PET imaging. The originally designed, full ring, multicrystal, whole body tomographs remain the gold standard. Improvements in software have impacted on their utility and acceptance. These instruments are expensive, but set the standard to be achieved. They make use of special bismuth germanate oxide radiation detectors and detector assemblies. Manufacturers are trying to address the need for cheaper instrumentation, and a range of different types of PET scanner are now available. New radiation detector technology is coming on to the market (lutecium orthosilicate and other types), and the basic Anger γ camera with sodium iodide crystals has been adapted such that PET imaging can also be performed. However, many, if not most, of these proposed solutions represent a technological compromise; their ultimate place and role have yet to be determined.

Procedure

A detailed description is not appropriate in this review. Patients are scanned fasting in order to maximize F-18-FDG uptake. In anxious patients an anxiolytic/myorelaxant is given to minimize confounding F-18-FDG uptake in muscle. Administration of hyoscine butylbromide may reduce uptake in normal bowel, which is another potentially

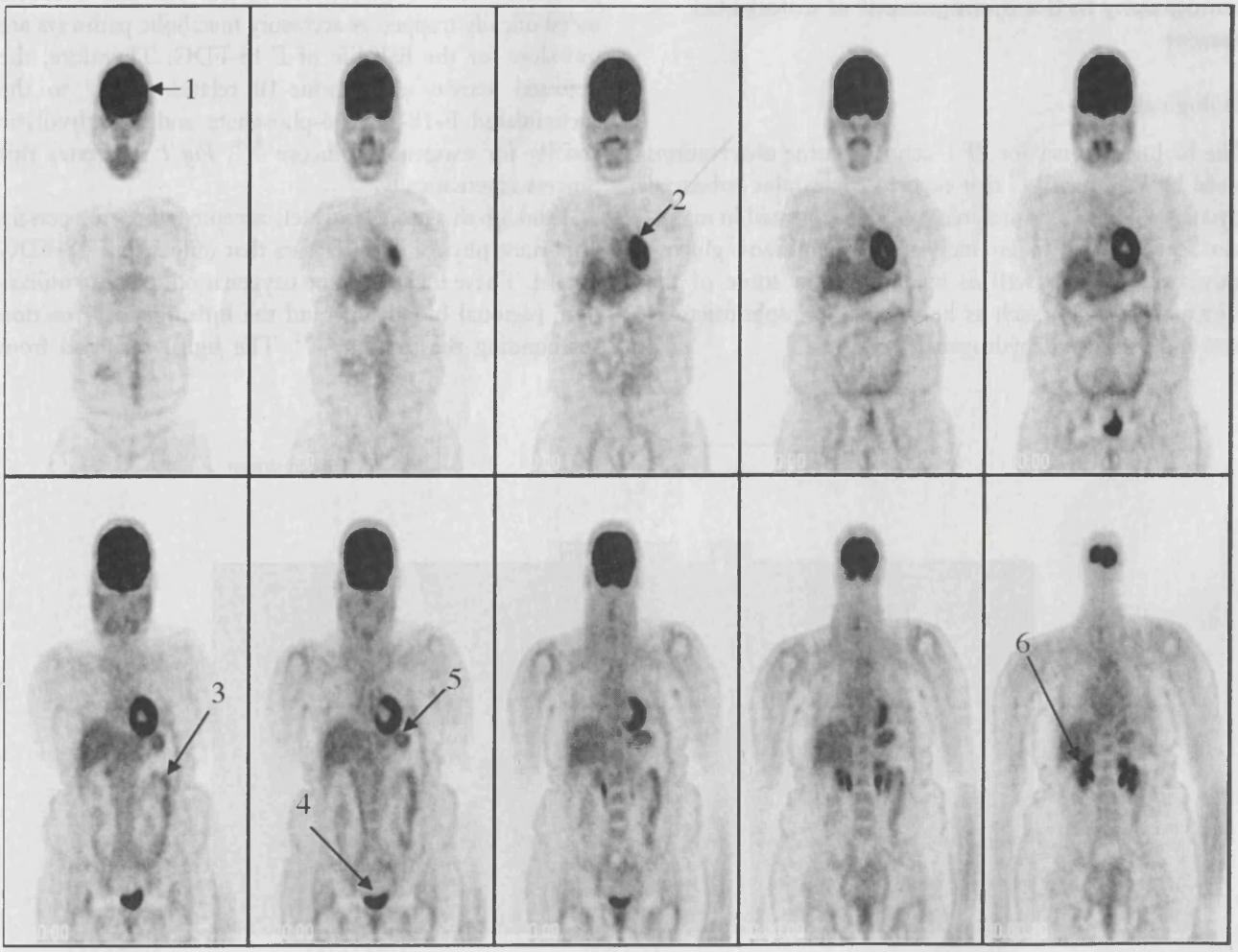


Fig. 2 Coronal sections of a normal 2-[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography study. The top left image is most anterior and subsequent images are more posterior until the final section is reached (bottom right). Normal uptake is seen in the brain (1), myocardium (2), colon (3), urinary bladder (4), stomach (5) and renal pelvis (6)

confounding factor. The scanning sequence can be tailor made, but scanning is usually optimized from the base of the skull to the upper third of the lower limb. Alternatively, whole body scans are recorded. Data can be obtained both from tracer emission and transmission data sets, for improved data analysis and quantification.

Image analysis

Whole body data can be analysed in terms of the pattern of distribution of labelled F-18-FDG and also with respect to the measurement of tracer uptake in a specific site. The quality of the data obtained depends significantly on the merits of the instrument used, the software available and the amount of tracer administered. A typical normal whole body scan for F-18-FDG is shown in *Fig. 2*. Normal and significant F-18-FDG uptake is always noted in the brain, and frequently, but variably, in the myocardium, stomach, liver, spleen, muscle and the lumen of the gastrointestinal tract. The bone marrow is highlighted, with variable intensity, often reflecting response to chemotherapy. The F-18-FDG tracer is eliminated by the kidneys, which are depicted along with the urinary bladder. Since the data are recorded in three dimensions, data sets can be formatted into any plane (transaxial, coronal and saggital).

F-18-FDG regional uptake is expressed in terms of semiquantitative standardized uptake values or differential absorption ratios (DARs). The DAR is calculated as (PET count × calibration factor)/(injected dose [millicuries]/body-weight [kilograms])[45,46]. These indices are useful in distinguishing inflammatory from neoplastic tissue uptake, and for monitoring disease *versus* time and/or therapy, but significant spread of this type of data must be taken into account. The use of a minimum DAR of 3 to diagnose malignant tissue, derived from PET studies of patients with colorectal cancer, may help to increase the specificity for this disease[47]. This method of analysing F-18-FDG accumulation has, however, been criticized[48] and normal gastrointestinal uptake with DAR values of 5–10 in the stomach, liver and intestine has been reported[49]. The accuracy of PET may be further enhanced by using external markers in order to compare conventional imaging with those acquired using F-18-FDG uptake. *Figs 3–5* are examples of PET images from patients with colorectal cancer studied at this institution. *Fig. 6* is a CT image of the patient presented in *Fig. 5*.

Possible applications of positron emission tomography in the management of colorectal cancer

Screening and diagnosis of primary colorectal cancer

Programmes of screening for colorectal cancer are described elsewhere[50] but evaluations of PET in this context are scarce. The availability and cost of PET (a PET study

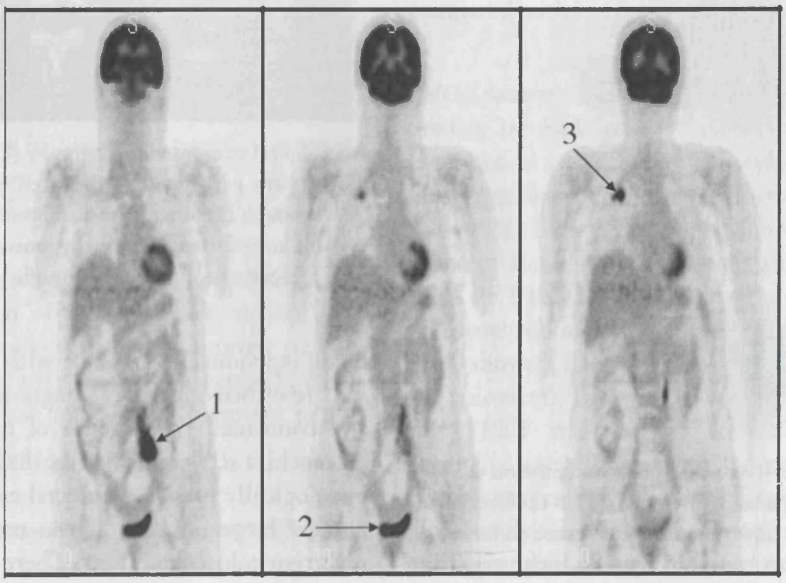
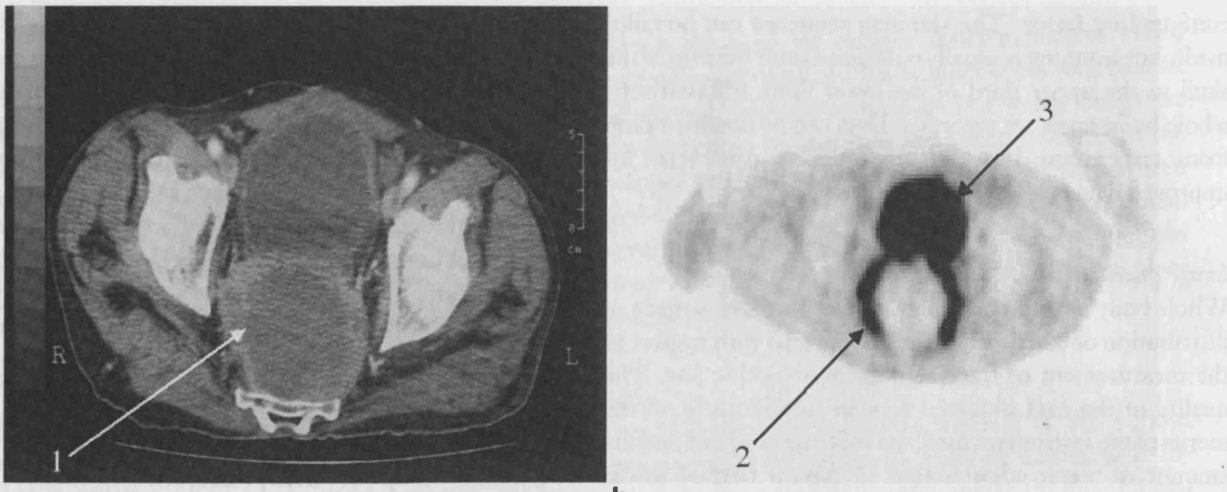


Fig. 3 Three coronal sections of a 2-[^{18}F]fluoro-2-deoxy-D-glucose (F-18-FDG) positron emission tomography study in a patient who underwent a Hartmann's procedure for a sigmoid adenocarcinoma followed by reversal. Sections are from anterior to posterior going from left to right. Increased F-18-FDG uptake representing local recurrence is seen in the region of the anastomosis (1). There is normal uptake in the urinary bladder (2). In addition, marked F-18-FDG uptake is seen in the upper zone of the right lung (3) representing a pulmonary metastasis. Computed tomography of the abdomen and pelvis was reported as showing benign fibrotic tissue at the anastomosis



a Computed tomography **b** Positron emission tomography

Fig. 4 **a** Computed tomography through the pelvis showing a large pelvic recurrence (1) in a patient who had previously undergone abdominoperineal resection for adenocarcinoma of the rectum. **b** Transaxial 2-[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography image confirms circumferential recurrence with central necrosis (2) behind the urinary bladder (3)

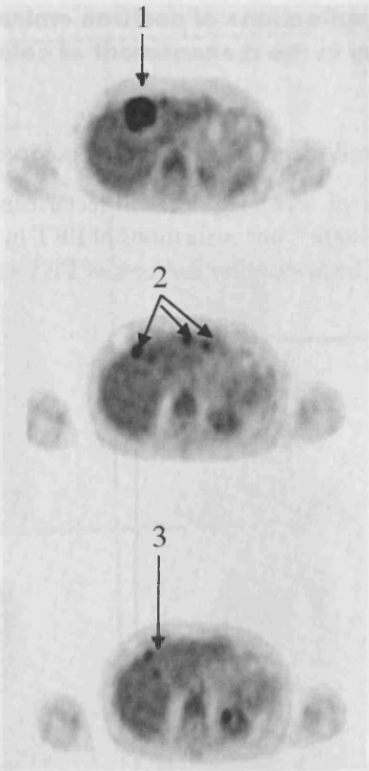


Fig. 5 2-[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography study showing a large metastasis (1) in the liver of a patient who had previously undergone colonic resection for adenocarcinoma. This is also evident in *Fig. 6*. In lower transaxial sections there are multiple lesions (2 and 3) which are not apparent on the computed tomography image shown as *Fig. 6*

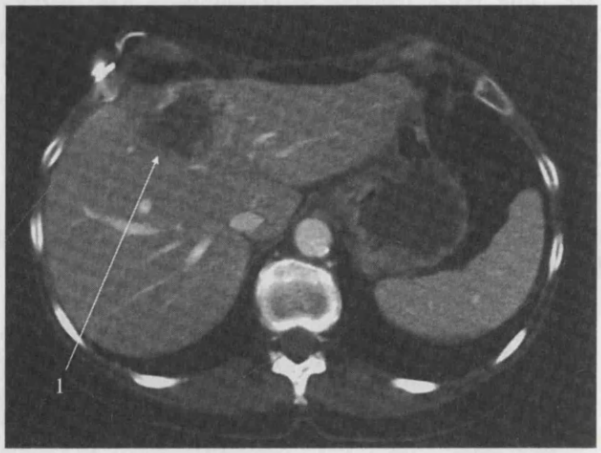


Fig. 6 Spiral computed tomography (CT) image at the level of the liver in a patient with an apparently solitary liver metastasis (1). Although no other abnormal lesions were detected on CT, 2-[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography (*Fig. 5*) clearly demonstrates multiple lesions

currently costs approximately twice as much as CT of the abdomen and pelvis[51]) are two important contributory factors. However, diagnosis of colorectal cancer in symptomatic individuals is possible with PET[45,52]. Ruhlmann *et al.*[53] described one patient diagnosed confidently with PET and confirmed the absence of tumour in two patients. Takeuchi *et al.*[45] confirmed the diagnosis in six patients with histologically proven colorectal cancer. Both reports were part of larger studies of the use of PET for imaging recurrent colorectal cancer. There are more published data on PET for recurrent cancer than on PET for primary cancer.

Currently, endoscopy and barium enema detect over 90 per cent of colorectal cancers[54], and are cheaper and more readily available than PET. Another technique, hydrocolonic sonography, is very accurate and has the potential to

become a diagnostic tool[55]. CT pneumocolon is an emerging technique that is minimally invasive, sensitive and specific for colorectal cancer[56,57]; it has a low morbidity and is cost effective. The application of three-dimensional CT reconstruction allows inspection of the mucosa and the possibility of 'virtual' colonoscopy[58,59]. This technique, however, requires further refinement[60]. These factors mean that PET is unlikely to play a significant role in diagnosing primary colorectal cancer at present, although its use as a screening investigation has yet to be fully evaluated. However, Rigo *et al.*[61] have stated that on current evidence inclusion of patients with low disease probability increases the likelihood of false-positive PET scans; this renders the technique unsuitable for unselected screening programmes.

Staging primary colorectal cancer

The aim of preoperative staging investigations is to identify the extent of local infiltration, involvement of lymph nodes and metastases to the liver. Accurate staging allows planning of any surgical procedure and informed decision making on additional treatments, for example neoadjuvant radiotherapy[62,63]. Liver metastases are found in 10–25 per cent of patients at the time of the initial operation for primary colorectal cancer. Of these patients 25 per cent are candidates for resection[64].

Local infiltration

CT is accepted as an accurate method of assessing local infiltration, especially in advanced tumours. Sensitivities of 61, 55 and over 70 per cent have been reported[11,12,65]. The accuracy of CT and MRI for detection and characterization of transmural penetration in low-stage tumours is poor. The development of more sophisticated CT, MRI and endoluminal MRI coils will affect these results[65]. Endoanal ultrasonography provides useful clinical evaluation of the depth of invasion of rectal cancers[21,66–70]. Laparoscopy allows direct visualization of the peritoneal surface and laparoscopic ultrasonography may further improve staging accuracy[71], but this is invasive, requires a general anaesthetic and information that could alter treatment is not available before operation.

Involvement of lymph nodes and extrahepatic intra-abdominal spread

Standard evaluation of lymph nodes and extrahepatic, intra-abdominal spread with CT and MRI is poor[12,72–74]; reported accuracy for CT ranges from 25 to 73 per cent with a sensitivity of 40 per cent for MRI. Overall sensitivity for malignant lymphadenopathy detected by CT is approximately 45 per cent[7]. Immunoscintigraphy has been shown by some to be significantly more sensitive for pelvic (74 per cent) and intra-abdominal (66 per cent) disease than CT (57 and 34 per cent respectively)[75], but other reports have noted a sensitivity of 23 per cent, a positive predictive value of 33 per cent and a negative predictive value of 37 per cent[76] for this technique.

Metastases to the liver

In the USA approximately 14 000 patients per year present with isolated liver metastases as their first recurrence[77] and about 20 per cent of these patients die with metastases exclusively in the liver. Ferrucci[78] suggests that the following questions should be answered when investigating the liver. (1) Are tumours present? (2) Are all lesions visible? (3) Are they malignant? (4) Are they resectable? The sensitivity of transabdominal ultrasonography is too low to exclude small lesions in the liver[50]. CT has a reported sensitivity of 72 per cent and specificity of 99 per cent; MRI yields similar results[12,79]. However, CT fails to demonstrate lesions in 7 per cent of cases and underestimates the number of lobes involved in 33 per cent[78,80]. Intraoperative ultrasonography is a sensitive investigation and is possible laparoscopically, but its use is not universal. Immunoscintigraphy has shown promise in this aspect of staging[81–84], with liver metastases not evident on CT being detected using indium-111-labelled anti-CEA antibodies. Although the sensitivity of immunoscintigraphy is high, specificity can be a problem, along with poor spatial resolution when compared with F-18-FDG PET.

Role of positron emission tomography

Studies by Falk *et al.*[51], Abdel-Nabi and colleagues[85], Ogunbiyi *et al.*[26] and Mukai and co-workers[52] form the most significant contribution to the debate on the use of F-18-FDG PET in the staging of primary colorectal cancer. None of these studies comments on the ability of F-18-FDG PET to stage local infiltration, but it should be noted that synchronous tumours can be detected if present. Falk's study showed, in a cohort of 16 patients with 15 cancer foci (12 colorectal, two liver and one mesenteric), that F-18-FDG PET was superior to CT for staging (positive predictive value 93 per cent and negative predictive value 50 per cent for F-18-FDG PET *versus* 100 and 27 per cent respectively for CT). The group contained patients with primary and recurrent colorectal cancer and, interestingly, one liver (2–3 mm in size) and one mesenteric metastasis were missed by F-18-FDG PET. In a more recent study, Abdel-Nabi *et al.*[85] investigated 48 patients with colorectal cancer (44 with biopsy-proven disease and four with highly suspicious findings). F-18-FDG PET had a positive predictive value of 90 per cent and a negative predictive

value of 100 per cent, but the sensitivity for lymph node metastases was 29 per cent, similar to that of CT. Detection of liver metastases by F-18-FDG PET was superior to that of CT (sensitivity 88 *versus* 38 per cent), but this was in only eight patients. So there appears to be a place for F-18-FDG PET in staging primary colorectal cancer and PET has the advantage of studying the whole body, thus requiring the patient to be submitted to a single staging investigation. F-18-FDG PET has been shown to be accurate for the detection of metastases to the liver in a small study group, but its accuracy for the detection of metastatic lymph nodes[52] is not fully established; further evaluation of F-18-FDG PET for staging primary colorectal cancer is required.

Surveillance and detection of recurrent colorectal cancer in treated patients

In up to 30 per cent of cases, recurrence following treatment of primary colorectal cancer is localized and so suitable for curative resection[86]. If detected early, survival may be improved, especially if radical surgery is performed[87]. To avoid unnecessary morbidity and mortality appropriate selection of patients is essential, as only 20–30 per cent of these particular cancers are curable[88,89].

Sensitivity (59 per cent) and specificity (84 per cent) for recurrence with serial measurement of CEA is low[10]. Routine surveillance with CT has gained acceptance, and its sensitivity for detecting intra-abdominal and pelvic abnormalities is high. However, differentiating benign fibrosis from tumour recurrence is difficult, if not impossible, without the use of a metabolic signal. This is especially so in the pelvis, where CT is not sufficiently specific[6]. MRI may give additional information and technology continues to improve, but there have been reports questioning its ability to distinguish recurrent tumour from fibrosis[90–92]. Immunoscintigraphy with indium-111-labelled B72.3 (sensitivity 74 per cent)[93], technetium-99m-radiolabelled anti-CEA monoclonal antibody (sensitivity 91 per cent)[94] and technetium-99m-labelled BW431/26 (sensitivity 92 per cent)[95] all show promise in the detection of recurrent colorectal cancer; this technique appears superior to CT for differentiating scar from tumour in the pelvis[96].

A dilemma also exists in the management of patients who present with an isolated increase in CEA level, with minimal symptoms and normal imaging. Observation may result in losing the opportunity to resect a curable recurrence, but aggressive investigation leads to psychological and physical morbidity, as well as incurring significant cost. In this context, tissue biopsy has a false-negative rate due to sampling error[97], even with CT guidance. Second-look laparotomy can lead to a definite diagnosis in 90 per cent of cases, yet between 12 and 60 per cent of these patients are unsuitable for resection[3] and suffer substantial morbidity. These findings contribute to the ongoing debate about the need for aggressive follow-up to detect recurrence after treatment for colorectal cancer[98].

Positron emission tomography versus *carcinoembryonic antigen measurement*

Flanagan *et al.*[99] assessed the potential role of F-18-FDG PET in patients with an unexplained increase in CEA level and normal CT scans. In 17 of 22 patients PET was abnormal, and tissue sampling and/or follow-up confirmed recurrence. Biopsy was performed in seven patients of whom four underwent curative surgical intervention. The clinical course and radiological follow-up confirmed extensive disease in eight of ten patients who did not undergo biopsy or operation. PET had a positive predictive value of 89 per cent and a negative predictive value of 100 per cent. While these results are encouraging, they should be interpreted cautiously as the study was small with the possibility of bias associated with retrospective analysis. The follow-up period of 6 months with CT or MRI to confirm a false-positive PET scan is probably insufficient, based on knowledge of the natural history of colorectal cancer. Finally, the method of analysis used to calculate F-18-FDG accumulation has been criticized and a more rigorous calculation of actual glucose metabolism suggested[48]. The superior accuracy of PET over CEA measurement for the detection of recurrent disease has also been discussed by Schiepers *et al.*[27], Takeuchi and colleagues[45], Delbeke and co-workers[43], and Beets and colleagues[100].

Positron emission tomography versus *conventional imaging*

Strauss and colleagues[25], Schlag *et al.*[44], Ito *et al.*[15] and Schiepers and colleagues[27] have all confirmed the value of F-18-FDG PET in differentiating scar tissue from local recurrence (*Table 1*). In Schiepers' study[27], 76 patients with confirmed or suspected recurrence were evaluated with F-18-FDG PET *versus* routine imaging (CT, ultrasonography, plain radiography). Sensitivity for disease in the pelvis was 93 per cent with F-18-FDG PET against 60 per cent with CT. The study also emphasized the value of F-18-FDG PET in detecting both hepatic disease (sensitivity 94 per cent with PET *versus* 85 per cent with CT/ultrasonography) and extrahepatic disease (14 foci in ten patients). Takeuchi *et al.*[45] also reported the accuracy of F-18-FDG PET in the diagnosis of pelvic recurrence in 15 of 16 patients with histologically proven pelvic recurrence (four of these patients had equivocal CT or MRI). These authors stated, by retrospectively analysing the DAR values and

Table 1 Studies of positron emission tomography in the detection and staging of recurrent colorectal cancer

Reference	Year	No. of patients	Sensitivity (%) PET	Sensitivity (%) CT	Specificity (%) PET	Specificity (%) CT
Yonekura *et al.*[18]	1982	3	100		100	
Strauss *et al.*[25]	1989	29	100		100	
Gupta *et al.*[101]	1991	18	100	70	86	43
Ito *et al.*[15]	1992	15	100		100	
Gupta *et al.*[102]	1993	16	90	60	66	100
Larson *et al.*[103]	1994	59	93		78	
Beets *et al.*[100]	1994	35	100 Local 47 Liver			
Pounds *et al.*[104]	1995	57	95		87	
Schiepers *et al.*[27]	1995	76	93 Local 94 Liver	60 85	97 100	72
Daenen *et al.*[105]	1996	19	95		87	
Lai *et al.*[106]	1996	34	93 Liver 100 Non-liver	100	100	100
Vitola *et al.*[107]	1996	24	90	86	100	100
Delbeke *et al.*[43]	1997	52	91	81 97*	96	60 5*
Ruhlmann *et al.*[53]	1997	59	100		67	
Ogunbiyi *et al.*[26]	1997	40	91 Local 95 Liver	52 74	100 100	80 85
Valk *et al.*[108]	1999	115	93	69	98	96
Flanagan *et al.*[99]	1998	22	100		71	
Takeuchi *et al.*[45]	1999	23	94		100	

*With computed tomographic portography. PET, positron emission tomography; CT, computed tomography

clinical findings, that a DAR cut-off value of 2·8 would have resulted in diagnosis with 100 per cent accuracy. It is also noteworthy that the CEA level was normal in five patients with recurrent lesions detected on F-18-FDG PET.

Staging of recurrent colorectal cancer

Current investigations are not sufficiently sensitive to differentiate isolated resectable disease from disseminated metastases. Reported sites most commonly affected by metastases vary. One study has reported 13 per cent to the liver, 4 per cent to abdominal lymph nodes, 3 per cent to lung, 2 per cent peritoneal, 1 per cent to bone and 1 per cent to brain[78]. Another suggests that the liver is affected in 33 per cent of cases, lung in 22 per cent, locoregional sites in 21 per cent, intra-abdominal sites in 18 per cent, retroperitoneal sites in 10 per cent and intraluminal sites in 6 per cent[5]. PET offers a highly sensitive, non-invasive means by which to detect recurrence and select the most appropriate treatment. Early reports suggest that F-18-FDG PET is more accurate than CT for the purpose of staging recurrent colorectal cancer[27,100].

Hepatic metastases

Beets *et al.*[100] demonstrated the value of whole body F-18-FDG PET for detecting colorectal cancer metastases to the liver. Schiepers et al.[27] confirmed a higher sensitivity and accuracy with F-18-FDG PET (94 and 98 per cent respectively) compared with CT/ultrasonography (85 and 93 per cent) in the detection of hepatic metastases. There were no false positives for F-18-FDG PET and one for CT/ultrasonography. There were two false-negative F-18-FDG PET scans for two nodules discovered in the liver at surgery. In each of the two patients the nodule was less than 1 cm in diameter and not detected by CT. Delbeke *et al.*[43] compared F-18-FDG PET with CT and CT portography; 52 patients were evaluated on 61 occasions (portography was not performed in all patients). The final diagnosis was made by histopathology in 44 patients and clinical/radiological follow-up in the remainder. For the 127 hepatic lesions identified in these patients, F-18-FDG PET had a sensitivity of 91 per cent, compared with 81 and 97 per cent for CT and CT portography respectively. For the 39 extrahepatic lesions the sensitivity of PET was 100 per cent, compared with 74 per cent for CT. Ogunbiyi *et al.*[26] assessed 40 patients with recurrent cancer and reported a higher sensitivity (95 per cent) and specificity (100 per cent) for F-18-FDG PET than for CT (74 and 85 per cent respectively) in the detection of hepatic metastases. These authors also found a higher accuracy for PET than for CT in delineating multiple liver lesions. More recent studies have demonstrated the value of F-18-FDG PET in the detection of both hepatic and extrahepatic metastases from colorectal cancer[43,107].

Extrahepatic metastases

Lai *et al.*[106] compared F-18-FDG PET with conventional imaging in 34 patients (CT in 34 with chest CT in 19 and chest radiography in 15). Unsuspected extrahepatic disease was confirmed in 11 patients and clinical management was affected in ten. Schiepers *et al.*[27] also reported that a significant number of unexpected extrahepatic metastases could be demonstrated using F-18-FDG PET. In this study, a total of 14 of 25 abnormal foci detected with F-18-FDG PET were confirmed by biopsy as metastases; the 11 false positives were all in the thorax. With image correlation and careful patient selection the false-positive rate may be reduced.

These studies demonstrate that PET is highly sensitive and accurate in the diagnosis and staging of recurrent colorectal cancer. Detection of unsuspected metastases by F-18-FDG PET ranges from 6 to 32 per cent[43,106] (*Table 2*). A multicentre study by the Institute of Clinical PET examined the cost effectiveness of 14 PET centres (reviewing the records of 267 patients who had been treated for

Table 2 Studies demonstrating that positron emission tomography detects colorectal cancer metastases unsuspected on conventional imaging

Reference	Year	No. of patients	Unsuspected metastases
Schiepers *et al.*[27]	1995	76	10 of 76 (13)
Lai *et al.*[106]	1996	34	11 of 34 (32)
Delbeke *et al.*[43]	1997	52	3 of 52 (6)
Valk *et al.*[108]	1999	115	23 of 78 (29)

Values in parentheses are percentages

colorectal cancer) and found that a potentially large saving could be made if F-18-FDG PET were to be incorporated into the routine management of recurrent disease. This is based on the reduction of unnecessary laparotomies performed (from 20 to 10 per cent) and the increased number of resections with curative intent[103].

Evaluating treatment in patients with colorectal cancer

Accurate information about the antitumour effect of radiotherapy and/or chemotherapy for colorectal cancer would guide planning and ongoing adjuvant therapy. Nagata *et al.*[109] demonstrated a correlation between F-18-FDG uptake and tumour response in patients treated for primary or metastatic liver lesions. Studies assessing the uptake of F-18-FDG measured by PET and correlation with the antitumour effects of chemotherapy have been reported for certain tumour types, including colorectal cancer[110–114].

Radiotherapy

The use of PET was evaluated by Haberkorn *et al.*[115] in 21 patients (41 examinations) with recurrent disease before and after radiotherapy treatment. A correlation was made between palliative benefit and reduction in F-18-FDG uptake in half of the patients, and F-18-FDG PET was found to be more accurate than CEA in assessing response. The authors postulated that the inflammatory response to radiotherapy might have caused an increase in F-18-FDG accumulation, which was wrongly interpreted as residual tumour. They suggest that a delay in post-treatment F-18-FDG PET evaluation of 6 months might increase the accuracy in terms of assessing tumour response. These findings mirror the results of other reports, such as those of Abe *et al.*[116] and Engenhart *et al.*[117].

Chemotherapy

The situation for monitoring chemotherapy in advanced colorectal cancer appears more promising. Early reports have shown high concentrations of [^{18}F]5-fluorouracil (F-18-FU) in responsive tumours[118–120]. Strauss and Conti[121] studied PET images of F-18-FU metabolite concentration and compared these with growth rate (using volume measurements of metastases on CT) before and during chemotherapy. Lesions with low FU uptake had a significant increase in volume and no response to treatment. The pharmacokinetics of FU[122–124] suggest that F-18-FU may be superior to F-18-FDG in predicting the response to treatment on an individual patient basis. Recently, Findlay *et al.*[110] evaluated the metabolism of colorectal cancer liver metastases using F-18-FDG PET before and at intervals after treatment in 18 patients. The findings were compared with tumour outcome as assessed conventionally by change in size on CT. Results were expressed as a ratio of F-18-FDG uptake in tumour and in normal liver. This ratio 4–5 weeks after treatment was able to discriminate response from non-response, both in lesion-by-lesion and overall patient terms (sensitivity 100 per cent for both, specificity 90 and 75 per cent respectively).

In 1994 a meeting of the European Community PET Oncology Concerted Action Group and the European Organization for Research and Treatment of Cancer PET Study Group brought together many members of the 31 European PET centres[125]. Their collaboration with oncologists led to the study of tumour response to chemotherapy in 12 groups and to radiotherapy in three groups. Although there was wide variation in the methodology between centres, assessment of F-18-FDG uptake was thought to be a satisfactory method for functionally imaging tumours, assessing metabolic rate and providing information on response to treatment. Patients with the biggest reduction in F-18-FDG uptake showed the best clinical response, and the use of [^{11}C]thymidine or [^{11}C]amino acids as tracers may provide an even more specific marker of cellular proliferation. These conclusions, along with proposals to advance PET methodology, to run PET studies in parallel with phase I/II clinical trials and to collect more information regarding the application of PET to specific tumours, provide an indication of the expectation of the role of PET in the management of colorectal cancer.

Conclusion

The application of F-18-FDG PET to oncology, and in particular to the management of colorectal cancer, continues to gain acceptance. PET is an expensive modality; start up costs are high because of the need to establish tracer production and distribution, purchase hardware and software, and train staff. There are approximately 200 PET systems in clinical use in the USA where state-of-the-art PET systems cost from US $800 000 to 2·5 million. In the

UK, PET systems cost between £1 and 1·5 million. The overall cost of whole body F-18-FDG PET is approximately £800 per study, of which £350 is required for a single dose of F-18-FDG. The cost of spiral CT of the abdomen and pelvis is £350.

There is a significant body of evidence to favour the use of F-18-FDG PET in the assessment of recurrent colorectal cancer mainly because it leads to alteration in clinical management[43,106,108] (for example, surgery may be avoided owing to the identification of non-resectable tumour). Valk *et al.*[126] studied patients with lung cancer (99 patients), recurrent colorectal cancer (57), melanoma (36), and head and neck cancer (29). They found that the savings from contraindicated surgical procedures exceeded the cost of PET by ratios of 2 : 1 to 4 : 1, depending on the indication. This same group also studied 115 patients with recurrent colorectal cancer and demonstrated that the potential saving from the diagnosis of non-resectable tumour by PET was approximately US $3000 per preoperative study[108]. This work confirms significant cost savings, similar to those obtained when F-18-FDG PET is used to assess solitary lung nodules[127], which must be considered when assessing the true cost of PET. The role of F-18-FDG PET in differentiating scar tissue from recurrent colorectal cancer is well established and PET is increasingly important for monitoring chemotherapy. More work is required to evaluate the use of F-18-FDG PET for screening, detection and staging of primary colorectal cancer.

Ongoing and future developments

Significant progress is to be expected with PET and other cross-sectional imaging modalities. Instrumentation continues to develop and multimodality imaging, using a single instrument, is a reality, with CT and/or MRI combined PET scanners and γ cameras capable of PET coming on to the market. This should allow cross-sectional imaging techniques (CT/MRI), which offer detailed anatomical information, and functional imaging techniques (PET), which offer metabolic information, to come together to increase the accuracy of imaging. As with any radionuclide tracer technique, PET will evolve in parallel with tracer development. A number of new tracers are being developed; the fluorine-18-labelled thymidines in particular are promising.

To fulfil its full clinical potential, PET must become more available, with instrumentation of a similar standard to that of the best PET technology currently available. Core centres able to label and distribute tracers form a fundamental infrastructure that must also be developed, if the promise of PET is to be realized worldwide.

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Systematic review

Somatostatin and octreotide in the prevention of postoperative pancreatic complications and the treatment of enterocutaneous pancreatic fistulas: a systematic review of randomized controlled trials

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Background: The aim of this study was to evaluate, through systematic review, the effectiveness of somatostatin and octreotide in the prevention of postoperative pancreatic complications and the treatment of established enterocutaneous pancreatic fistulas.

Methods: Electronic databases, including Medline and EMBASE, were searched systematically by using keywords including 'somatostatin', 'octreotide', 'fistula' and 'randomiz(s)ed controlled trial'. In addition, citations of relevant primary and review articles were examined. Particular authors were contacted when necessary. Data on patient recruitment, intervention and outcome were extracted from the included trials and analysed.

Results: Use of somatostatin or octreotide for the prevention of postpancreatectomy complications, including pancreatic fistulas, was identified in 14 randomized controlled trials, including one abstract and one conference proceeding, involving a total of 1686 patients. Use of somatostatin or octreotide for the treatment of established enterocutaneous pancreatic fistulas was identified in ten trials involving a total of 301 patients. Significant heterogeneity was found among the identified trials with regard to the definition of fistula, dosage of octreotide, starting time and duration of the treatment, among other factors.

Conclusion: There was major disagreement between the studies on whether use of the drugs in question is of value in preventing postoperative complications. This analysis suggests that, in units where the postoperative fistula rate following pancreaticoduodenectomy for neoplasia and other pancreatic conditions exceeds 10 per cent, somatostatin or octreotide administered before operation may significantly reduce the rate of major postoperative complications, particularly pancreatic fistulas. The identified evidence also suggests that there may be a limited role for such drugs in the treatment of established postoperative enterocutaneous pancreatic fistulas. A major conclusion is that further clarification of the roles of these drugs is still required through large, high-quality, randomized trials.

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Introduction

Discovered in 1972, somatostatin is a naturally occurring tetradecapeptide with a wide spectrum of mainly inhibitory biological actions[1]. Within the gastrointestinal tract, somatostatin has been found in the pancreas, stomach, intestinal mucosa and mesenteric neurones. Because of its inhibitory actions, it has been used in the management of upper gastrointestinal haemorrhage, secretory diarrhoea, dumping syndrome and peptide-secreting tumours. Since the mid-1980s, somatostatin has been advocated as an adjuvant therapy in the conservative treatment of patients with enterocutaneous pancreatic fistula. However, its short half-life (1·1–3·0 min) mandates continuous administration. Long-acting somatostatin analogues, such as octreotide acetate (Sandostatin SMS 210-995; Novartis Pharmaceuticals, East Hanoven, NJ, USA) and lanreotide, have been developed[2,3]. Octreotide has a biological half-life of 90–120 min and can be administered subcutaneously two or three times per day. Compared with somatostatin, it not