

Positron Emission Tomography, Computed Tomography, Magnetic Resonance Imaging and Staging in colorectal cancer

**A thesis submitted to the UCL (University College London)
for the Degree of Doctorate of Medicine (Research)**

by

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September 2019

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Abstract

The value of positron emission tomography magnetic resonance imaging (PET/MRI) and positron emission tomography computed tomography (PET/CT) in oncological imaging is based on the fundamental principle that abnormal alterations in intra-cellular biochemical reactions result in the development of malignancy. Positron-emitting analogue tracers may be synthesised from organic matter and utilised to demonstrate these intra-cellular sequential processes.

The principle aim of this study was to prospectively evaluate if PET/MRI may be considered to be a more accurate imaging modality than PET/CT or an equivalent or complimentary imaging modality to conventional imaging (CT or MRI) for the complete staging of patients with primary colon and rectal cancers. The purpose was to conduct investigations to enable evaluation of the diagnostic accuracy of PET/MRI and PET/CT for T, N and M colon and rectal cancer staging in a clinical setting.

The work in this thesis may help to evaluate PET/MRI as a new imaging modality by providing high-resolution anatomical, molecular and functional information, which in combination may allow the comprehensive assessment of tumour location and stage in a single imaging examination. PET/MRI may also potentially provide loco-regional and systemic staging of CRC disease. Through incorporation into CRC protocols, patient pathways may be streamlined and provide an effective algorithm for more appropriate and timely treatment, resulting in improved long-term survival.

Impact Statement

The work in this thesis in evaluating PET/MRI as a new diagnostic imaging modality for colon and rectal cancer may have significant research and clinical implications.

The benefits of work from this thesis may result in improved academic understanding of the pathogenesis of colo-rectal cancer and research methodology regarding optimising imaging protocols. This may result in further publications and international presentation of the values of PET/MRI.

The benefits of work from this thesis may potentially help to define a clinical pathway for improved single examination complete colorectal cancer staging. This may lead to more prompt diagnosis and subsequent treatment in this group of patients. The may ultimately result in improved clinical outcomes in this group of patients.

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Statement of originality

I declare that the studies described and presented in this thesis are the original work of the author. Data collection and analysis relating to the clinical aspect of this thesis are the sole work of the author.

All CT, MRI, PET/CT and PET/MRI image and data reconstruction was performed by senior qualified radiographers at the Institute of Nuclear Medicine at University College London Hospitals NHS Trust. Image analysis and tumour staging was carried out by senior radiologists and/or Consultant level Nuclear Medicine physicians. Histological tumour grading was performed by Consultant histopathologists with the assistance of laboratory technicians at University College London Hospital or the referring hospital.

All of the clinical studies performed within this thesis were conducted in accordance with protocols approved by the Ethics Committees of University College London Hospitals NHS Trust and University College London. Informed patient consent was obtained from each patient recruited (Ethics Committee Reference Number 05/Q0505/34).

This thesis has not been submitted in support of an application for another qualification or higher degree of this or any other university or institute of learning.

Mr Sanjay Dindyal.

Acknowledgements

I would like to firstly thank all of the patients who kindly agreed to participate in this thesis. Their strength, courage and humility I have found truly inspiring.

I would like to sincerely thank Professor Ashley Groves and Mr Daren Francis for permitting me to undertake this period of research. Their advice, support and encouragement during difficult periods have been invaluable.

I am eternally grateful to Simon Wan, Asim Afaq and Shih-hsin Chen for their help with my thesis analysis and statistics. Their kindness, support and wisdom have been much appreciated.

I would like to thank Miss Gabrielle Azzopardi, Raymond Endozo, Robert Shortman and John Hoath and all of the staff in the Institute of Nuclear Medicine at University College Hospital for their support of my research and without their help completion of this work would not have been possible.

Finally I would like to dedicate this thesis to my wonderful nieces, Mari and Liya, my parents Selvon and Drupattie, brother Shiva, sister in law Cathy, late grandfather Sonny Dindyal, late grandmothers Sheila Hanuman and Dolly Dindyal, for their continued support and encouragement throughout my career and without which none of this would have been possible.

In loving memory of the late,

Sonny Dindyal (12th November 1927 – 16th July 2011),

Dolly Dindyal (24th March 1928 – 23rd July 2019)

Sheila Hanuman (18th July 1934 – 24th October 2017)

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List of Abbreviations

AA	Abdominal aorta
AJCC	American Joint Committee on Cancer
APC	Adenomatous polyposis coli
ARSAC	Administration of Radioactive substances
CME	Complete meso-colic excision
CRC	Colorectal cancer
CRM	Circumferential resection margin
CT	Computerised Tomography
CE-CT	Contrast enhanced CT
DAR	Differential absorption ratio
DCBE	Double contrast barium enema
EORTC	European Organisation for the Research and Treatment of Cancer
FDG	[¹⁸ F] fluoro-2-deoxy-D-glucose
5FU	5-Fluorouracil
5-FUTP	5-Fluorouridine triphosphate
GLUT	Glucose transporter protein
HNPCC	Hereditary non-polyposis colorectal cancer
MDT	Multidisciplinary team
MRI	Magnetic Resonance Imaging
MSI	Microsatellite Instability
NICE	National Institute for Clinical Excellence
NPV	Negative predictive value
PET	Positron Emission Tomography.
PPV	Positive predictive value
ROI	Region of interest
SD	Standard deviation
SUV	Standardised uptake value
TA	Thoracic aorta
TME	Total meso-rectal excision
TNM	Tumour, Nodes, Metastases
UCL	University College London
UCLH	University College London Hospitals

CHAPTER 1

Introduction

1.1 Colorectal cancer

1.1.1 Epidemiology

The life expectancy in the United Kingdom (UK) has steadily increased for both sexes over the last decade. The life expectancy for men has increased from 73.4 years in 1993 to 74.8 years in 1999 and furthermore to 76.4 in 2018. There has also been a corresponding increase for women from 78.9 years in 1993 to 79.7 years in 1999 and 81.2 years in 2018.

The mortality data for the UK in the year 2017 shows that the leading cause of mortality in men was circulatory disease accounting for 22.2% of deaths, neoplasms 17.1%, respiratory disease 10.5%, dementia and Alzheimers' disease 5.1% and others 45.1%. Neoplasms in men of the colon, sigmoid, rectum and anus amounted to 7758 deaths per year (3.2%). The leading cause of mortality in women was circulatory disease accounting for 19.4%, neoplasms 14%, respiratory disease 11.3%, dementia and Alzheimers' disease 10.3% and others 45%. Neoplasms in women of the colon, sigmoid, rectum and anus amounted to 6428 deaths per year (2.6%). For non-smokers, colorectal cancer (CRC) is the leading cause of cancer death in the UK for both sex groups (Callum 1998).

In 2017 in England and Wales, two hundred and sixty eight thousand seven hundred and fifty eight (268,758) people were diagnosed with cancer and 141,446 people died from the disease. According to population statistics this surmounted to more than one in three people developing cancer during their lifetime and one in four people who died from cancer in England and Wales. Cancer of the colon, rectum and anus affected 67,352 people (Hiam et al. 2017). In the UK, as treatment of ischaemic heart disease has continued to improve and the general population continues to age,

trends show that cancer will become the leading cause of death within the next 10 years.

1.1.2 Aetiology

Over the last thirty years molecular genetic studies have progressively evolved and epidemiological data has been accurately captured. Together these have been applied to colorectal cancer. It is now a widely accepted concept that colorectal cancer is caused by a complex multi-step interaction between genetic and environmental factors. The common genetic factors influencing the progression of colorectal cancer are detailed below.

i) Genetic Factors

CRC occurs from a series of complex intra-cellular sequential genetic alterations. A combination of simultaneous inappropriate activation of intra-cellular oncogenes and inactivation of DNA repair sequences and tumour suppressor genes result in the loss of normal cell growth regulatory control mechanisms (Arnold et al. 2005). There is now a selective growth advantage to altered colonic epithelial cells. This results in the transformation of normal epithelium to invasive cancer in the colon wall.

CRCs are usually sporadic in nature; although in 5-6% of cases a distinct genetic component has been found (Arnold et al. 2005). Experimental *in vivo* studies have noted that colorectal cancers may arise from dysplastic adenomatous polyps (Muto, Bussey, and Morson 1975). Data from the United States of America has demonstrated that by the age of seventy, 50% of the population will have developed at least one polyp and in one tenth of these cases the polyp will progress to develop into a

colorectal cancer (Johns and Houlston 2001). Fearon and Vogelstein in 1990 quantified this concept and found that in 1% of patients, colonic adenomas were precursors of CRC (Fearon and Vogelstein 1990). Fearon and Vogelstein also described a genetic model of intracellular changes leading to the development of a carcinoma from an adenoma. This model is known as the “Vogelgram” and is illustrated in Figure 1.1. The “Vogelgram” demonstrates the sequential genetic alterations leading to the inappropriate activation of intra-cellular oncogenes and inactivation of DNA repair sequences and tumour suppressor genes resulting in the development of a carcinoma. There are two currently accepted pathways in the development of a carcinoma and both are shown in Figure 1.1. Eighty five percent of tumours develop according to pathway A, whilst 15% of tumours progress via pathway B.

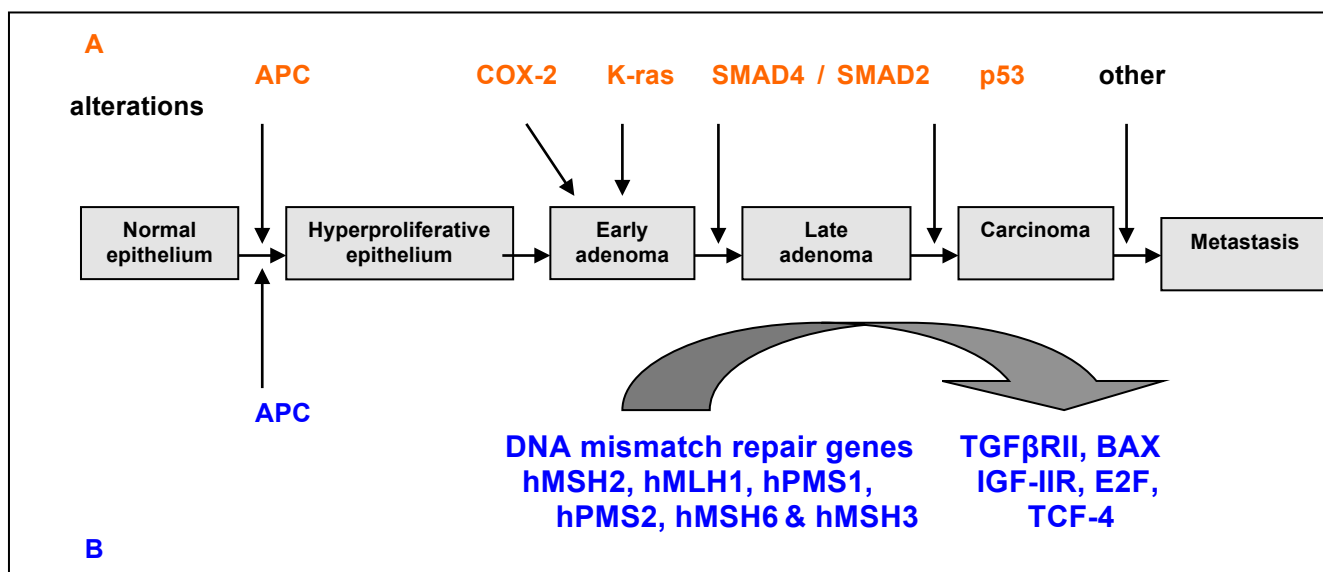


Figure 1.1 Diagram of the key genetic events in colorectal cancer development.

APC = adenomatous polyposis coli, tumour suppressor gene; COX-2 = Cyclo-oxygenase-2; K-ras = oncogene; SMAD 4/2 = signaling molecules in the anti-proliferative TGF-β pathway; p53 = tumour suppressor gene; TGFβRII = transforming growth factor-β receptor class II; 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.

Sporadic cancers arise from the sequential accumulation of somatic genetic mutations (Arnold et al. 2005). The adenomatous polyposis coli (APC) gene has principal effects on ordered cell motility. Mutations of the APC gene occur early in the transformation of normal epithelium to an adenomatous polyp due to them being present in 60% of all adenomas and carcinomas (Powell et al. 1992). The K-ras gene induces cell growth through activating growth factor signal transduction. Mutations of the K-ras gene have been found to occur in adenomas as well as invasive carcinomas. They are however noted to be more apparent in large adenomas than small adenomas suggesting K-ras mutations presents as a latter event (Scott et al. 1993). K-ras mutations have also been associated with a poorer prognosis in node negative disease (Conlin et al. 2005). The p53 gene regulates the normal cell cycle by having an important role in DNA repair and the induction of apoptosis (Kastan et al. 1991). Mutations of the p53 gene are common in invasive colonic cancers but rare in adenomas. They accompany the development of tumour invasion and occur as a relatively late event (Kikuchi-Yanoshita et al. 1992).

ii) Environmental Factors

Population studies have shown that Japanese individuals living in the U.S are more likely to develop CRC in their second decade of life than Japanese individuals living in their native Japan (Wynder and Reddy 1974). These study findings suggest that there may be an environmental component, which contributes to the development of CRC in genetically susceptible individuals.

The world cancer research fund systematic review on foods has shown a decreased risk for lifetime development of colon cancer with increased dietary fibre, non-starch based vegetables, pulses and increased exercise. In contrast an increased

risk of colon cancer risk was associated with red meat ingestion, processed food, alcohol, sugar and a sedentary lifestyle (Ogimoto, Shibata, and Fukuda 2000). This study suggests a reduced level of physical activity in addition to being overweight is major risk factors in developing colon cancer.

1.1.3 Natural Distribution of Colorectal Cancer

The distribution of colon and rectal cancers at endoscopy are shown in Figure 1.2. The majority of CRCs are found to be located in the rectum, closely followed by the sigmoid colon.

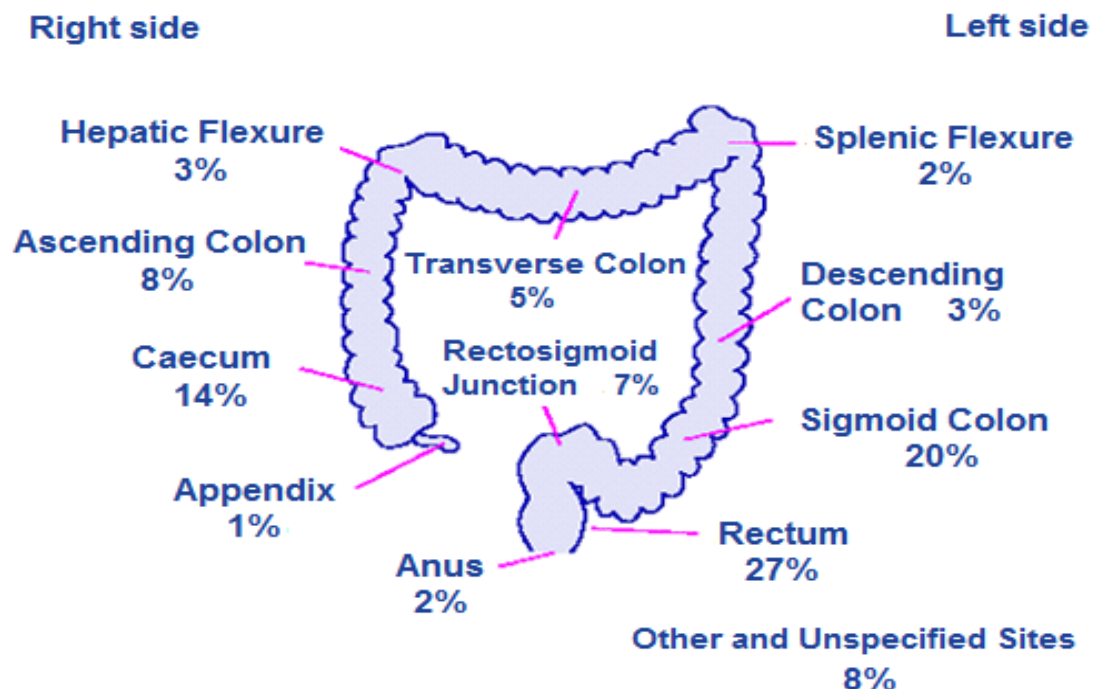


Figure 1.2 The distribution of colon and rectal cancers. Adapted from cancer Research UK 2017 with contributions from, the office of national statistics, welsh cancer intelligence and surveillance unit and the information services division Scotland.

1.2 Staging of colorectal cancer

1.2.1 Background

Typically when a tumour extends through its surrounding walls into adjacent structures, it is considered to be invasive in nature. In advanced CRC invasive tumours tend to further spread by lymphatic, haematogenous and peritoneal means. These cases of advanced CRC are generally associated with a poor overall prognosis.

The stage of the disease at presentation may be correlated to the rate of tumour growth and extension into surrounding structures. In addition the type of tumour and its relationship with its host also influences the disease stage. Therefore accurate clinical and pathological staging is essential to define an appropriate treatment plan.

In order to compare groups of patients with similar characteristics around the world, an international classification system has been developed by the American Joint Committee on Cancer in 2002 (Edge 2010). This has led to the selection of primary and adjuvant therapy for CRC, guidelines for the evaluation of results of treatment and estimation of patient prognosis. Overall this has resulted in the exchange and integration of information, which contributes to the further investigation of CRC.

1.2.2 Clinical staging

Clinical assessment in patients with suspected CRC typically involves a full history and physical examination with digital rectal examination and/or rigid sigmoidoscopy. Patients with high clinical suspicion of CRC are then further investigated with a colonoscopy to enable direct endoscopic endoluminal evaluation of the rectum and colon with biopsies of any potential lesions. Extra colonic metastases are identified via radiological imaging, which is further explained below.

1.2.3 Radiological staging

Radiological advances over the last forty years have significantly impacted on the early diagnosis and treatment of CRC. The section below explains the conventional imaging modalities used for diagnosis of CRC.

i) Barium enema

A colonic or rectal polyp may exhibit malignant transformation and develop over time into a CRC. Polyps in the colon and rectum are assessed according to their size, morphology (the presence or absence of a stalk), location and histo-pathological analysis according to the Kudo classification of pit patterns and cell atypia. The use of barium enema was the routine investigation of choice until the 1980s for loco-regional staging of CRC. However this imaging modality has since been superseded by more modern investigations due to the limitation in histo-pathological lesion analysis.

Single and double contrast barium enema (DCBE) have traditionally been used for evaluation of the colon and rectum and a reported sensitivity for CRC detection of 62-100% has been reported (de Zwart et al. 2001; Ott 2000). DCBE tends to be the preferred investigation in patients with an increased suspicion of CRC. This is due to a reported increased detection rate for polyps less than one centimetre in size (Gelfand 1997; Smith 1997).

ii) Virtual colonoscopy

Virtual colonoscopy, otherwise known as CT colonography, is an imaging technique which produces three-dimensional axial images from sequential data obtained from helical CT. CT colonoscopy has reliably been used for detecting colorectal neoplasia in symptomatic older patients at risk of complications from colonoscopy (Halligan et al. 2013). However, CT colonoscopy has also been shown to have limitations such as poor patient compliance and complications such as electrolyte imbalance (McFarland and Brink 1999).

Incomplete diagnostic colonoscopy rates have been reported to be as high as 12 percent (Atkin et al. 2013). In these patients evaluation of the colon is required and virtual colonoscopy may provide a diagnostic role. In patients who have a distal obstructing lesion and require proximal colon evaluation, virtual colonoscopy may be considered (Pijl et al. 2002). This is especially important, as 5% of patients have been found to have a synchronous tumour (Levine et al. 2000). Virtual colonoscopy should only be reserved for patients who are able to tolerate oral pre-procedure bowel preparation and are able to pass flatus.

Pilot data based on the performance of PET/CT colonography, has suggested this imaging modality to be safe, well tolerated and an accurate diagnostic test for high-risk symptomatic patients with clinically significant colorectal neoplasia (Taylor and Ward 2010). The levels of physical discomfort are much reduced in comparison to colonoscopy even with sedation (Taylor and Ward 2010). Additionally PET/CT colonography assesses extra-colonic organs and has been shown to identify incidental tumours. It may also be used to stage colonic tumours if they are detected (Taylor and Ward 2010). However, PET/CT colonography requires a relatively prolonged examination time and is more expensive per patient in comparison to CT colonography alone, hence its clinical use has been limited.

iii) Ultrasound

Ultrasound (USS) imaging concentrates on the echogenic properties of high frequency sound waves and creates images of differing tissue density at various corresponding depths. The use of USS also enables generation of high-resolution (<1mm) images that can be registered with corresponding molecular data. However USS is limited by the relatively large size of imaging particles, which may in turn restrict tissue penetration and imaging quality of vascular organs.

USS imaging may be subclassified as transabdominal or transrectal. Transabdominal USS is generally not used for the detection of primary CRC although previously it has a historically role in the detection of colorectal liver metastases. Trans-rectal ultrasound (TRUS) has an established role in the staging of rectal cancer as it accurately distinguishes between the various layers of the rectal wall (Heriot, Grundy, and Kumar 1999; Rifkin, Ehrlich, and Marks 1989). TRUS

consists of the patient lying in a left lateral decubitus position whilst a flexible fibre-optic endoscope is inserted. TRUS has been used to assess primary tumour stage, where an accuracy of 67-93% has been reported (Beynon 1989). Superior spatial resolution has been reported with TRUS as opposed conventional imaging modalities such as CT and MRI. This may allow a more accurate assessment of the depth of tumour invasion and is of particular value when distinguishing T2 from early T3 tumours in the rectum, which have been equivocal with conventional imaging.

iv) Magnetic resonance imaging (MRI)

MRI exploits the biochemical property that two thirds of the body is composed of water, thus allowing protons (H^+ ions) to be aligned in a magnetic field. When the body is placed within a strong electromagnetic field, a temporary radiofrequency pulse causes unpaired H^+ ions to change their normal alignment of spin within the direction of the field. Once the electromagnetic is stopped, there is a return of alignment of spin to baseline or thermodynamic equilibrium. This causes a radio frequency signal to be emitted, which can be recorded as an electromagnetic flux by receiver coils and subsequently used to formulate measurements (Kapse and Goh 2009). MRI is an effective diagnostic imaging technique in CRC and is able to provide both molecular and anatomical information. MRI provides high-resolution images in soft tissue ($<1\text{mm}$) with a good penetration depth ($>10\text{cm}$), whilst providing no ionizing radiation to the subject. However, in contrast to CT and US, lower test sensitivity has been observed with MRI. This deficit may be partly overcome through the use of specific signal amplification to create a higher target to background contrast.

The National Comprehensive Cancer Network (NCCN) recommend that diagnostic MRI should be the primary imaging modality for diagnosing and staging rectal cancers (Burt et al. 2013). In this relatively fixed part of the bowel, soft tissue resolution with MRI is not degraded by peristalsis or respiratory motion. MRI is acquired via the use of endoluminal phased array coils, which allow detailed images to be generated of the tumour and its associated rectal wall. However, due to the limited field of view or poor spatial resolution associated with MRI, the mesorectum is poorly imaged. However the more clinically relevant circumferential resection margin (CRM) may still be accurately assessed with MRI (Beets-Tan et al. 2001).

Newer MRI research based techniques have not yet been integrated into clinical practice, but have been considered to have potential as prognostic tools in tumour staging (Kapse and Goh 2009). These include dynamic contrast enhanced MRI (DCE-MRI) which can assess tumour angiogenesis, diffusion-weighted MRI (DWI-MRI) to assess tumour cellularity and blood oxygenation level-dependent MRI (BOLD-MRI) to assess tumour hypoxia (Kapse and Goh 2009).

DCE-MRI utilises the principle that contrast medium kinetics differ between normal tissue and tumour. Therefore, injection of a low molecular weight (<1kDa) gadolinium based contrast medium may be used for tumour detection and evaluation. Tumour angiogenesis may subsequently be evaluated by using different MRI sequences, which investigate tumour vasculature (Kapse and Goh 2009). This is confirmed by phase 1-drug trials of bevacizumab in CRC treatment demonstrating a reduction in primary rectal cancer perfusion and blood volume with DCE-MRI, correlating with a reduction in micro-vessel density.

DWI-MRI explores the motion of water molecules in the body. The lower the cell density or when the cell membrane has been breached, the more the free

movement of water motion that may be allowed, such that water molecules can freely diffuse between the extravascular extracellular space into the intravascular space. Conversely, the higher the cell density and the greater the presence of a lipophilic cell membrane, the more restricted water molecules are. This novel property of water molecules may be exploited to provide an indirect assessment of tumour cellularity. The DWI signal is predominantly derived from the motion of water molecules in the intravascular space but also to a lesser extent the extracellular space as well as the intravascular space. In highly vascular tumours the intravascular water diffusion will account for a large proportion of the DWI signal (Kapse and Goh 2009).

Blood oxygenation level-dependent MRI (BOLD-MRI) is still presently a research based imaging technique. It is sensitive to deoxyhaemoglobin within red blood cells in surrounding tissue and perfused vessels. BOLD-MRI has been hypothesised to provide information on red cell delivery and blood oxygenation through the principle of deoxyhaemoglobin increasing the transverse relaxation rate of water in blood (R_2). At present there are no studies, which correlate R_2 with histologic markers of hypoxia and the role of BOLD-MRI has not yet been proven in staging, radiation therapy planning or therapeutic assessment. BOLD-MRI does have a number of limitations in clinical practice. This is because carbogen vasomodulation has proven challenges where as many as 35% of patients are unable to successfully tolerate it. Chronic hypoxia is less well reflected by BOLD-MRI, as tissue perfusion is required in this imaging modality to result in the oxygenation status. For these reasons BOLD-MRI at present remains a research tool rather than having a defined clinical role in CRC.

v) Computerised Tomography

Godfrey Hounsfield initially introduced the concept of CT in 1971 and highlighted the use of anatomical sectional imaging (Hounsfield 1973). The underlying basis for CT imaging is that x-ray beams are generated and directed directly at the patient. Depending on the density of the subject matter, x-rays are either transmitted or absorbed. Typically the quantity of x-ray beam traversing the subject's tissue is inversely proportional to the tissue density. A detector placed at 180 degrees from the origin of the x-rays registers the resultant induced signal and is subsequently converted to an electronic stream, which is then digitised. This digital signal is assigned a numerical value, known as a Hounsfield Unit (HU). Each Hounsfield Unit represents a quantification of x-ray energy absorbed by the patient's body. Computer software is then used to reconstruct this data as white, grey or black images. On a standard CT image viewed on a monitor, bone is depicted as white whilst air is black. The resultant effect is that CT imaging is able to generate a two dimensional map of x-ray absorbance of the patient's body tissue.

The original description by Hounsfield of a patient undergoing conventional CT imaging involved patients lying prone on a couch and in increments progressing through a gantry, where the x-ray tube and detector are located at 180 degrees in a circular assembly point. Both the x-ray tube and detector rotate 360 degrees around the patient with the resultant effect being the generation of cross sectional image slices between 1 and 10mm in thickness of the patient's body (Hounsfield 1973).

Throughout the 1980s and 1990s rapid image acquisition and processing improved with the advancement of spiral CT systems. Spiral or helical CT involves the patient continuously progressing through the gantry whilst the x-ray tube and detector encircle the patient continuously as opposed incrementally moving along the

patient in a step-wise manner. This advancement in CT imaging technology resulted in faster subject coverage and improved resolution with image reconstruction in a coronal, sagittal and trans-axial plane (Kalender et al. 1990).

Toward the latter half of the 1990s, multi-slice CT has been utilised to further reduce rotation times to as low as 0.5s and improve image resolution. Multi-slice CT consists of a series of detectors working cohesively to detect x-rays as they traverse body tissue.

The latest advancement of CT imaging is diffusion contrast enhanced CT (DCE-CT) or perfusion CT. The principle behind this experimental imaging modality is to utilise the differences in contrast medium kinetics of normal and tumour tissue. The change in contrast enhancement over time following contrast medium injection allows blood flow and blood volume as well as permeability surface area product to be estimated (Kapse and Goh 2009). This allows an accurate assessment of tumour angiogenesis to be made.

CT imaging of CRC

The National Comprehensive Cancer Network (NCCN) recommends chest, abdominal and pelvic CT imaging be used for the initial staging of patients with CRC (Burt et al. 2013). CT imaging is typically utilised for pre-operative planning in surgical candidates to assess tumour extension, regional lymph node involvement and the presence of distant metastases. In addition, CT is also able to confirm clinical suspicion of obstruction or perforation in selected patients, which may alter surgical management (Horton, Abrams, and Fishman 2000).

The sensitivity of CT in detecting the depth of trans-mural tumour extension, malignant lymph node involvement and metastases to the liver is 55%, 73% and 79% respectively (Balthazar et al. 1988). The criteria for detecting malignant lymph node metastases are based on size. It is accepted that regional lymph nodes greater than 1cm may precipitate potential malignant disease. However, micro-metastatic deposits have been noted in regional lymph nodes less than 1cm and as such an assessment of lymph node morphology is also recommended (Rodriguez-Bigas et al. 1996). CT is considered a poor imaging modality for the detection of peritoneal metastases (Jacquet et al. 1993). The sensitivity of CT for detecting peritoneal metastases has been reported to be 11% and 37% for peritoneal nodules of 0.5 cm and 0.5-5cm respectively (Koh et al. 2009). However despite the above limitations, CT remains the most widely available cross sectional imaging modality and is able to provide high quality anatomical information about CRC tumours and their surrounding structures.

1.2.4 Pathological staging

Complete CRC staging typically involves pathological examination of the resected surgical tumour specimen. Sir Cuthbert Duke devised the first universally accepted pathological staging criteria for CRC (Gabriel, Dukes, and Bussey 1935) (Table 1.1). In 1954, Astler and Coller modified this classification (Astler and Coller, 1954), which was widely used, until the 1990s when the American Joint Committee on Cancer (AJCC) (Burt et al., 2013) introduced the now internationally accepted Tumour, Nodes, Metastases (TNM) system of pathological staging (Table 1.2).

Stage	Definition	% of Cases	5-Year Survival
A	Confined to bowel wall	10	97%
B	Extended through bowel wall, but no lymph node involvement	35	80%
C1	Lymph node involvement, apical node disease-free	30	65%
C2	Apical lymph node involved		35%
D	Distant metastases	25	5%

Table 1.1 Dukes staging and classification.

Classification	Definition of TNM classification
Primary Tumour (T)	
TX	Primary tumour cannot be assessed.
TO	No evidence of primary tumour.
T _{is}	Carcinoma in situ.
T1	Tumour invades the submucosa.
T2	Tumour invades muscularis mucosa.
T3	Tumour invades through muscularis mucosa into subserosa or into nonperitonealised pericolic or perirectal tissues.
T4	Tumour directly invades other organs or structures or perforates visceral peritoneum
Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases in 1 -3 regional lymph nodes
N2	Metastases in ≥ 4 regional lymph nodes
Distant Metastases (M)	
MX	Presence of distant metastases cannot be assessed
M0	No distant metastases
M1	Distant metastases

% of Cases represents the percentage of cases with that stage at diagnosis at first presentation.

Table 1.2 Modified TNM classification system for the staging of colorectal cancer.

1.2.5 Histological grade

The histological grade is considered to be a qualitative assessment of the differentiation of a tumour. This is expressed as the extent to which a tumour resembles the normal tissue. Histological grading is shown below:

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

Low-grade tumours are considered to range from G1-G2 whilst high-grade tumours are G3-G4 tumours.

1.3 Positron Emission Tomography components

1.3.1 The cyclotron

A cyclotron is comprised of two hollow, semi-circular metal electrodes called ‘dee electrodes’, due to their shape. Each electrode is located 1m apart between the poles of a large electromagnet. Negative ions are generated between the dee electrodes from an ion source, which is usually an electrical arc device in a gas. The ions are generated in bursts and move from one dee electrode to the other via a high frequency alternating current (AC) voltage generated by a high frequency oscillator. Once the ions are between each dee there is no electric field present but the particles are within a magnetic field. This strong magnetic field is placed at right angles to the plane of each dee electrode. This helps to coerce them into a curved circular pattern of orbit. The ions increase their diameter of orbit from energy generated and transferred from this applied electric field. As the particles accelerate they may gain about 30KeV of energy through this process and continue along a circular path within the opposite dee. Each time the particles cross the gap between each electrode they gain further energy, the orbital radius increases and the particles follow an outwardly spiralling pathway. The achieved energies are limited by the dee sizes and magnetic field strength. Once the negatively charged ions have reached their outermost orbit within the dee electrodes they are transferred through a thin (5-25 μm) carbon stripping foil. This resulting in the electrons being sequentially stripped producing an anti-matter counterpart of the electron or H^+ ion. Interactions between the magnetic beam and this positive ion result in bending of its direction of motion outwards outside of the magnetic field. This H^+ ion then interacts with the specific target material resulting in the production of a positron emitting radionuclide. High

photon/particle emission ratios may be achieved producing positron-emitting radionuclides. Of particular interest to nuclear imaging are short-lived positron emitter such as ^{15}O , ^{11}C , ^{13}N , ^{64}Ga and ^{18}F generated in a cyclotron through the above process. Table 1.3 shows some common radionuclides used in nuclear medicine and energy thresholds.

Radionuclide	Energy Threshold (MeV)	Half Life
^{15}O	0	2.07 min
^{11}C	3.1	20.4 min
^{13}N	5.5	9.96 min
^{64}Ga	18.8	21.9 μs
^{18}F	90.5	109.8min

Table 1.3 - the general characteristics of common radionuclides adapted from Physics in Nuclear Medicine 4th edition (2012). Cherry S, ed. (Elsevir Saunders).

The above radionuclides, ^{15}O , ^{11}C , ^{13}N , ^{64}Ga all have an extremely short half live, less than thirty minutes each. As a result of this the scanner needs to be sited in close proximity to the cyclotron to be effective. The positron emitting radionuclide ^{18}F is incorporated in the glucose analogue compound [18F] Fluoro-2-Deoxy-D-glucose otherwise known as FDG. Hence a radiopharmaceutical agent may be generated from the principle of incorporating a tracer molecule and a positron emitting isotope. FDG is the most widely used biological ligand or tracer compound in clinical PET scanning. One of these reasons FDG is such a practical isotope may be due to the relatively long half-life of FDG, which is of the order of 109.8 minutes.

This allows transfer to imaging centres where a cyclotron radiotracer distribution laboratory is not available on site.

1.3.2 The PET scanner

In order to produce high resolution imaging positron-emitting tracer activity needs to be captured via a detector. A PET detector unit consists of scintillation crystals in a ring formation to detect coincidence events, and external radiation source for attenuation correction and a computer system for reconstructing data into a three dimensional image. Detectors also vary and according to their composite materials and may be broadly classified as below.

1. Thallium sodium iodide gamma cameras with lead collimators
2. Rotating sodium iodide cameras with modified electronics used for coincidence detection
3. Sodium iodide PET cameras with ring detectors
4. Bismuth germinate oxide (BGO) PET cameras with a full or partial ring detection system.

The further details of these various detectors lie outside of the realms of this thesis. However the dedicated PET scanners used for the accrued images in this thesis utilise BGO scintillation crystals with a ring detection system which surrounds the patient. BGO crystals are more suited to the high energy 511KeV photons expelled from the unstable nucleus of a positron. This produces a higher count rate performance and thus better resultant image quality.

1.3.3 Annihilation coincidence detection

Once a positron is produced it may only travel a short distance (roughly 1mm) in soft tissue before colliding with an electron. This mutual annihilation event results in the production of two 511KeV γ rays emitted at almost 180° relative to each other. If these photons are detected within a certain time of each other (known as the *coincidence time window*) then it can be assumed that both γ rays originated from the same annihilation event and hence the same point source. A line which joins the two detection positrons will allow an accurate estimate of the position of the annihilation event. A collection of 'coincidence events' may be accumulated from a BGO ring surrounding a patient with detectors placed on each side of the ring. This allows each detector to operate in coincidence relative to the other. These 'coincidence events' may then be reconstructed and can produce three dimensional subject colour images. The intensity of the colour usually reflects the isotope concentration.

1.3.4 Attenuation Correction

Jakobs et al in 1988 defined attenuation as the process by which a radiation beam is reduced in energy after it passes through tissue or other material (Jakobs et al. 1988). Attenuation in the context of PET imaging is considered to be the loss of detection of true coincidence events due to soft tissue absorption of energy outside the field of view of the detector. This attenuation effect results in an increase in image artefacts, noise and resultant image distortion. To counter this effect attenuation correction may be performed utilising an external γ ray transmission source. This enables photon attenuation to be directly measured and corrected by producing an attenuation map. This map is created by the fraction of photon flux attenuated by soft tissue to be considered to be independent of a line joining the detectors where the radionuclide lies. Mathematical correction factors are obtained through a calculation of the ratio between a blank scan and a transmission scan both performed with external positron emitting sources in the form of germanium rods. However transmission scans typically take at least thirty minutes to perform, hence increasing the overall scanning time. Dual modality PET/CT scanners have aimed to reduce the level of artefact and noise whilst also performing attenuation maps within a shorter time frame, as short as thirty seconds. Visvikis et al., 2003, noted the use FDG, CT images for PET attenuation correction with a multimodal PET/CT scanner did not require a rod source to produce an external positron-emitting source (Visvikis et al. 2003). Also whole body acquisition of images could be reduced from 20 minutes to 05-1.5 minutes. Therefore, attenuation correction of data can be used to produce good qualitative and quantitative measurements demonstrating PET tracer activity *in vivo*.

1.3.5 Image Reconstruction

There are two methods of image reconstruction. Filtered back projection (FBP) utilises the principle that activity distribution may project as acquired planar images. These projections may be in turn back projected onto a matrix centrally in a camera's field of view producing an image. To reduce the degree of blurring of this image, a filter is applied to the data which controls both artefact and noise. This is therefore called FBP. This mechanism of image reconstruction is used with gamma cameras and can provide quick accurate results. Ordered Subsets Expectation Maximisation (OSEM) modifies reconstructed data enabling the projections from the reconstructed dataset to match those obtained from the patient. This mechanism of image reconstruction is traditionally far slower than FBP but is the most widely applied reconstructive technique as it can include corrections for attenuation correction as well as variations in depth response.

1.4 PET/MRI imaging in colorectal cancer

1.4.1 Background

Diagnostic imaging modalities may be classified into two groups. These consist of those producing detailed morphological information in relation to the physical properties of the tissue being imaged and those that produce functional images utilising dynamic scintigraphy. Examples of the former are x-rays, CT, MRI and USS and these are further discussed in section 1.2.3. Examples of the latter are radioisotope-imaging techniques such as single photon emission computed tomography (SPECT) and positron emission tomography (PET) imaging. PET/CT and its role in CRC staging and subsequent change in patient management are discussed further in chapter 3. The role of PET/MRI in CRC is discussed below.

1.4.2 Basics of PET/MRI

PET/MRI is a hybrid imaging technique that has been developed over the last 9 years and has been utilised as an oncological imaging modality over the last 5 years. PET/MRI maintains the inherent advantages unique to MRI based imaging, which include superior soft tissue resolution and a broad range of acquisition sequences, whilst producing no ionizing radiation to the subject (Bashir et al. 2015). The development of PET/MRI and use in clinical practice has been limited by a number of factors. These include the technical challenge of combining both PET and MRI imaging modalities. This is because the photomultiplier tubes, which are present in PET detectors, are extremely sensitive to magnetic fields, which are essential for MRI imaging (Bashir et al. 2015). Therefore, the PET detector must be

physically located away from the MRI scanner. Also as with any integrated imaging modality, there is potential for radiofrequency cross talk between scanners, hence appropriate radiofrequency shielding is required. Recent engineering advantages have improved this inherent limitation with fully integrated hybrid PET/MRI scanners. In addition, attenuation correction using MRI image data is far more complicated than CT data used in PET/CT processing. This is because generated MRI images have no direct relationship to tissue attenuation and thus, tissue segmentation and assignment to a particular attenuation factor are utilised (Bashir et al. 2015). This is further discussed in the below sections.

1.4.3 PET/MRI design considerations

Early PET/MRI imaging consisted of retrospective software based fusion of PET and MRI images from the patient undergoing two separate scans. Advances in engineering have resulted in improved co-registration and the development of hybrid PET/MRI with hardware being sequential or simultaneous in design (Beyer et al. 2008). Sequential design typically requires the patient to be imaged initially on a PET system then physically transferred to an MRI system. This technology is the most economical, however it requires two separate scanners to be located in close proximity. It is also more time consuming, with longer scan acquisition times resulting from the patient transferring between each scanner. This may potentially lead to movement artefacts being generated in the acquired images (Zaidi and Del Guerra 2011). Simultaneous PET/MRI hardware enables both PET and MRI to be performed simultaneously. Apart from the physical constraints of housing PET and MRI detectors both in the same gantry, the series of potential limitations of

sequential PET/MRI hardware explained above may be overcome (Mackewn et al. 2010).

1.4.4 Attenuation Correction in PET/MRI

Attenuation correction is relatively poor with PET/MRI imaging when compared to PET/CT. Attenuation correction plays a key role in PET imaging (Hofmann et al. 2009). The basic principle of PET imaging involves PET radionuclide decay with two resultant opposing 511keV photons being emitted, which are subsequently attenuated or scattered after interaction with normal body tissues. Photons that are detected after being scattered by body tissues have had signal loss, which is proportional to the distance from the surface, which is also dependent on the regional tissue density (Goh et al. 2016). Without attenuation correction, PET data would significantly underestimate tracer activity. Integrated PET/CT scanners are attenuation corrected according to CT based X-ray attenuation for accurate quantification (Kinahan, Hasegawa, and Beyer 2003). However PET/MRI is reliant upon MRI signal intensity, which is not based on tissue density like PET/CT. In contrast MRI and thus PET/MRI is based on proton density, and therefore an alternative method of attenuation correction to that from PET/CT is required (Hofmann et al. 2009). Present PET/MRI workflow systems derive attenuation correction from 2-point Dixon 3D gradient echo which is based on four tissues which are namely, background air, lungs, soft tissue and fat. However, this method is limited by bone being classified as soft tissue, which may result in underestimation of bone lesions due to underestimation of SUVs. This limitation of attenuation correction is relevant to PET/MRI. In the future anatomical structures

may be segmented with special consideration to differentiating bone and soft tissue. At present ultra-short tissue time to echo (TE) MRI sequences are being considered however at present these sequences may adversely increase acquisition times (Goh et al. 2016).

In this thesis for hybrid PET/MRI imaging, the MRI field of view is noted to be smaller than the PET field of view. As a consequence the MRI attenuation correction may have been affected if the anatomical structures were located outside of this field of view. This may be most apparent in patients with large body habitus. Therefore, to counteract this the contours of the arms were iteratively extracted from PET data and this information was then further used for the MRI based attenuation correction body map. This technique has previously been described and validated (Goh et al. 2016).

1.4.5 PET/MRI imaging in CRC

PET/MRI would be expected to show higher diagnostic accuracy than PET/CT when imaging cancers in the brain, breast, liver, musculoskeletal system and bowel (Czernin, Ta, and Herrmann 2014). The soft tissue resolution of the MRI component of PET/MRI is advantageous for locating and staging tumours in these anatomical regions. This is because the MRI component of PET/MRI may have a selective advantage in assessing variations in the water content of these soft tissue tumours. In contrast the CT component of PET/CT, is a density based imaging modality and there may be little contrast resolution between soft tissues due to similar densities for tumours in these regions. The value of PET/CT imaging may be more appropriate for solid tumours with variations in tumour density.

A small prospective study of 12 patients compared PET/MRI with PET/CT

for the staging and restaging of patients with CRC (Paspulati et al. 2015). In this study PET/MRI conferred a more accurate T-stage whilst providing a comparable N and M stage to PET/CT. Using a per-patient analysis, the true positive rate with PET/CT was 5/7 (71%) whilst that of PET/MRI was 6/7 (86%).

A prospective study by Kang et al in 2016 evaluated the added benefit of PET/MRI when compared to conventional imaging (contrast enhanced CT, CE-CT) alone for lesion detection, characterization and the subsequent change in management (Kang et al. 2016). Fifty-one patients with CRC underwent PET/MRI and CE-CT within 90 days using histopathology, repeat imaging and clinical follow up as the reference standard. Two reviewers assessed via consensus if PET/MRI added any diagnostic value to CE-CT for lesion detection and if any changes in treatment strategy were made. In 14/51 (27.5%) of patients PET/MRI conferred an added value of which 12/51 (23.5%) of patients were noted to have better lesion characterization with PET/MRI. Significantly in 2/51 (3.9%) of patients, extra-colonic disease was detected with PET/MRI. A change in treatment strategy was noted in 11/51 (21.6%) of patients and therefore, the author's concluded that PET/MRI was able to help provide a more appropriate treatment strategy for patients with CRC.

A recent retrospective study by Brendle et al., 2016 compared PET/CT with PET/MRI for the detection of colon and rectal cancer lesions and the diagnostic performance of differing combinations of anatomical and functional imaging techniques (Brendle et al. 2016). Fifteen patients with metastatic colo-rectal cancer were reviewed, of which image data revealed 180 lesions, of which 110 were malignant. The reference standard in this study was histology and/or follow up imaging. Two readers reviewed image data of anatomical MRI, anatomical MRI with

diffusion MRI (DWI), anatomical MRI with PET, anatomical MRI with diffusion MRI and PET and PET/CT. The diagnostic accuracy for the detection of colorectal lesions was found to be highest for anatomical MRI with diffusion MRI and PET whilst the lowest diagnostic accuracy was noted to be with anatomical MRI. This study concluded that PET/MRI (anatomical MRI with diffusion MRI and PET) was a comparable imaging modality to PET/CT for evaluating patients with metastatic colo-rectal cancer. Therefore, a combination of imaging modality data may improve the diagnostic accuracy of lesion detection.

PET/MRI has been used as an imaging modality for the detection and characterization of liver metastasis. A study by Biederwellen et al in 2015 of 26 patients with 113 lesions (45 malignant) underwent PET/MRI and PET/CT imaging (Beiderwellen et al. 2015). The reference standard in this study was further imaging in all recruited patients and histology, which was available in only 8 patients. The authors reported that PET/MRI showed improved sensitivity (93.3% vs 71.1%), specificity (100% vs 97.1%) and overall diagnostic accuracy (96.7% vs 84.1%) when compared to PET/CT.

The largest study evaluating PET/MRI and PET/CT compared 70 patients where 36 patients (51%) had liver lesions (Beiderwellen et al. 2013). All patients underwent PET/MRI and PET/CT imaging, and two readers reviewed datasets. The visibility of hepatic lesions and diagnostic confidence were compared for both imaging modalities. The authors found that PET/MRI was superior to PET/CT in detecting more lesions, which resulted in an increase in diagnostic confidence for distinguishing malignant from benign lesions.

CHAPTER 2

Materials and Methods

2.1 Patients

To maintain consistency, this chapter outlines the basic methodology common to all clinical studies. In each subsequent chapter the individual methodology relevant to the specific study protocol is outlined further.

2.1.1 Patient recruitment

All patients that participated in the following clinical studies were prospectively recruited from both surgical and oncology clinics after having been discussed at a colorectal multidisciplinary team (MDT) meeting. The inclusion criteria were patients at or above the age of 45 with a newly diagnosed colorectal adenocarcinoma. This encompassed patients with primary or metastatic CRC. These patients had their diagnosis of CRC confirmed by clinical suspicion and radiological imaging or histological biopsies. Radiological imaging comprised of virtual colonoscopy (VC) or computerised tomographic colonography (CTC) or a combination of both modalities. Histological biopsies were taken during endoscopically via flexible sigmoidoscopy or colonoscopy. The exclusion criteria for participation in this these were patients below the age of 45, pregnancy, a previous surgical resection or chemotherapy and/or radiotherapy therapy treatment, a previous adverse reaction to an intra-venous contrast agent, renal impairment with an eGFR<60 or creatinine >120 μ mol/L, poorly controlled diabetes and incompatible implanted metallic material.

In order for this study to proceed, ethical approval was successfully obtained from the joint Local Ethics Committees of University College London (UCL) and University College London Hospital NHS Trust (UCLH). In addition the relevant

approval from the Administration of Radioactive Substance Advisory Committee (ARSAC) was also obtained. All studies were performed after the patient had read an approved patient information sheet and with full verbal and informed patient consent.

All of the patient related data sets were stored within a departmental DellTM desktop computer using Microsoft ExcelTM software on a secure departmental network. The data was handled at all times in accordance with the Data Protection Act. Unique patient specific identifiers used included, the patient's name, age, date of birth, unique NHS number, disease/pathological information and imaging results.

During the course of this thesis, no investigations were performed which delayed or hindered the routine investigation and treatment of patients recruited. Any research imaging was done in accordance with the referring team and in addition to any routine clinical imaging.

2.2 Whole body 18-FDG-PET imaging

2.2.1 18F-FDG

The 18F-FDG used for the individual studies in this thesis was obtained from PET NET Pharmaceuticals (Siemens mMR Biograph, Erlangen, Germany) and was produced from the cyclotron situated at Mount Vernon Hospital in Middlesex, London.

Written notification was received from PET Net Pharmaceuticals by fax or email ensuring that the tracer planned for delivery had successfully passed stringent quality control testing. No patients were administered with a dose of 18F-FDG until this information had been received. The tracer was delivered to UCH on the morning of imaging. At the point of delivery documentation was received from the cyclotron unit regarding the time period at which the 18F-FDG was measured prior to dispatch, the volume of liquid dispensed into each of the 18F-FDG vials and the assayed activity of the tracer. This information was all documented on an individual radiopharmaceutical patient record sheet and kept securely within the department. A dose calibrator such as that shown in Figure 2.1 in addition to a decay chart was utilised to assay the 18F-FDG by a trained nuclear medicine radiographer in accordance to departmental Standard Operating Procedures (SOP). SOPs are shown in further detail in appendix F. Doses of 250MBq and 370MBq were prepared for patients who required a research only scan and clinical scan respectively. All injections were undertaken by a trained nuclear medicine radiographer on a specialised dispensing station using a 23-gauge hypodermic needle attached to a 10ml syringe secured in a lead syringe collimator.



Figure 2.1 - Dose calibrator

2.2.2 Patient preparation

All patients were given pre-scanning written and verbal information in the form of a patient information sheet informing them of the need to starve for at least six hours prior to imaging. This was outlined to ensure that normoglycaemia could be achieved, however patients were allowed to consume clear fluids for comfort up to the point of their scan. An individualised patient information sheet was used to record patient specific values such as a brief medical history, height (cm) and weight (kg). These values were used to calculate standardised uptake values (SUVs) and thus quantitative image analysis. Blood glucose levels (mmol/l) were also checked on a commercial glucometer (Glucometer Elite, Bayer Pharmaceuticals, Berkshire, UK) and an acceptable threshold level of less than 10 mmol/l was used. This cut off value was used in this thesis so as to maintain continuity with the clinical imaging protocols accepted by the Institute of Nuclear Medicine at UCLH London. Also recorded in the patient specific information sheet was the dose of tracer injected and

the residual activity post injection left in the syringe. This allowed an accurate administered dose to be calculated for each patient.

To allow effective radiotracer uptake, venous access was achieved by cannulating each patient with a 16-gauge cannula sited in the anti-cubital fossa or dorsum of the hand. Oral diazepam of dose 5mg was also routinely given to each patient, unless contra-indicated, to aid relaxation and prevent unnecessary ¹⁸F-FDG uptake to skeletal muscle. After radiotracer injection each patient was left in a comfortable position in a darkened room for 45-60 minutes before scanning. This was done to minimise non-specific tracer uptake by skeletal muscle, which could potentially affect image quality on the resultant scans.

¹⁸F-FDG is excreted via the renal system and a full bladder may produce high signal artefacts. To achieve a standard methodology all patients were asked prior to scanning to empty their bladder to reduce renal tract accumulation of tracer. No patients involved in this thesis were routinely catheterised or given a diuretic.

All patients were positioned with their feet facing away from the gantry with a pillow placed for comfort under the knees on the scanning bed. The arms were placed above their head to produce clear fields of the thorax and abdomen. Where patients were physically unable to do this, they were strapped on each respective side to provide support and minimise movement. To reduce patient anxiety radio intercom contact was maintained throughout the scanning process and all patients were provided with a patient alarm system. For all whole body scans, images were obtained from the base of the skull to the upper third of the lower limbs.

2.2.3 Acquisition of CT scans of the abdomen and pelvis

Routine standard of care CE-CT performed for staging purposes were obtained from each referring hospital. An example protocol is detailed below.

CE-CT imaging of the abdomen and pelvis was acquired using the Siemens Plus 4, four slice multi-detector spiral CT (Siemens AG Medical Engineering Group, Forchheim, Germany), which produced 5mm contiguous slices. The selected contrast used was Omnipaque 350 (Nycomed Amersham, Amersham Place, Little Chalfont, Buckinghamshire, UK) and was injected via a peripheral vein at a dose of 100mls, at a rate of 4ml/s with a chosen delay of 45 seconds. In the instances that bi- or tri-phasic imaging of the liver was chosen for appropriate patients, they were scanned with 20s, 50s and 180s delays with 5mm thick slices at 2.5mm intervals or with 35s, 50s and 180s with 3mm slices at 1.5mm collimations. All of the 3mm and 5mm thickness images were subsequently reconstructed.

2.2.4 Acquisition of MRI scans of the abdomen and pelvis

MRI imaging of the rectum analysed in this chapter was acquired as part of routine standard of care performed at the patient's local hospital. As such, there are variations to the finer details in acquisition parameters due to differences in vendor of scanners used and individual hospital's practice. However each MRI scan generally conformed to contemporaneous clinical standards (Brown et al. 2005).

An example protocol would consist of initial scout views followed by large field of field T1 and T2 turbo spin echo acquired axially to cover the whole pelvis. Sagittal T2 turbo spin echo sequences are then obtained. With these, small field of field, high resolution and fine T2 turbo spin echo slices are planned and acquired, in

axial and coronal planes to the long axis of the rectal segment containing the tumour. For larger lesions, which extend over different sections of the usual curvature of the rectum, more than one such pair (axial and coronal) of small field of view images may have been acquired. Diffusion weighted imaging is only acquired in some specialist centres and therefore was not considered in this chapter.

2.2.5 Acquisition of whole body 18F-FDG PET/CT scans

For all patients who underwent whole body 18F-FDG PET/CT imaging in this thesis, a Discovery VCT dual modality integrated PET/CT scanner (GE Healthcare, Waukesha, WI, USA) was used. This hybrid PET/CT scanner is shown in Figure 2.2. The examinations covered from the patient's skull base to mid-thighs.

PET acquisition is performed approximately 60 minutes after injection of 250MBq of 18F-FDG, in 2D mode with an emission scan of 8min/bed position. The PET emission datasets were attenuation corrected using the CT potential of the Discovery VCT. Trans-axial emission images of $4.3 \times 4.3 \times 4.25 \text{mm}^3$ (matrix size $128 \times 128 \times 35$) were reconstructed utilising ordered subsets expectation maximisation (OSEM) with 2 iterations and 20 subsets. The axial field of view was 148.75mm.

Spiral non-contrast CT images were acquired at 140kV, 40mAs and 5mm collimation, using a rotational speed of 0.8s, couch movement of 22.5mm per rotation with 8 mins per bed position and slice thickness of 5mm. The CT images were then converted to PET attenuation coefficient maps using bilinear

transformation. Whole body coronal and sagittal images were then produced from re-orientating these slices and these were used for image analysis.



Figure 2.2 - Discovery VCT hybrid PET/CT scanner (GE Healthcare, Waukesha, WI, USA)

2.2.6 Acquisition of whole body 18F-FDG PET/MRI scans

18F-FDG PET/MRI imaging (3T Siemens mMR Biograph, Erlangen, Germany) was performed immediately after PET/CT imaging for all suitable patients. All patients remained fasted for these studies and only the FDG radio-tracer given initially during the PET/CT imaging process was used. This resulted in uptake times being longer for the PET/MRI studies in relation to the PET/CT studies. Prior to the PET/MRI scan, 20mg of Buscopan was administered unless contra-indicated to reduce study artefact resulting from bowel motility.

The PET/MRI protocol started with the acquisition of four-tissue class (soft tissue, fat, lung and air) Dixon sequences in order to calculate μ -maps for attenuation correction (AC) of PET data (Kalemis, Delattre, and Heinzer 2013).

After the AC sequences a single PET bed position of the tumour was acquired simultaneously with structural and functional MR sequences. Free breathing transaxial T2 HASTE (TR 1600ms, TE 100ms, FoV: 376×501, 5mm slice thickness, 36 slices) sequence was acquired and used for localization, followed by free breathing transaxial EPI diffusion data at 3 b-values in 3 directions (0,400,800 s/mm², TR 8700ms, TE 88ms, TE 88ms, 2 averages, FoV 282×350, 5mm slice thickness, 30 slices, STIR fat suppression), used for the evaluation of the tumour. Corresponding ADC maps were derived by DWI images and calculated (Kalemis, Delattre, and Heinzer 2013; Kaur et al. 2012) with Siemens software (version Syngo MR B18P). The in-plane pixel resolution for the ADC map was 1.41mm×1.41mm. PET data was reconstructed using OSEM with 21 subsets and 3 iterations and a 5mm full width half maximum (FWHM) Gaussian filter (FoV 369×359, 2mm slice thickness, 127 slices).

Due to the constraints of PET/MRI being a relatively new imaging modality and the subsequent evolving imaging protocols, axial and coronal small field of view images were not acquired.

2.2.7 Acquisition of whole body CT Perfusion scans

For all patients that underwent a whole body ¹⁸F-FDG PET/CT scan, a whole body CT perfusion scan was also performed afterwards on the same Discovery VCT dual modality PET/CT scanner (GE Healthcare, Waukesha, WI, USA) as long as there were no relevant contra-indications. The ¹⁸F-FDG PET/CT study performed prior was used to localise the colorectal tumour and its CT coordinates were used to plan the subsequent CT perfusion scan. The contrast agent used was iohexol at a concentration of 50ml, 350mg of iodine per milliliter (Omnipaque, GE Healthcare) and was injected into a peripheral vein via a cannula with 20mg of buscopan to aid patient relaxation. The contrast medium was injected via a pump injector followed closely by a 50 mL saline flush at 5mL/s. After a 10 second delay the perfusion CT was performed over the region of the tumour. The acquisition parameters were 120kV, 60mA axial mode with 2-s intervals for the first 40 seconds then 5 second intervals between acquisitions. The total imaging time was 150 seconds with an effective dose of 9mSv (18).

2.2.8 Image Analysis and Interpretation

Whole body PET/MRI and PET/CT images of all colon and rectal primary tumours were reviewed on a GE based workstation, version 4.6 (GE Healthcare, Waukesha, WI, USA) or on Osirex, depending on reader preference to replicate routine clinical practice. The MRI, CT and PET data were also presented together with fused images for PET/MRI and PET/CT scans respectively. The tumour was localised by all imaging data available and a three dimensional cuboid region of interest was placed around the entire tumour on the fused data prior to staging analysis.

Two dual accredited nuclear medicine radiologists reviewed the PET/CT studies and shared and discussed their findings. When there was a discrepancy between the reader's interpretations, a consensus was reached after discussion. This enabled a single diagnostic accuracy to be determined by consensus. In a similar fashion, two further dual accredited nuclear medicine radiologists also reviewed the PET/MRI studies and a single consensual diagnostic accuracy was determined. Separate reading sessions were organised at independent times for PET/CT and PET/MRI image analysis and no clinical information except for the clinical indication of the patient was disclosed to each reader.

The CE-CT, diagnostic MRI, PET/CT and PET/MRI images were all evaluated as above and the tumour location and T, N and M stage determined. For identification of each lesion in the colon or rectum, the tumour was required to be depicted by each reader either morphologically (polypoid, annular or semiannular lesions) or metabolically (abnormal FDG uptake). Within each study of this thesis abnormal FDG uptake was defined as, focal increased activity within the colon that was objectively higher than the background activity of soft tissues or surrounding

organs with PET/CT and PET/MRI imaging. Diffuse radiotracer uptake was considered to represent normal or non-malignant bowel activity. The evaluation of radiotracer uptake was qualitative. This method has been previously validated and used by Mainenti et al., 2011. For assessment of the location of each lesion, the large intestine was divided into eight anatomical segments, which consisted of the caecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon and rectum (high, mid and low).

For assessment of tumour staging, the TNM staging criteria used by each reader in this thesis was abbreviated from the international TNM classification as described by the American Joint Committee on Cancer 7th edition (Edge 2010). Due to the limited resolution with PET/CT and PET/MRI imaging, tumour infiltration of individual layers of the bowel wall could not be confidently or accurately assessed. Therefore any primary tumour confined to the bowel wall and hence invading the submucosal, muscularis propria or subserosa were grouped together and assessed as T2. These tumours would be conventionally staged as T1 or T2 with CE-CT or diagnostic MRI, but for consistency in each chapter were staged as T2 with all imaging modalities. The reason for this was to primarily overcome the limited resolution with PET imaging, but also current treatment algorithms suggest similar clinical treatment pathways for T1 and T2 tumours confined to the colon or rectum. Tumours invading through the peritoneal lining were classed as T3, a tumor invading through the muscularis propria into peri-colonic tissues and perivisceral fat; and T4, a tumor invading the visceral peritoneum or invading or adhering to adjacent organs or structures.

Regional lymph node metastases were evaluated by assessing regional lymph node morphology with all imaging modalities or abnormal FDG uptake with PET

imaging. Abnormal nodal morphology was defined as a maximal axial diameter of ≥ 10 mm (Monig et al., 1999). Abnormal regional lymph node uptake was defined as an avid FDG node with a cut-off maximum SUV value of 1.5, at a location corresponding to a lymph node. Tsunoda et al., 2008 have previously validated an SUV cut-off value of 1.5, where the greatest accuracy for regional lymph node metastatic evaluation was produced and hence this SUV value was used in each study of this thesis. The N-stages were defined as: N0, no regional lymph node metastasis, N1, one to three regional lymph nodes are positive on PET imaging or have morphology measuring ≥ 10 mm in axial diameter or any number of tumour deposits are present and all identifiable lymph nodes are otherwise negative, and N2, metastasis in four or more regional lymph nodes.

The M-stages were as follows: M0, no distant metastasis on conventional imaging or no evidence of tumour in distant sites or organs; M1a, metastasis to one site or organ identified without peritoneal metastasis; M1b, metastasis to two or more sites or organs identified without peritoneal metastasis; M1c, metastasis to the peritoneal surface identified alone or with another site or organ metastases.

2.3 Histopathological analysis

Consultant Pathologists with more than 10 years of specialist experience in gastrointestinal disease performed all histopathological analysis in this thesis. Specimens were requested from the referring hospital only after there was no longer a clinical requirement for their use. All histological examinations were performed on surgical specimens rather than biopsy samples.

All surgical resection specimens were first fixed in a 10% neutral buffer solution of formalin for a minimum of twelve hours after being received from the operating theatre, at the parent hospital site. Each tumour block was then processed in a conventional way and embedded into paraffin wax before being macroscopically analysed. At this point an initial assessment of a surgical resection specimen with clear margins (R0 resection) could be made. The formalin fixed paraffin embedded specimen was then sliced transversely and each tissue block was capable of producing 4 to 5 slices each of 4µm thickness. At this point the surgical resection specimen was requested from the referring hospital and transferred to UCH main site for further pathological analysis, which is detailed below.

Once the fixed paraffin embedded specimen slices were obtained from the referring hospital, they were all further stained as a baseline with haematoxylin and eosin (H & E) stain. This enabled the identification of the muscularis propria and relevant lymph nodes and thus an initial pathological grading to be determined.

2.4 Evaluation of Tracer Uptake

There are a variety of different techniques for quantifying tracer uptake. In this thesis visual (qualitative) analysis and quantitative analysis of reconstructed coronal, sagittal and axial planes were undertaken. All image sets were viewed in these three planes utilising a Xeleris PET/CT and PET/MRI workstation (GE Healthcare).

2.4.1 Visual analysis

Visual analysis is a qualitative measure of evaluating tracer uptake from inspection of static images. All 18F-FDG PET images were acquired 60 minutes after the tracer was injected into the subject of study. This time frame was chosen as it represents the most acceptable plateau phase of tracer accumulation and is routinely used in most clinical sites. Visual analysis of tracer uptake is most effective when focal areas of tracer accumulation may be accurately distinguished from normal surrounding metabolically active tissue. High physiological uptake of 18F-FDG is always seen in the brain and myocardium due to their high rates of glucose metabolism. There are varying levels of 18F-FDG uptake seen in the stomach, spleen, liver and muscle of the gastrointestinal tract and bone marrow. 18F-FDG is excreted by the kidneys, and hence tracer accumulation may also be noted in the bladder and urinary tract.

Visual inspection of static images is a relatively simple method to perform and allows the accurate identification of focal areas of high tracer accumulation

within metabolically active areas of tissue. The main limitation to this technique is that subtle changes in these metabolically active tissues may be difficult to interpret or in some cases missed from the initial analysis.

All 18F-FDG PET/CT and PET/MRI scans were analysed and clinical reports generated by consensus reporting. This technique involved the visual inspection of image sets for each patient in three orthogonal planes being reviewed by two nuclear medicine physicians of Consultant grade and a collective result being reached by consensus.

2.4.2 Regions of interest

To quantify tracer uptake in malignant and normal tissue, a region of interest (ROI) technique was used. For tumours, ROIs were delineated in all image sequences over any identifiable lesions. In order to determine an accurate activity concentration at the location of the tumour, 5 consecutive slices were used for each ROI. These selected slices were required to have been obtained from the individual slice with the maximal count density and their consecutive adjacent slices.

2.4.3 Semi-quantitative analysis of tracer uptake (Standardised uptake values)

Qualitative data may be obtained in oncological studies via the means explained previously in section 2.4.1. More quantitative methods exist for evaluating tracer uptake in malignant tissue. One commonly used technique is to determine the standardised uptake value (SUV). The below formula demonstrates how the SUVs used in the studies in this thesis were calculated.

$$SUV = \frac{A \times W}{A_{inj}}$$

In the above equation (A) is the average tumour activity concentration in kBq/ml, (W) is the body weight of the patient in kg and (A_{inj}) is the injected activity in kBq (Graham et al., 2000; Takeuchi et al., 1999).

The above calculation allows correction for variations in the patient's body weight and the injected activity of tracer. Therefore, the SUV value obtained may be considered to represent an accurate index of the tracer accumulation within tissue. This allows the accurate differentiation between benign and malignant lesions as well as a quantification of treatment response when serial SUV values are measured.

The calculated value relates to the activity concentration found in a certain tissue region of interest (ROI) to the activity per the patient's body weight. In this way inter individual differences and varying amounts of administered activity are taken into account. The amount of activity found in a region is, however, not always static and may change after tracer injection by increased uptake of the tracer or by washout of the tracer from the tissue.

2.5 Computerised Tomography

2.5.1 Patient preparation

i) CT scan of the thorax, abdomen and pelvis.

Before the above imaging was undertaken, all patients were asked to refrain from eating for a minimum period of six hours. They were however allowed to drink clear fluids up to one hour before the onset of their scan. An appropriate oral contrast agent was given to the patient immediately prior to the CT imaging of regions involving the abdomen and pelvis. No other further patient preparation was required.

ii) CTC (CT pneumocolon)

To produce high-resolution images of the colon, bowel preparation was required to adequately clean the colon from any potential artefacts that may adversely influence image analysis. This procedure involved patients ingesting one sachet of oral Picolax the day before their scan, between 07:30 and 09:00 for morning appointments the following day and before 19:00 for afternoon appointments the following day. A low residue diet was allowed up to 18 hours prior to imaging and all patients were asked to drink clear fluids at a rate roughly of 500mls per hour continuously. Immediately before imaging took place, all patients were required to drink two glasses of water.

2.5.2 Image acquisition

i) Abdomen and pelvis

Routine standard of care CE-CT performed for staging purposes were obtained from each referring hospital. An example protocol is detailed below.

CE-CT imaging of the abdomen and pelvis was acquired using the Siemens Plus 4, four slice multi-detector spiral CT (Siemens AG Medical Engineering Group, Forchheim, Germany), which produced 5mm contiguous slices. The selected contrast used was Omnipaque 350 (Nycomed Amersham, Amersham Place, Little Chalfont and Buckinghamshire, UK) and was injected via a peripheral vein at a dose of 100mls, at a rate of 4ml/s with a chosen delay of 45 seconds. In the instances that bi- or tri-phasic imaging of the liver was chosen for appropriate patients, they were scanned with 20s, 50s and 180s delays with 5mm thick slices at 2.5mm intervals or with 35s, 50s and 180s with 3mm slices at 1.5mm collimations. All of the 3mm and 5mm thickness images were subsequently reconstructed.

ii) Chest

Contrast, standard imaging was performed as detailed previously above.

2.5.3 Image reconstruction and analysis

Images were analysed preferentially in the trans-axial planes although when required sagittal and coronal planes were also available. All reconstructed image data was processed on the CT scanner Siemens workstation.

All images were analysed by a radiologist of Consultant grade. Further analysis took place at a weekly colo-rectal MDT meeting where these images were again reviewed by a Radiologist of Consultant grade with at least 5 years of experience in colo-rectal cancer and CT imaging.

2.6 Confirmation of diagnosis and follow up

A multi-disciplinary team (MDT) managed all patients recruited in this thesis, in line with U.K government guidelines on optimal individualised care for patients. The MDT consisted of medical and associated healthcare professionals. These included radiologists, surgeons, clinical oncologists and nursing staff. The consensual decision made by the MDT ranged from the most appropriate further investigations to the optimum clinical management of each patient discussed. All PET/MRI, PET/CT. CT and MRI scans were discussed with the appropriate patient specific clinical information.

CHAPTER 3

The impact of PET/CT on loco-regional staging in primary CRC: A Systematic Review and Meta-analysis.

3.1 Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide affecting both men and women after lung and breast cancers (Boyle and Ferlay 2005). In 2011, 141 210 new cases were diagnosed, resulting in 49 380 deaths in the USA (Siegel et al. 2011). Pre-operative staging of CRC is an essential process, as the optimal treatment strategy and the long term prognosis for patients are determined by their tumor, node, metastasis (TNM) classification (Sun et al. 2005). Patients with CRC are staged according to the international tumor, node, metastasis (TNM) classification described by the American Joint Committee on Cancer (Edge 2010).

PET/CT uses a form of radiolabeled glucose, fluorine-18 2-fluoro-2-deoxy-D-glucose (^{18}F -FDG) and is able to combine both anatomic localization and metabolic imaging. It has been shown to improve staging in a number of different cancers, which include non-small cell lung cancer (Mac Manus et al. 2001), oesophageal cancers (Leong et al. 2006) and lymphoma (Blum et al. 2003). PET/CT has resulted in a change in management in a large proportion of patients with these cancers, hence has become a useful primary staging investigation in selected patients.

The National Comprehensive Cancer Network (NCCN) presently recommends that contrast enhanced CT of the chest, abdomen and pelvis should be the primary imaging modality for staging CRC. The overall accuracy for T-staging in patients with colon cancer with CT has been shown to vary between 41% and 86% (Ahmetoğlu et al. 2011). The wide range of reported T-staging accuracies may be partially explained by difficulty distinguishing between tumour invasion of the submucosa or the muscularis propria and subserosa with CT. Consequently, CT has been traditionally poor at differentiating between T1 and T2 tumours which may

contribute to the poor overall T-staging accuracy in patients with colon cancers. In patients with rectal cancer, diagnostic MRI is recommended for T-staging (Park et al. 2014), due to superior soft tissue definition and improved diagnostic accuracy when assessing the meso-rectal fascia and potential circumferential resection margin. However, in patients with rectal cancer this often results in both CT and MRI imaging both being performed for CRC staging before treatment may be initiated. PET/CT in the context of CRC is currently recommended for the detection of recurrent disease and some practices advocate its use in pre-therapeutic assessment of patients with potentially resectable hepatic metastasis prior to hepatic resection (Fletcher et al. 2008; Poston et al. 2011). The present available literature on the role of ^{18}F -FDG PET/CT in detecting primary CRC and loco-regional staging (T and N-Staging) is still limited and unclear. PET/CT may potentially provide a single examination diagnostic investigation for loco-regional staging in newly diagnosed CRC patients.

3.2 Aims

The aim of this chapter is to perform a qualitative analysis via a systematic review and meta-analysis of the literature regarding the role of FDG-PET/CT in loco-regional staging (T and N-staging) in patients with primary colorectal cancer.

The objectives are,

- i) to assess the role of PET/CT in T-staging in patients with primary pre-therapeutic colon and rectal cancers.

- ii) to assess the role of PET/CT in N-staging in patients with primary pre-therapeutic colon and rectal cancers.

3.3 Methodology

This systematic review was carried out in accordance with the PRISMA statement (Moher et al. 2009). A systematic search was performed covering all studies with databases between January 2000 and April 2019. This start date reflects the point at which the first combined FDG-PET/CT became commercially available (Townsend 2008). This study was registered in PROSPERO and may be accessed (CRD42016034163). In the absence of randomised controlled clinical trials, a traditional meta-analysis could not be performed and therefore an alternative strategy was defined to evaluate the current literature, and is explained further in the subsequent sections.

3.3.1 Search Strategy

The search terms, agreed by consensus among the authors across relevant specialties with more than 10 years-experience in surgical academia, are listed in table 3.1.

Concept	Search terms
Cancer	crc OR (colo* OR rectal) AND (neoplasm OR cancer OR tum* OR malig*)
Imaging	pet OR positron emission tomography OR pet/ct OR pet/mr*
Outcome	staging OR tnm OR node OR metas*

Table 3.1. - Search concepts and terms.

The search terms under the generic headings were conducted and the results of the searches were combined by use of Boolean characters “AND” and “OR”. The following databases were systematically searched using the above search terms: PubMed, MEDLINE, Ovid and Embase.

In order to identify further additional papers, the “related” function was utilised from Pubmed. A hand search was also performed for references of the articles identified and, where necessary, abstracts reviewed. References from relevant systematic reviews were examined and when relevant papers were not retrieved in the original search they were the subsequently included. Figure 3.1 provides the PRISMA flow diagram of included studies.

3.3.2 Eligibility criteria

All English language peer-reviewed studies that investigate the diagnostic accuracy and impact of PET/CT imaging in patients with colorectal cancer were examined. There were no search restrictions on study type or cohort size. Abstracts presented at conferences, case reports, letters, editorials and comments were excluded. The full eligibility criteria is shown in Figure 3.1.

Inclusion Criteria

Study participants in included studies were pre-therapeutic confirmed CRC patients.

- The index test used was ^{18}F -FDG PET/CT imaging.
- Only studies utilising hybrid combined PET/CT scanners were considered for inclusion.
- The comparator used in all of the individual studies was either the gold standard histopathology specimens, or conventional imaging.
- The outcomes of included studies had to report a measure of accuracy of FDG-PET/CT, including sensitivity, specificity, Positive Predictive Value (PPV) or Negative Predictive Value (NPV), for T and N staging.

Exclusion Criteria

- Abstracts presented at conferences, case reports, letters, editorials and comments were excluded.
- Studies assessing the role of PET/CT in detection or assessment of recurrent disease were excluded.
- Studies utilizing PET scanners rather than hybrid PET/CT scanners were excluded.
- Studies only investigating biochemical changes or any other non-staging investigations.

PRISMA 2009 Flow Diagram

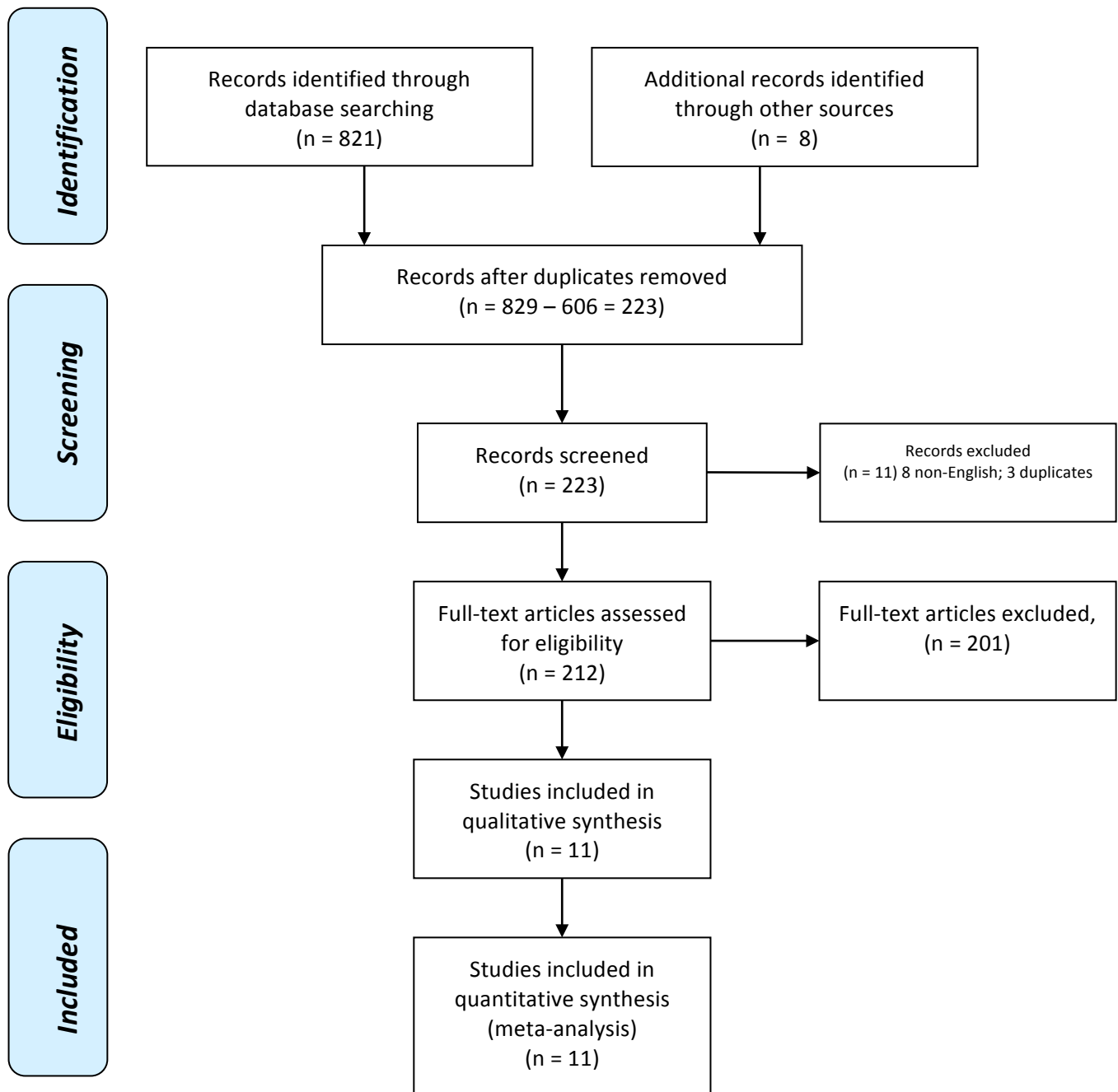


Figure 3.1. - PRISMA flow diagram of Systematic review and Meta-analysis.

3.3.3 Risk of bias of included studies

The risk of bias of each included study has been assessed against the QUADAS -1 tool. This is the recommended tool for diagnostic accuracy studies by the Cochrane collaboration (Whiting et al. 2003). A full copy of the QUADAS -1 tool is present in appendix 1. The QUADAS -1 is a 14 question tool against which each study is scored. A score of 10 or more, as validated in previous studies, indicates a good reliability of the study. Questions were grouped into 7 domains: selection bias, reference standard reliability, verification bias, index test blinding, reference test blinding, reporting bias, and withdrawals. The overall risk of bias across the studies is presented in Figure 3.2.

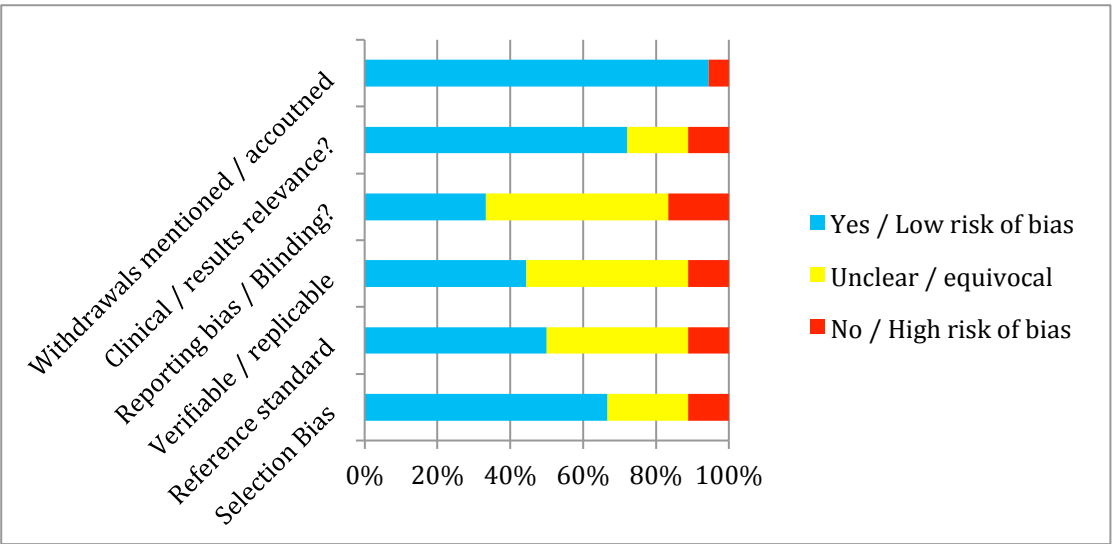


Table 3.2 - The overall risk of bias across all of the included studies.

3.3.4 Data synthesis

Data collected included study characteristics, such as year of publication, year of database, country of origin, study design, number of participants, and whether participants had colon cancer, rectal cancer, or both. The reference standard used in each study was either gold standard histopathology results or conventional imaging. Outcomes extracted included accuracy measures such as, sensitivity, specificity, Positive Predictive Value, and Negative Predictive Value. The proportion was changed into percentages for standardised comparison.

3.3.5 Statistical Analysis

The results of this study were finalised by three separate meta-analyses: the accuracy of PET/CT in tumour T-staging; the accuracy of PET/CT in nodal staging; and the pooled impact across studies PET/CT had on changing the management plan of patients. Studies eligible for inclusion into the meta-analyses were required to report an accuracy measure in relation to a reference standard and the confidence interval. A random effect model was used for all of the meta-analyses in this study, as it was anticipated that the accuracy of PET/CT would be varied amongst individual studies. The I^2 test was used to measure heterogeneity of included studies. The I^2 index ranges from 0-100%; values of 25%, 50% and 75% are considered to represent low, moderate and high heterogeneity respectively.

3.4 Results

Twelve studies were included in this systematic review (Table 3.3). In total, 1,618 lesions were included, of which 781 (48.3%) were in the colon and 837 (51.7%) in the rectum. Five studies were prospective cohorts, and four were retrospective analyses; two studies did not clearly state their study designs (Tsunoda et al. 2008; Uchiyama et al. 2012) although from the methodology it appears one was prospective and the other retrospective. Six of the 12 studies assessed accuracy in T-staging; ten studies assessed nodal staging with PET/CT imaging.

QUADAS scores ranged from 7 to 12 and 9 of which scored 10 or higher. The most common reasons for score reductions were: unclear description of reference standards and index test executions; failure to report specifically whether the reporting was blinded; and unclear description of the timing between reference tests and index test (Table 3.2).

Author	Year	Number of Participants	Study Design	Colon or Rectum	Imaging Modality assessed	Reference Standard
Veit-Haibach	2006	47	Prospective	13 rectum	PET/CT colonography vs. CT alone Vs. PET + CT.	Histopathology
Cipe	2013	64	Prospective	25 colon 39 rectum	PET-CT	C/I (CT)
Mainenti	2010	34	Prospective	37 CRC (6 in rectum)	PET-CT	Histopathology
Engelmann	2014	62	Prospective	63 colon (2 benign) 2 rectum	PET/CT	Histopathology, C/I (CT)
Uchiyama	2012	77	Retrospective	42 Colon 38 Rectum	PET-CT vs histopath PET-CT vs CT	Histopathology, C/I (CT)
Eglinton	2010	20	Prospective	20	PET/CT	

				Rectum		Histopathology. C/I (CT)
				190 Colon 283		
Kwak	2012	473	Retrospective	Rectum	PET-CT vs CT	Histopathology
				30 Rectum		
Kim	2011	30	Retrospective		PET-CT vs MRI	Histopathology
Tateishi	2007	53	Retrospective	53 rectal	non-CE PET-CT vs CE PET CT	Histopathology
Lee	2014	266	Retrospective	266 colon	PET-CT	Histopathology, C/I (CT)
Tsunoda	2008	88	Prospective	37 colon, 51 Rectum	cohort / proximal group vs. Distant group	SUV, visual diagnosis and diameter correlation with histopath
Squillaci	2008		Prospective	20 colon	PET/CT vs MRI	Histopathology, C/I (MRI)

Table 3.3 – Summary of PET/CT studies assessing loco-regional staging.

T-staging

Six of the 12 studies assessed accuracy or sensitivity of PET/CT in CRC T-staging. Five studies were prospective, while one study (Uchiyama et al. 2012) failed to clarify whether it was prospective. All studies, except Cipe (Cipe et al. 2013) compared PET/CT results to gold standard histopathology results. Five studies reported sensitivities ranging from 58% to 100% (Engelmann et al. 2014; Eglinton et al. 2010), specificity was measured in two papers, both reporting results of 86% (Engelmann et al. 2014; Cipe et al. 2013). Only one paper (Cipe et al. 2013) reported values for PPV and NPV, which were 91.8% and 85.7% respectively.

Three of these studies explicitly reported accuracy (Table 3.4). These studies were selected for inclusion in the meta-analysis. The accuracy of PET/CT in tumour staging ranged from 81% to 94.3% (Mainenti et al. 2011; Engelmann et al. 2014). The pooled %-accuracy of PET/CT in tumour staging was 88% (95% CI: 77% - 94%). We noted moderate heterogeneity amongst the studies with I^2 value of 53.3%.

Author	T-staging accuracy
Engelmann	Sensitivity: 58% [28–85], Specificity: 86% [73-95], Accuracy 80% [68-90]
Cipe	Sensitivity: 95.7%, Specificity:75% , PPV: 91.8%, NPV: 85.7%, Accuracy:90.5%
Mainenti	Accuracy: 94.3% (95% CI: 87-100%) T1, T3, and T4 all correctly staged. 2 T2 cancers over-staged as T3
Veit-Haibach	PET/CT colonography was more accurate in defining TNM stage (difference, 22%; 95% CI, 9%-36%; P = .003). T was correctly identified in 86% on PET/CT colonography. No Accuracy stated for PET/CT
Uchiyama	Sensitivity PET: 95%, CT: 78.8% (p=0.0023) No Accuracy stated for PET/CT
Eglinton	Sensitivity 100% (correctly identified all)

Table 3.4 – PET/CT studies assessing T-staging accuracy.

Table 3.5 shows the forest plot of the pooled accuracy of PET/CT for T-staging. The three reported studies that specifically reported a diagnostic accuracy value for T-staging with PET/CT are shown. The point estimate from the study by Engelmann et al., 2014 very clearly lies away from those of the other two studies as well as to the left of the line of no effect. However, the 95% confidence intervals of all studies were broad and all overlapped and crossed the line of no effect. Hence from the individual and cumulative forest plots, PET/CT may not be considered to have had an effect on the outcome, which was in this study T-staging in patients with CRC.

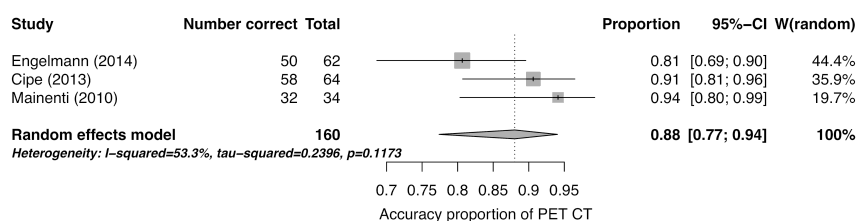


Table 3.5 – T-staging meta-analysis forest plot of pooled accuracy.

N-staging

Ten studies assessed the accuracy of PET/CT in detecting nodal metastases in CRC (table 3.6). Five were prospective studies; five were retrospective in study design. All studies used the gold standard histopathology results for comparison, except for Cipe (Cipe et al. 2013) which utilised conventional imaging (MRI imaging for rectal and CT for colonic lesions) as the reference standard. Reported sensitivities of PET/CT in staging nodal metastases ranged from 33% (Engelmann et al. 2014) to 86% (Veit-Haibach et al. 2006). Reported specificities ranged from 68% (Tateishi et al. 2007) to 100% (Uchiyama et al. 2012). PPV and NPV ranged from 63% (Veit-Haibach et al. 2006) to 94% (Kwak et al. 2012), and 47.4% (Cipe et al. 2013) to 88% (Veit-Haibach et al. 2006) respectively (Figure 4).

Eight studies reported nine accuracy values for nodal staging, and these studies were selected for inclusion in the meta-analysis (table 3.7). One paper (Lee and Lee 2014) reported two separate accuracies for stage III and IV disease. The accuracy of PET/CT in detecting nodal metastases ranged from 42% (Lee and Lee 2014) to 79% (Tateishi et al. 2007; Mainenti et al. 2011). The pooled percentage accuracy of PET/CT in nodal staging was 66% (95% CI: 58% - 74%). We noted high heterogeneity amongst included studies with I^2 value of 89.8%.

Author	N-staging accuracy
Tsunoda	SUV 1.5 sens: 53.1 (26/49) spec: 90.6 (115/127) Accuracy: 80.1 (141/176)
Tateishi	non-CE PET-CT: sens: 85%, spec: 42%, PPV: 73%, NPV: 62%, Accuracy: 70%. CE-PET-CT: sens: 85%, spec: 68%, PPV: 83%, NPV: 72%, Accuracy: 79
Engelmann	PET/CT N-staging: sens 33% [16-55]. Spec: 90% [74-98]. Accuracy 66% [51-78]
Cipe	PET: sens 52.4%, spec: 85%, PPV: 88%, NPV: 47.4%, Accuracy: 63.5%
Kim	PET: sens: 61% spec:83%, PPV: 84%, NPV: 58%, Accuracy 70% MRI: sens:94%, spec: 67%, PPV: 81%, NPV: 89% Accuracy:83%
Kwak	PET: Sensitivity 66%, Spec 60%, PPV 63%. NPV 62%, Accuracy: 63% CT: sens 87% (p=0, spec 29% PPV 57% NPV 68%. Accuracy: 59%
Mainenti	PET-CT Accuracy N stage: 79.4% (66-93%)
Lee	Stage III: accuracy of PET-CT : 42%. CT: 36.2% (p=0.822)
Lee	Stage IV: accuracy of PET-CT: 63.5%. CT:60.3% (p=0.509)
Squillaci	Lymph node involvement was determined in 15/20 cases and considered to be N-positive with PET/CT and 10/20 cases with.
Veit-Haibach	PET/CT N-staging: sens 80 % (56-94). Spec:97% (83-100). PPV: 94% (71-100). NPV (88%(72-97) No Accuracy stated for PET/CT

Table 3.6 – PET/CT studies assessing N-staging accuracy.

Table 3.7 shows the forest plot of the pooled accuracy of PET/CT for N-staging. The eight studies that specifically reported a diagnostic accuracy value for N-staging with PET/CT are shown. The point estimates from the studies by Engelmann, Cipe, Kwak and Lee all lay away from those of the other included studies as well as to the left of the line of no effect. However, the 95% confidence intervals of all studies were broad and all essentially overlapped and crossed the line of no effect, except for those from the study by Lee et al., 2014, which reported an accuracy for N-staging in stage 4 CRC disease. From the cumulative forest plot, PET/CT may not be considered to have had an effect on the outcome, which was in this study N-staging in patients with CRC.

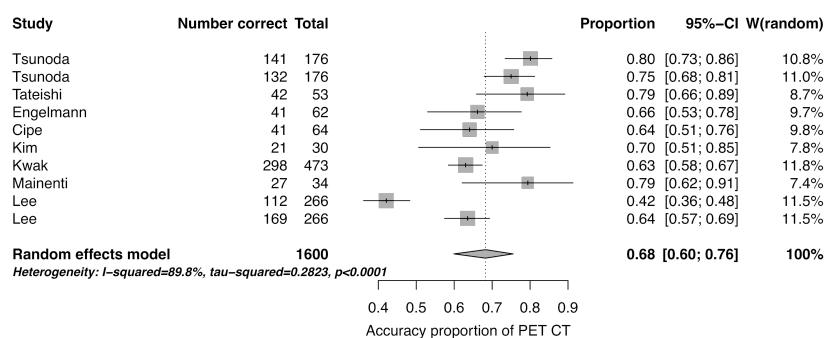


Table 3.7 – N-staging meta-analysis forest plot of pooled accuracy.

3.5 Discussion

The reported accuracies in T staging across included studies ranged between 80% and 94.3%. The highest reported accuracy for T staging by PET/CT was noted to be 94.3% (Mainenti et al. 2011). This was a prospective study of 34 CRC patients where PET/CT was compared to gold standard histopathological specimens. Similar results were obtained in a further study of 64 CRC patients where PET/CT T-staging accuracy of 90.5% was noted using CT imaging as the reference standard (Cipe et al. 2013).

As expected and proven from other studies, PET/CT is more reliable in identifying disease when it is present (true positive) than in ruling out disease when it does not exist (true negatives). This is reflected from the consistently higher sensitivities than specificities across the studies.

One study by Englemann et al., noted a relatively low T-stage accuracy of 82% with a relatively low sensitivity of 58% and specificity of 86% which was in stark contrast to our other included studies (Engelmann et al. 2014). This study of 62 patients with 63 colonic and 2 rectal lesions compared PET/CT and CT to histopathological specimens. The authors from this study suggested that PET/CT had a lower accuracy in determining T-staging. Possible explanations for the differing T-staging accuracy determined by Engelmann et al., are that there was a clear selection bias, such that only patients with T4 lesions were included. In all other included studies patients with a range of T-stages (T1-T4) were included. For example in a study by Uchiyama et al., a sensitivity of 95% was achieved when patients with varying T stages were imaged (Uchiyama et al. 2012). This variation in T-staging accuracy, may also be due to the accuracy for T-staging not being reached by consensus and discussion of up to three separate readings by senior radiologists as

was the case by Mainenti et al., (Mainenti et al. 2011), who achieved the highest percentage accuracy.

Node positive disease detected with conventional imaging (MRI and CT) is a criterion for locally advanced cancer. These patients have been shown to benefit from pre-operative chemotherapy to improve their long-term prognosis (Arredondo et al. 2013). Therefore the detection of involved lymph nodes defines the treatment path and prognosis of patients.

For N-staging the studies that compared PET/CT to CT all showed similar individual accuracies for PET/CT and also that PET/CT had superior accuracy to CT. The study with the largest patient sample was by Kwak et al., and was a retrospective analysis of 473 CRC patients which showed PET/CT had a diagnostic accuracy of 63% for nodal staging (Kwak et al. 2012). Engelmann et al. compared PET/CT and CT accuracies for N-staging in colon cancer patients and showed PET/CT to have a similar accuracy of 66% (Engelmann et al. 2014). Lee et al., 2014 also measured the accuracy of PET/CT and CT, but did so in advanced disease patients. Accuracies in stage 3 disease patients of 42% and stage 4 disease patients of 63.5% for PET/CT was noted (Lee and Lee 2014).

On the other hand, Cipe et al., compared the accuracy of PET/CT and CT for nodal staging and found PET/CT had an accuracy of 63.5% whilst CT had an accuracy of 100% (Cipe et al. 2013). This result contradicts all of the previous mentioned studies, but may be explained as CT was used as the reference standard rather than gold standard histopathology, which was used in all of the other studies. Another explanation is the limited ability of PET/CT in picking up lesions less than 1 cm in size, while it is now widely accepted that lymph nodes less than 1 cm in size may still harbor metastatic disease (Brown et al. 2003).

A prospective study of 34 CRC patients compared PET/CT directly to the reference standard post-operative histopathological specimens, rather than CT as used in the above mentioned studies. PET/CT correctly identified the N-stage in 27 patients and was shown to have an accuracy of 79.4% (95% CI 66%-93%) (Mainenti et al. 2011). A further study by Tsunoda et al., 2008 also compared PET/CT to the reference standard histopathology in 88 CRC patients. Accuracies were calculated according to standardised uptake values (SUVs) and by visual analysis. The mean SUVs of malignant lymph nodes were significantly higher than benign lymph nodes ($p=0.01$). Utilizing an SUV cut-off value of 1.5, as determined by a ROC analysis, the overall N-staging accuracy of PET/CT was 80.1% and through assessing lesions by abnormal SUV uptake alone, the N-staging accuracy was 75% (Tsunoda et al. 2008).

Squillaci et al., compared PET/CT to whole body MRI (WB-MRI) in staging 20 colon cancers, lymph node involvement was determined in 75% and 50% of cases respectively (Squillaci et al. 2008). This study supported the findings in both studies by Mainenti et al., 2011 and Tsunoda et al., 2008 by achieving almost identical N-staging accuracies, despite using a different imaging modality as a comparator to PET/CT.

Pelvic MRI is the most reliable conventional imaging modality for the pre-operative staging of patients with rectal cancer (Brown et al. 2003; Torricelli 2007). However MRI still has difficulties in differentiating benign reactive lymph nodes from true metastatic lymph nodes. Traditionally lymph node size was used to assess the presence of metastatic lymph nodes, however due to the presence of micro-metastasis, lymph node size is not a reliable tool for assessing metastatic node involvement (Brown et al. 2003; Shin et al. 2008).

In another study PET/CT was compared to MRI in 30 surgical patients with rectal cancer (Kim et al. 2011). PET/CT showed an accuracy of 70% whilst MRI showed an accuracy of 83% when compared to the reference standard of histopathology. A retrospective study of 53 rectal cancer patients where contrast enhanced PET/CT was compared to non-contrast enhanced PET/CT showed accuracies of 79% and 70% respectively (Tateishi et al. 2007). The accuracies of both of these PET/CT studies in rectal cancer patients, despite differences in study design, were similar in value. In both studies of rectal cancer patients, the accuracy of PET/CT in N-staging was consistently higher than those studies involving colon cancer patients.

This meta-analysis has only assessed the impact of PET/CT on loco-regional staging in patients with primary CRC. The accuracy of the identification of distant metastases (M-staging) was not assessed in this systematic review due to a recent meta-analysis and systematic review by Maffione et al., 2015 addressed this question comprehensively (Maffione et al. 2015).

3.6 Conclusion

This systematic review and meta-analysis has demonstrated high levels of accuracy (88%) for the pre-therapeutic T-staging of colorectal cancers with PET/CT. Regarding N-staging accuracy, PET/CT had a lower overall accuracy (66%) for N-staging in comparison to T-staging. PET/CT also had a higher accuracy for N-staging of rectal cancers as opposed to colon cancers.

PET/CT may potentially have a role as an alternative or complimentary imaging modality to conventional imaging in providing a loco-regional assessment of the T and N stage in patients with primary CRC. PET/CT may be of most benefit in patients with primary rectal cancer without systemic metastases. In these patients, an early assessment of the loco-regional tumour stage may result in the earlier initiation of surgical treatment or more appropriate neo-adjuvant therapy options prior to surgery and have an impact on improving long-term survival and prognosis.

CHAPTER 4

Loco-regional staging in colon cancer with PET/MRI and PET/CT – an observational cohort study

4.1 Background

Colorectal cancer (CRC) is a frequent and life limiting disease. In 2015 approximately 140,250 new cases of CRC were diagnosed in the United States, of which 97,220 affected the colon (Siegal, Naishadham, and Jemal 2012). CRC cancer mortality rates have progressively declined since 1990, in part due to advances in the early detection and treatment of the disease (Cronin et al. 2018). However, CRC still remains globally the third leading cause of diagnosed cancers in men and second in women with 835,000 deaths reported in 2015 (Cronin et al. 2018). Due to this persistently high morbidity and mortality rate, early diagnosis with accurate disease staging is crucial to determining treatment strategies and thus improving survival.

Accurate staging of disease consists of determining the depth of invasion (T-staging) and the presence of lymph node metastases (N-staging), which constitutes regional staging. In addition, an assessment of distant metastases (M-staging) is essential for complete cancer staging. Consideration of these variables contributes to determining the long-term prognosis. For patients with primary CRC, pre-operative tumour assessment and staging is challenging despite considerable advances in technology.

The current reference standard for detection of colon cancer is colonoscopy. Colonoscopy allows direct endo-luminal visualisation with potential for tissue sampling of lesions to enable histo-pathological confirmation of colon cancer (Rockey et al. 2005). However, colonoscopy does not allow the depth of tumour invasion to be accurately determined despite high levels of tumour identification. Therefore, in the UK conventional colon cancer staging requires the addition of contrast-enhanced multi detector CT (CE-CT) imaging to better evaluate tumour invasion depth as well as potential metastatic spread to local nodes and more distant

solid organs (Saunders, Mendes Ribeiro, and Gleeson 2002). In patients with suspected colon cancer, CT imaging of the abdomen, pelvis and thorax are mandatory (Fountzilas and Kaklamani 2017). The overall accuracy of multi detector CT has been shown to be 86% for T-staging in colon cancers (Ahmetoğlu et al. 2011).

The PET tracer glucose analogue [18F]-fluoro-deoxy-glucose has been used in positron emission tomography (FDG-PET) for CRC imaging. This has demonstrated functional information, resulting in high sensitivity and specificity rates for the detection of colon and rectal tumours (Abdel-Nabi et al. 1998). However, FDG-PET imaging is limited by special resolution, which makes anatomical localisation of a potential lesion difficult to evaluate (Falk et al. 1994). As a consequence, advances in medical technology have led to fusing of functional FDG-PET imaging with the anatomical virtues of CT imaging in the form of integrated PET/CT imaging (Antoch et al. 2004).

PET/CT has an established role in the detection of recurrent disease in CRC patients as well as the assessment of patients regarding suitability for surgical resection of colo-rectal liver metastases (Fletcher et al. 2008; Poston et al. 2011). However, there are limited studies that evaluate the diagnostic accuracy of PET/CT for initial tumour staging and local nodal involvement in patients with newly diagnosed primary colon cancer. The limited pre-existing PET/CT studies that exist have assessed loco-regional staging by comparing it to conventional imaging rather than a reference standard of resected histopathological specimens (Cipe et al. 2013). This is despite the accepted standard of care for localised colon cancer being surgical resection (Poston et al. 2011). Some studies have also used various other imaging modalities for comparison such as PET/CT colonography (Veit-Haibach et al. 2006),

CT (Engelmann et al. 2014; Eglinton et al. 2010) or MRI (Squillaci et al. 2008). Furthermore published studies have concentrated on the results from mixed patient cohorts of colon and rectal cancer patients, despite the inherent differences in tumour location and pathology as well as accepted treatment pathways. Therefore due to the considerable variations in study design and patient selection, it is difficult to interpret these results and apply the findings to an isolated colon cancer patient population.

Hybrid PET/MRI is a recent imaging advancement, which has demonstrated some promising use in clinical practice by addressing the challenges posed from co-registration of PET and MRI data sets (Paspulati et al. 2015). However there presently remains limited assessment of the role of PET/MRI in colon cancer staging. PET/MRI may potentially provide value to loco-regional staging for patients with colon cancer and subsequently enhance their treatment pathway. This study aims to address this gap in knowledge.

4.2 Aims

The aim of this chapter is to prospectively evaluate if PET/MRI is a more accurate imaging modality than PET/CT or conventional imaging (CE-CT), in relation to the accepted reference standard of the post-operative histo-pathological tumour grade, for determining loco-regional staging in pre-therapeutic patients with primary colon cancer.

The objectives are,

- i) To compare the diagnostic accuracy of PET/MRI, PET/CT and CE-CT imaging using the resected histo-pathological specimens as the gold standard for determining the precise location of tumour within the colon in patients with primary colon cancers.
- ii) To compare the diagnostic accuracy of PET/MRI, PET/CT and CE-CT imaging using the resected histo-pathological specimens as the gold standard for determining the depth of tumour invasion (T-staging) in patients with primary colon cancer.
- iii) To compare the diagnostic accuracy of PET/MRI, PET/CT and CE-CT imaging using the resected histo-pathological specimens as the gold standard for determining the presence of lymph node metastases (N-staging) in patients with primary colon cancer.

4.3 Methods

4.3.1 Patient recruitment

Patients were recruited prospectively for this study with histological biopsy proven primary colon cancer. All patients were asked to give written informed consent following a full explanation of the procedure.

Institutional ethical review board approval, pre-scanning preparation details and patient informed consent details from this chapter can be found further detailed in Chapter 2.1.1, Methodology.

4.3.2 Patient population

A total of 114 patients were initially recruited in this study. However, 17 patients did not proceed to have PET/MRI imaging despite undergoing both other imaging modalities and thus were excluded from this study. Therefore, a total of 97 patients with suspected malignant lesions were successfully recruited in this study. All patients were imaged with PET/MRI, PET/CT and CE-CT imaging. Fifty three patients had histology proven colon cancer and 44 patients had rectal cancer. Of the 53-colon cancer patients recruited, four patients were excluded from the final analysis. This was because the post-operative resected specimens were not available from the referring hospitals and therefore histological analysis could not be confirmed, in each of these 4 patients. The resultant 49 patients with 49 colon cancer lesions were successfully analysed in this chapter and consisted of 29 men and 20

females. The median age of all recruited patients was 66 years old and average age 66.1 years old. The flow of patients in this study is further demonstrated below in Figure 4.1.

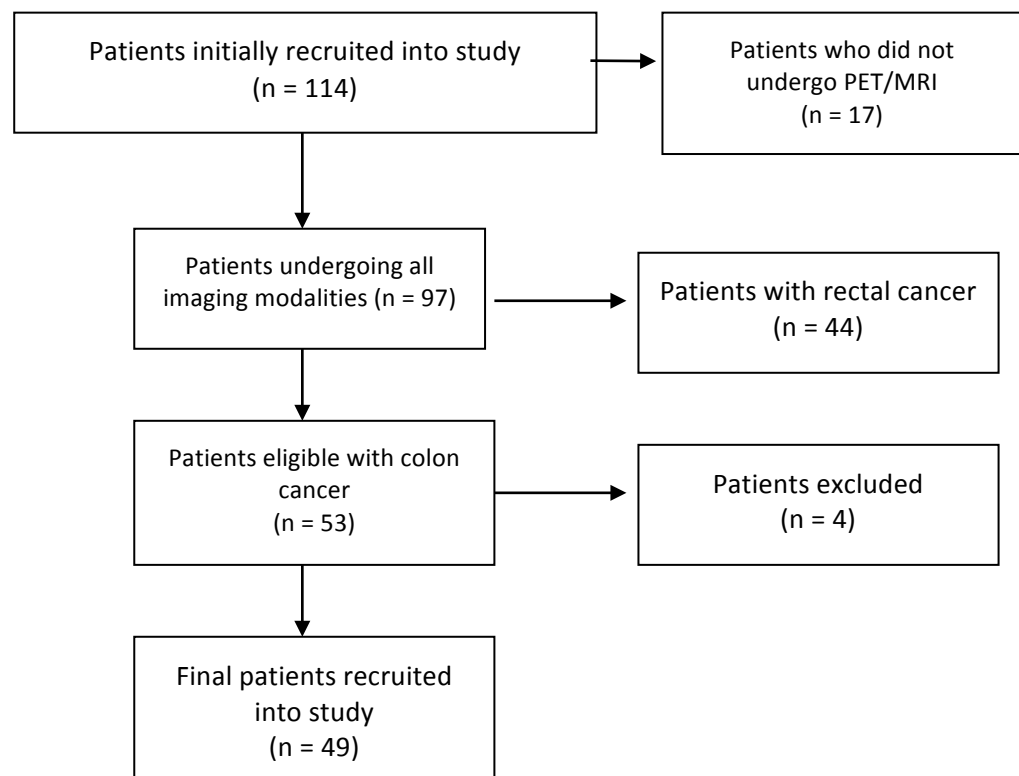


Figure 4.1 - Flow chart of patients in the study. n = number of patients in the study.

4.3.3 Imaging

Patients underwent whole body ^{18}F -FDG PET/CT and PET/MRI scans on the same day, as per the protocols in chapter 2, methodology. ^{18}F -FDG radio-tracer was prepared as described in chapter 2 with a mean administered dose of 250MBq or 370MBq for research or clinical scans respectively.

Visual analysis and standardised uptake values (SUVs) were obtained for each lesion using the methodology described in section 2.4.1. For each patient, regions of interest (ROI) were drawn over the tumour and normal tissue images.

Figures 4.2, 4.3, 4.4 and 4.5 show a 62 year old patient with a T2 adenocarcinoma of the ascending colon colon recruited into the study and the resultant CE-CT, PET/CT and PET/MRI images that were made available to each reader for subsequent staging.



Figure 4.2 – the Contrast enhanced CT image.

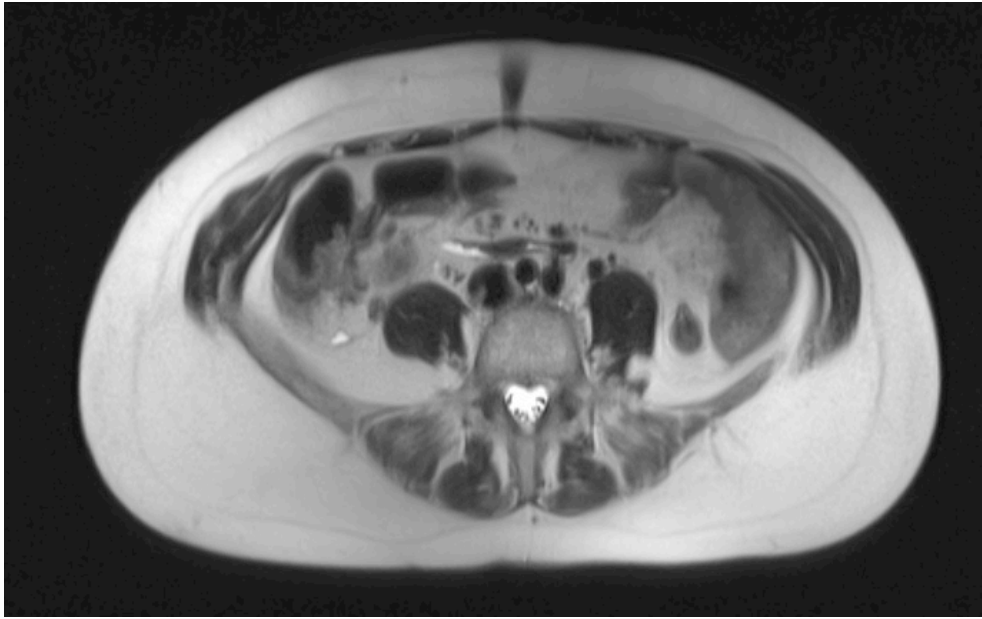


Figure 4.3 – the diagnostic magnetic resonance image.

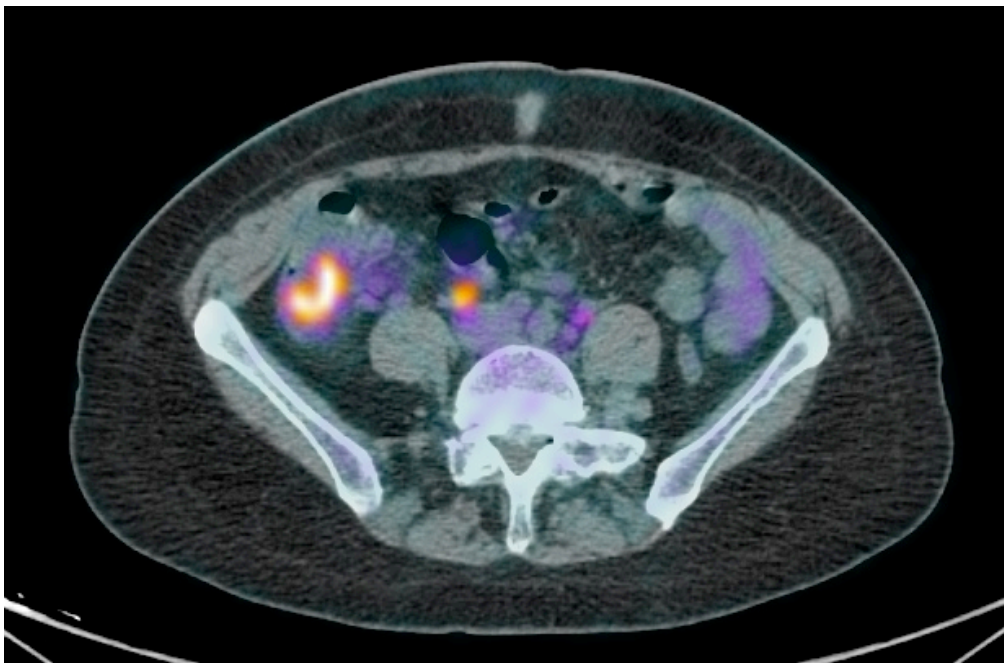


Figure 4.4 - the fused positron emission tomography/computed tomography.

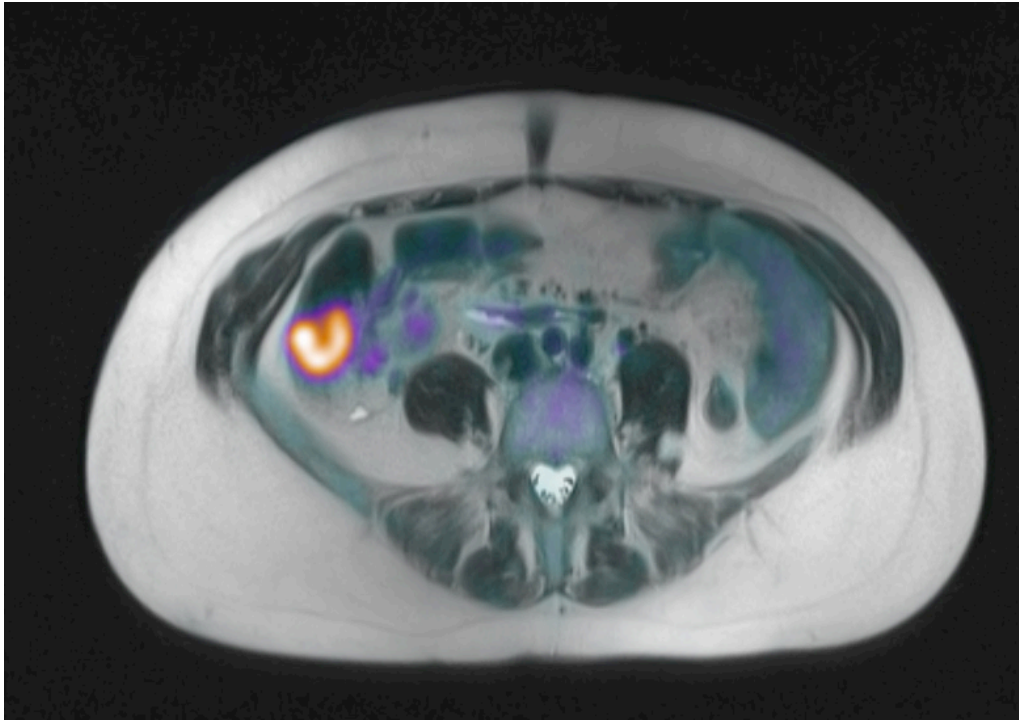


Figure 4.5 - fused positron emission tomography/ magnetic resonance image.

4.3.4 Reference Standard

From the final 49 patients recruited with colon cancer, post-operative resected histopathology specimens were available in all cases, which were subsequently analysed.

4.3.5 Statistical analysis.

All data from this study are expressed as mean \pm two standard deviations or as a proportion as appropriate. The two commercial statistical software packages used were, Microsoft ExcelTM and SPSS software (version 25). All statistically significant levels were set at 5%, where a p value <0.05 was considered significant.

4.4 Results

4.4.1 Standard of reference

A total of 49 adenocarcinomas were found after histo-pathological analysis of the resected specimens in patients diagnosed with colon cancer. Two adenocarcinomas demonstrated a mucinous component on further histo-pathological analysis. No patients had any synchronous lesions and none of the patients had known inflammatory bowel disease. Per-patient and per-lesion analyses were used and are further detailed below.

Histo-pathological analysis demonstrated, 0 out of 49 tumours were classified as T1, 6 (12.2%) as stage T2, 26 (53.1%) as T3 and 17 (34.7%) as T4. Regarding regional lymph node metastases, 24 out of 49 (49%) nodes when examined from the resection specimen were classified as N0, 14 (28.6%) nodes were classified as N1 and 11 (22.4%) as N2.

4.4.2 Tumour localisation and identification

The regional distribution of the 49 tumours affecting the colon noted at the time of surgical resection, were as follows: caecum (n = 6), ascending colon (n = 5), hepatic flexure (n = 1), transverse colon (n = 5), splenic flexure (n = 1), descending colon (n = 7) and sigmoid colon (n = 24). This is illustrated in Figure 4.6.

PET/MRI, PET/CT and CE-CT imaging modalities all showed concordance in locating the site of each tumour.

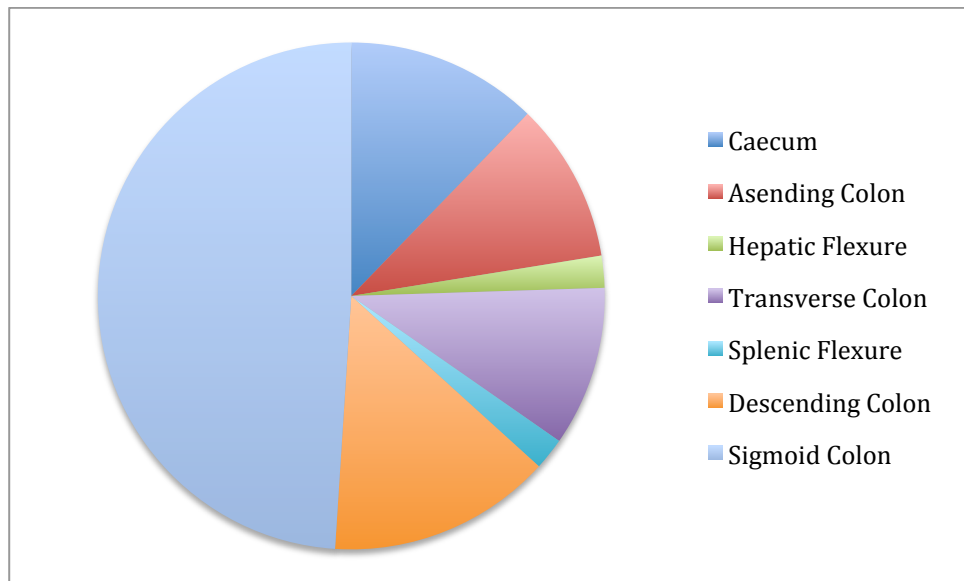


Figure 4.6 – A graphical representation of tumour distribution within the colon.

4.4.3 Colonic tumour T-staging accuracy

PET/MRI staged 34/49 (69.4%) tumours of the colon concordantly when compared to histo-pathological analysis of the post-operative resected specimens. PET/CT also staged 34/49 (69.4%) tumours correctly, whilst diagnostic contrast enhanced CT (CE-CT) was concordant with histo-pathology in 40/49 (81.6%) of colon tumours. Table 4.1 shows the overall diagnostic accuracy for T-staging of colon cancers with each imaging modality.

Imaging Modality	Accuracy	% Accuracy	P-Value (compared to CT)
PET/MRI	34/49	69.40	0.07
PET/CT	34/49	69.40	0.07
CT	40/49	81.60	

Table 4.1 – T-staging overall diagnostic accuracy

A sub-group analysis was performed and individual diagnostic accuracies for T2, T3 and T4 tumours were calculated for all three imaging modalities investigated in this chapter, and are shown in Table 4.2.

Imaging Modality	Imaging modaility T-stage	Number of patients correctly staged	Mean Accuracy (%)	95% CI low	95%CI high	p-value compared to CT
PET/MRI	T2	5/6	83.33	50.33	116.33	1
	T3	24/26	92.31	82.31	102.31	1
	T4	5/17	29.41	7.41	51.41	0.063
PET/CT	T2	3/6	50.00	6.00	94.00	0.5
	T3	22/26	84.62	70.62	98.62	0.375
	T4	9/17	52.94	28.94	76.94	1
CT	T2	5/6	83.33	50.33		
	T3	25/26	96.15	88.65		
	T4	10/17	58.82	34.82		

Table 4.2 – Individual diagnostic accuracies for T2, T3 and T4 colon tumours for all three imaging modalities, when compared to gold standard histopathology specimens.

The highest concordance between PET/MRI and histo-pathology was with the staging of T2 and T3 colon cancers and are shown in tables 4.2 and 4.3. Respective accuracies of 83.3% (95% CI: 50.3%-116.3%) and 92.3% (95% CI: 82.3%-102.3%) were achieved. Only one T2 lesion was incorrectly upstaged as a T3 tumour by PET/MRI and two T3 lesions were incorrectly down staged as T2 tumours. In comparison to T2 and T3 tumours, PET/MRI showed the lowest concordance for T4 tumours with only 5/17 tumours being correctly staged as T4 and an accuracy of 29.4% (95% CI: 7.4%-51.4%). 12 tumours were down staged by PET/MRI with ten tumours being classified as T3 and two tumours as T2.

Histology

		T2	T3	T4	Total
PET/MRI	T2	5	2	2	9
	T3	1	24	10	35
	T4	0	0	5	5
	Total	6	26	17	49

Table 4.3 – PET/MRI colon cancer T- stage vs Histology T-stage

PET/CT was concordant with histo-pathology stage in 34/49 of colon tumours (Tables 4.1, 4.2 and 4.4). Higher rates of concordance for T3 as opposed to T2 and T4 tumours were shown with PET/CT with accuracies of 84.6% (95% CI: 70.6%-98.6%) compared to 50% (95% CI: 50%-94%) and 52.4% (95% CI: 28.9%-76.9%) respectively. 22/26 patients were concordantly staged by PET/CT as T3 tumours, whilst 2 patients were over staged as T4 and two patients down staged as T2.

Histology

		T2	T3	T4	Total
PET/CT	T2	3	2	0	5
	T3	2	22	8	32
	T4	1	2	9	12
	Total	6	26	17	49

Table 4.4 – PET/CT colon cancer T- stage vs Histology T-stage

CE-CT imaging staged 40/49 colon tumours correctly, which was the largest number of concordant staged tumours from all imaging modalities (Tables 4.2 and 4.5). The highest concordance with histo-pathology was shown for T3 tumours, with an accuracy of 96.2% (95% CI: 88.7%-103.7%). CE-CT imaging showed a higher concordance for T2 tumour staging with an accuracy of 83.3% (95% CI: 50.3%-116.3%) than T4 tumour staging where an accuracy of 58.2% (95% CI: 34.8%-82.8%) was demonstrated in this study.

Histology

		T2	T3	T4	Total
CT	T2	5	1	0	6
	T3	1	25	7	33
	T4	0	0	10	10
	Total	6	26	17	49

Table 4.5 – CE-CT colon cancer T-stage vs Histology T-stage.

4.4.4 Colonic tumour N-staging accuracy

PET/MRI and PET/CT staged regional lymph node metastases according to PET tracer uptake to determine the number of lymph node deposits and nodal morphology when nodes $\geq 2\text{mm}$ were detected.

CE-CT was concordant with histo-pathology for overall N-staging in 65.3% of cases and showed the greatest accuracy of all imaging modalities. PET/CT showed concordance to histo-pathology for overall N-staging in 57.1% and PET/MRI in 44.9% of colon cancer patients (table 4.6).

Imaging Modality	Accuracy	% Accuracy	P-Value (compared to CT)
PET/MRI	22/49	44.90	0.021
PET/CT	28/49	57.14	0.30
CT	32/49	65.31	

Table 4.6 – N-staging overall diagnostic accuracy

PET/MRI and PET/CT images were further evaluated by two different criteria. These were, nodal morphology on the MRI component of PET/MRI and CT component of PET/CT respectively and abnormal uptake on the PET component of the PET/CT and PET/MRI. This method of analysis has previously been validated by Tsunoda et al., 2008 (Tsunoda et al. 2008) and was used in addition to comparing the overall diagnostic N-staging accuracy for each imaging modality.

PET/CT and PET/MRI imaging, when analysed according to PET tracer uptake both staged more regional lymph nodes concordantly in comparison to when nodal morphology analysis with each imaging modality was used. However CE-CT was concordant with histo-pathology in 65.3% of cases and showed the greatest accuracy of all imaging modalities (table 4.7).

Imaging Modality	Accuracy	% Accuracy	P-Value (compared to CT)
PET/MRI_morphology	22/49	44.9	0.02
PET/MRI_PET	24/49	49.0	0.12
PET/CT_morphology	28/49	57.1	0.29
PET/CT_PET	28/49	57.1	0.45
CT	32/49	65.3	

Table 4.7 – N-stage imaging modality accuracies.

Both PET/MRI and PET/CT PET uptake imaging showed greater concordance with histo-pathology than all other imaging when assessing the N0 individual stage and thus excluding the presence of positive regional lymph nodes. However, for detecting the presence of one or more lymph nodes, CE-CT showed the best level of concordance (table 4.8).

Imaging Modality	Imaging modality N-stage	Number of patients correctly staged	Mean Accuracy (%)	95% CI low	95%CI high	p-value compared to CT
PET/MRI (morphology)	N0	12/24	50	0.31	0.69	0.45
	N1	5/14	35.71	0.16	0.61	0.13
	N2	5/11	45.45	0.21	0.72	0.50
PET/MRI (PET)	N0	18/24	75	0.55	0.88	0.51
	N1	3/14	21.42	0.08	0.48	0.01
	N2	3/11	27.27	0.10	0.57	0.13
PET/CT (morphology)	N0	14/24	58.33	0.39	0.76	1
	N1	8/14	57.14	0.33	0.79	0.63
	N2	6/11	54.54	0.28	0.79	1
PET/CT (PET)	N0	19/24	79.17	0.60	0.91	0.22
	N1	5/14	35.71	0.16	0.61	0.13
	N2	4/11	36.36	0.15	0.64	0.25
CE-CT	N0	15/24	62.50	0.43	0.79	
	N1	10/14	71.43	0.45	0.88	
	N2	7/11	63.64	0.35	0.85	

Table 4.8 – N-stage imaging accuracy according to individual stage.

4.4.5 Imaging Sensitivities and Specificities

The T-staging and N-staging sensitivities and specificities for colon cancer with each imaging modality are shown in Table 4.9 and Table 4.10 respectively.

CE-CT showed a superior sensitivity and specificity in comparison to PET/MRI and PET/CT for T-staging.

Regarding regional lymph node metastases, the CT component of PET/CT then CE-CT imaging showed the best sensitivities whilst the PET component of PET/CT then PET/MRI showed the best specificities.

Imaging Modality	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR(+)	LR(-)
PET/CT	95.30	50.00	93.20	60.00	1.91	0.09
PET/MRI	90.70	83.30	97.50	55.60	5.43	0.11
CE-CT	97.70	83.30	97.70	83.30	5.85	0.03

Table 4.9 – T-staging sensitivity and specificities for colon cancers with all imaging modalities.

Imaging Modality	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR(+)	LR(-)
PET/CT overall	88.00	58.33	68.75	82.35	2.11	0.21
PET/CT (CT)	88.00	58.33	68.75	82.35	2.11	0.21
PET/CT (PET)	52.00	79.20	72.20	61.30	2.50	0.61
PET/MRI overall	68.00	50.00	58.62	60.00	1.36	0.64
PET/MRI (MRI)	68.00	50.00	58.62	60.00	1.36	0.64
PET/MRI (PET)	48.00	75.00	66.70	58.10	1.92	0.69
CE-CT	80.00	62.50	69.00	75.00	2.13	0.32

Table 4.10 – N-staging sensitivity and specificities for colon cancers with all imaging modalities.

4.5 Discussion

When identifying and locating colonic tumours, all imaging modalities in this investigation showed concordance. However our data did not include any T1 tumours. This may partially explain the investigation findings in this chapter, due to the distinct lack of any tumour lesions that were morphologically flat or confined only to the colonic wall. A study by Mainenti et al., 2011 found a rate of 94.6% (Mainenti et al. 2011) whilst Engelmann et al., 2014 noted a rate of 98% (Engelmann et al. 2014) for tumour identification and localisation with PET/CT imaging in patients with colon cancer supporting the high rates observed in this chapter. However in the study by Mainenti et al., 2011, in total 2 out of 37 tumours were not identified with PET/CT and both had flat morphology after histo-pathological analysis of the resected surgical specimen. Also of note, both of these colonic lesions were staged as T1 after histological analysis. Similarly a study by Veit-Haibach et al., 2006 was unable to correctly differentiate T1 tumours from T2 tumours in the colon in 3 out of 4 patients (Veit-Haibach et al. 2006). Therefore despite 100% concordance for tumour localisation with each imaging modality in this study, care and consideration should be taken for the precise localisation of T1 tumours.

On a per-patient basis this investigation showed the highest diagnostic accuracy for T-staging was achieved by CE-CT with an accuracy of 81.6%. PET/CT and PET/MRI both correctly staged 69.4% of patients and hence were still reasonable diagnostic tools for assessing tumour stage. However PET/CT and PET/MRI did not result in an improved overall diagnostic accuracy for T-staging in comparison to conventional imaging. Previous PET/CT studies in colon cancer have noted that T-staging accuracy is based on the anatomical aspect from the CT component as opposed to the metabolic localisation from PET (Cipe et al. 2013).

This was confirmed from our study findings and this was expected to be the case. This is because T-staging for colonic tumours with diagnostic imaging relies on visualisation of tumour across the depth of the colonic wall and surrounding structures. Hence, this is dependent on high spatial resolution, which is lacking with PET/CT and PET/MRI imaging. Soft tissue contrast resolution is also important to distinguish between tumour, normal mural stratification of the colonic wall and the surrounding structures. In this regard, the non-contrast CT component of PET/CT is expected to be inferior to contrast enhanced CT. Unlike the rectum, the colon is a mobile structure and the fast MRI sequences necessary for PET/MRI imaging and any residual motion artefact, despite the administration of buscopan, may have potentially degraded the ability of PET/MRI to effectively T-stage the colonic tumour.

Further analysis of individual T-stages showed that PET/MRI was superior to PET/CT for assessing the T-staging accuracy in T2 and T3 tumours. PET/MRI showed accuracies of 83.3% and 92% as opposed to PET/CT where 50% and 84.6% for T2 and T3 tumour staging was shown. This study also demonstrated that PET/MRI showed equivalence to conventional imaging (CE-CT) for staging T2 and T3 tumours where accuracies for CE-CT were 83.3% and 96.2% respectively. The study findings of high rates of T3 colon tumour staging, is supported by Mainenti et al., 2011 where PET/CT correctly staged all T3 tumours in 31 colonic cancer patients. This study also found that the T-staging sensitivity of PET/MRI was essentially equivalent to that of CE-CT where rates of 90.7% and 97.7% respectively were achieved. The specificity for PET/MRI and CE-CT were both 83.3%, which was higher than PET/CT, which was only 50%. Considering the high diagnostic accuracy for T2 and T3 lesion staging with PET/MRI, in conjunction with a

specificity of more than 90%, PET/MRI may have a role in staging uncomplicated localised colon cancers in patients who may be candidates for early curative surgical intervention. In clinical practice, PET/MRI may be utilised as an alternative imaging modality to CE-CT, to pre-operatively select patients with no prior abdominal surgery who may benefit from a laparoscopic as opposed to open colonic resection. This would confer the advantage of faster recovery with no adverse impact on recurrent disease or overall survival (Bonjer et al. 2007). These select patients undergoing laparoscopic surgery may then benefit from a shorter hospital stay, reduced parenteral analgesic use (Nelson et al. 2001) and improved quality of life measures long term (McCombie et al. 2018). PET/MRI may also have a potential role for identifying patients who are suitable for an enhanced recovery pathway from laparoscopic resection and shorter hospital duration of stay with the added cost saving implications. From this study PET/MRI may have a further role in detecting patients at risk of having a positive post-operative radial margin, who would benefit from extensive surgery in the form of an en-bloc resection of adjacent organs to achieve a negative resection margin. This is because colonic surgical resection margins should be at least 5 to 7 centimetres away from the tumour to ensure adequate resection of the associated lympho-vascular supply (Nelson et al. 2001). Due to the high sensitivity of PET/MRI these patients may be identified thus allowing more radical definitive curative surgical resection rather than repeated surgery with development of further regional recurrence or distant metastases.

Figures 4.7, 4.8, 4.9 and 4.10 show a 67 year old patient with a T3 adenocarcinoma of the caecum recruited into the study and the resultant CE-CT, PET/CT and PET/MRI images that were made available to each reader for subsequent staging. Figures 4.7 and Figure 4.8 below, demonstrate neoplastic

thickening of the peri-lesional fat whilst Figures 4.9 and 4.10 demonstrate tumour uptake of 18-FDG. This lesion was correctly classified as T2.

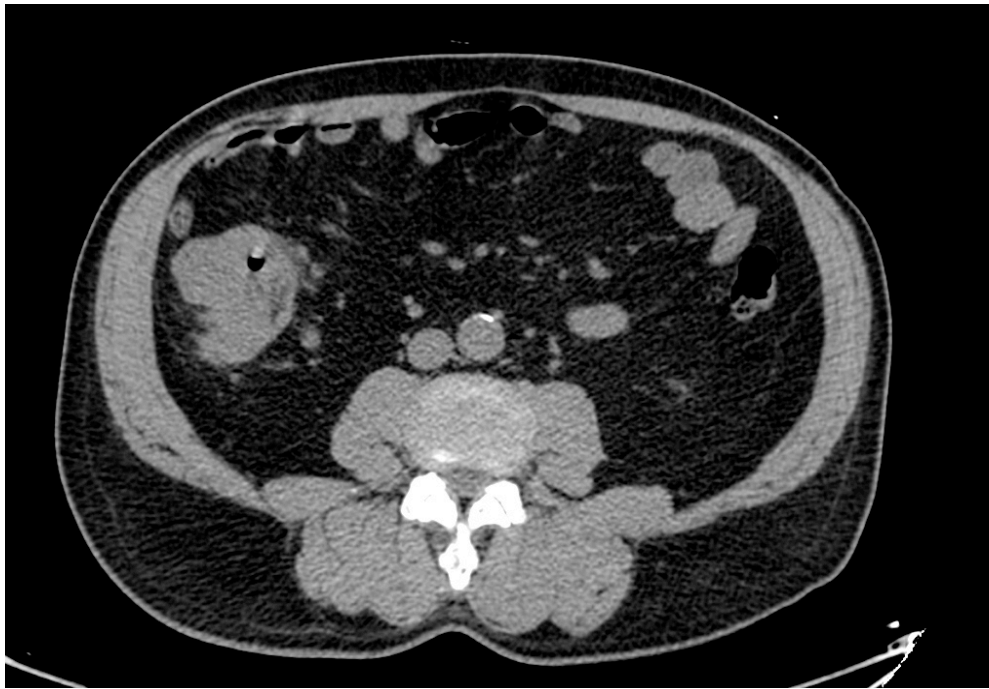


Figure 4.7 – the contrast enhanced computed tomography image.

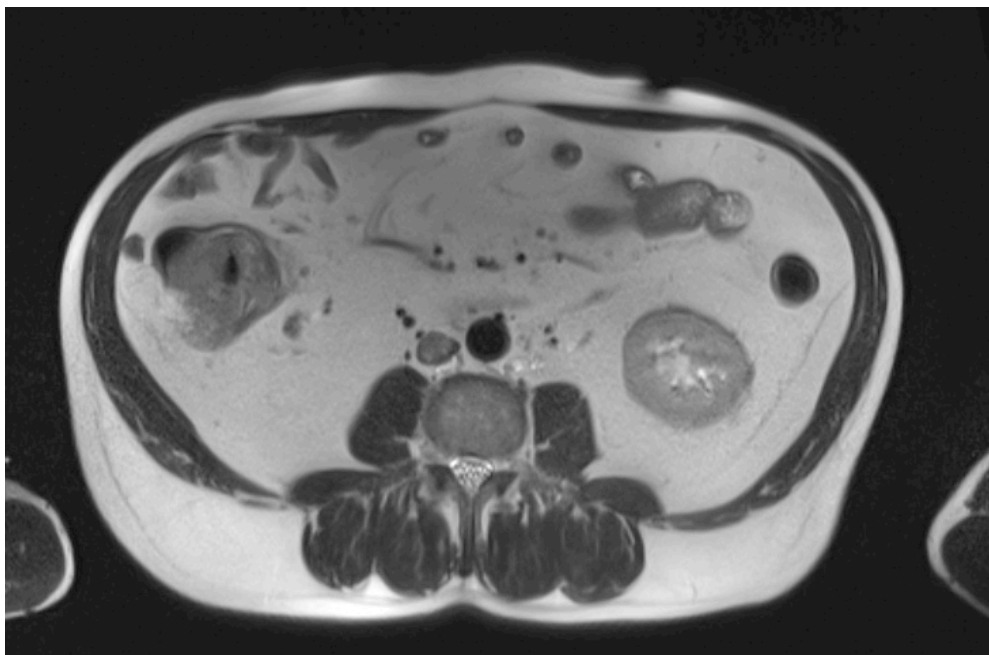


Figure 4.8 – the diagnostic MRI.

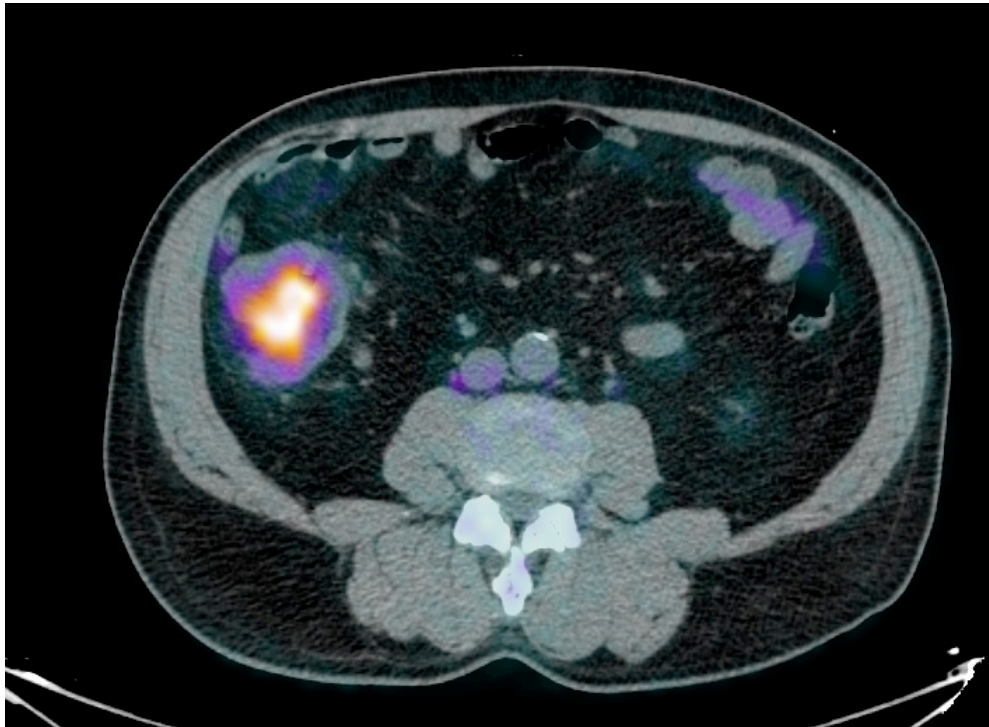


Figure 4.9 - the fused PET/CT.

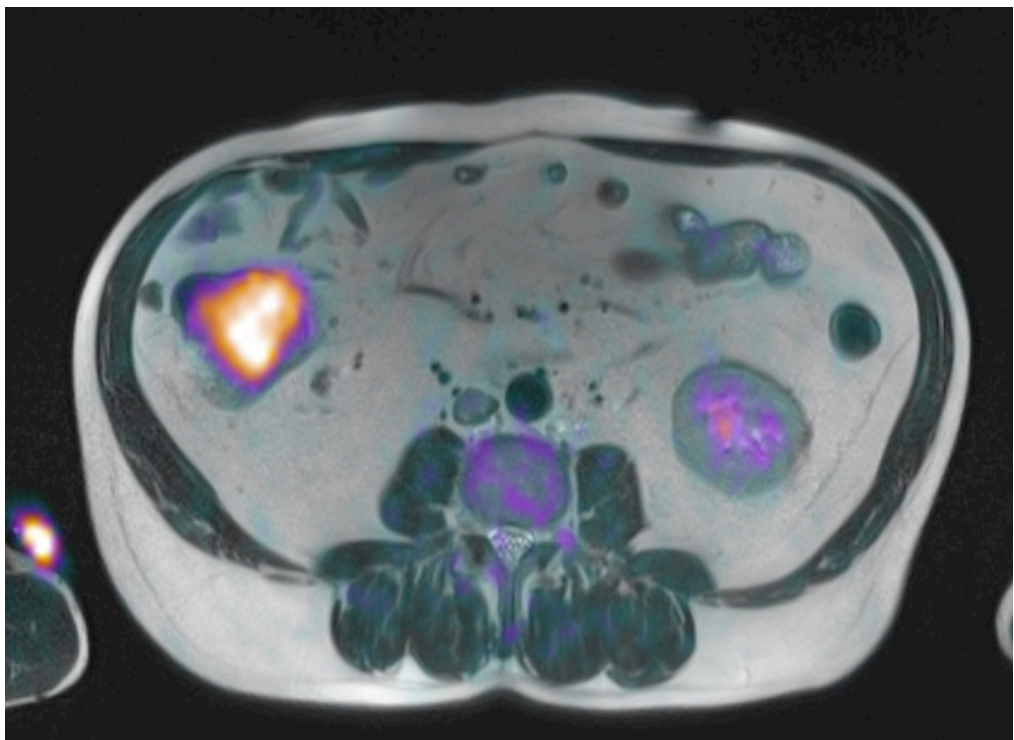


Figure 4.10 - the fused PET/MRI.

All three imaging modalities used in this study were poor at predicting the staging of T4 colon tumours. CE-CT and PET/CT showed comparable accuracy rates of 58.8% and 52.9% respectively, whilst PET/MRI was significantly weaker with an accuracy of only 29.4%. PET/MRI also under staged two T4 lesions as T2, which CE-CT or PET/CT did not show. In a clinical context this could have adverse prognostic and therapeutic implications for a number of patients with advanced colon cancers. On further analysis both T4 colonic tumours incorrectly staged as T2 were located in the left side of the colon, in the sigmoid and descending colon, and both were moderately differentiated adenocarcinomas more than 4cm in longitudinal length. Therefore consideration must be taken when staging advanced left sided colonic tumour with PET/MRI.

Figures 4.11, 4.12, 4.13 and 4.14 show an 82 year old patient with a T4 adenocarcinoma of the descending colon recruited into the study and the resultant CE-CT, PET/CT and PET/MRI images that were made available to each reader for subsequent staging. Figures 4.11 and Figure 4.12 below, demonstrates concentric wall thickening suggestive of colonic wall infiltration and a T4 tumour whilst Figures 4.13 and 4.14 demonstrate tumour uptake of 18-FDG. This lesion was correctly classified as T4.



Figure 4.11 – the contrast enhanced computed tomography image.

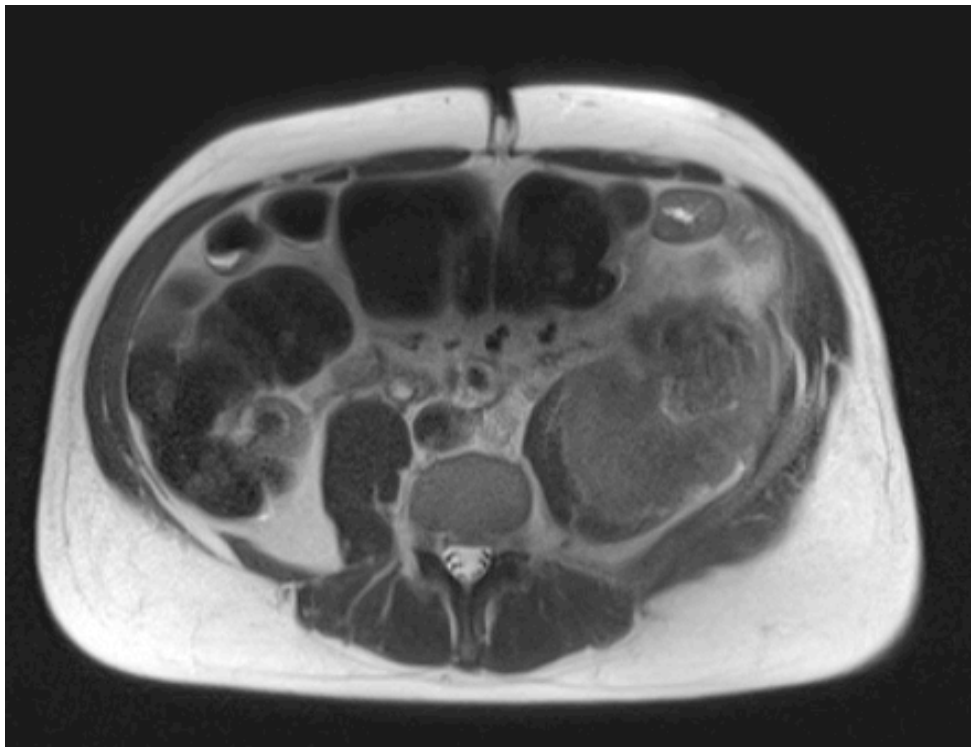


Figure 4.12 – the diagnostic magnetic resonance image.

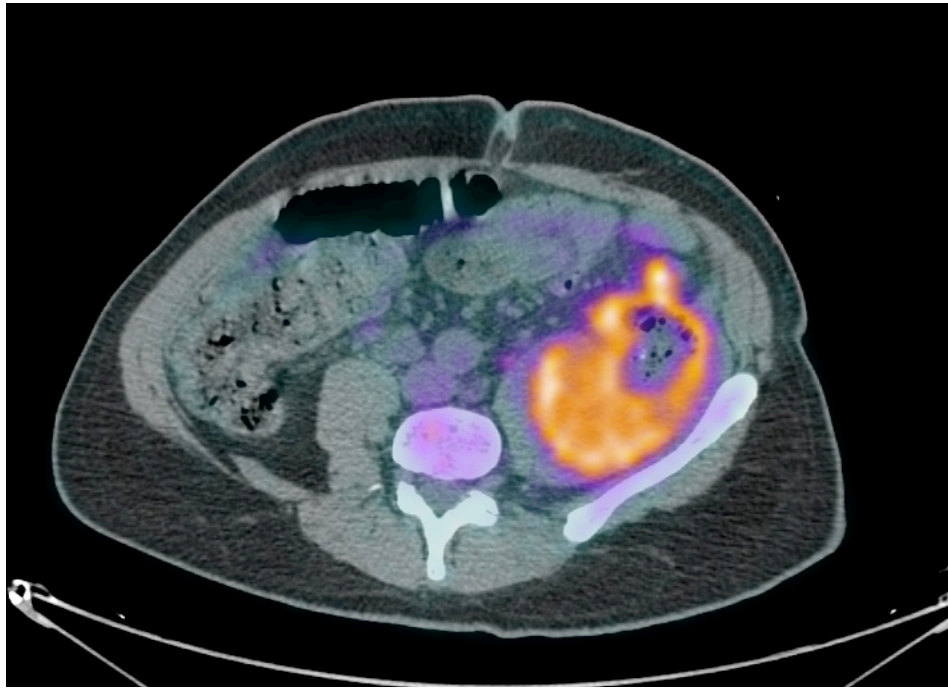


Figure 4.13 - the fused positron emission tomography/computed tomography.

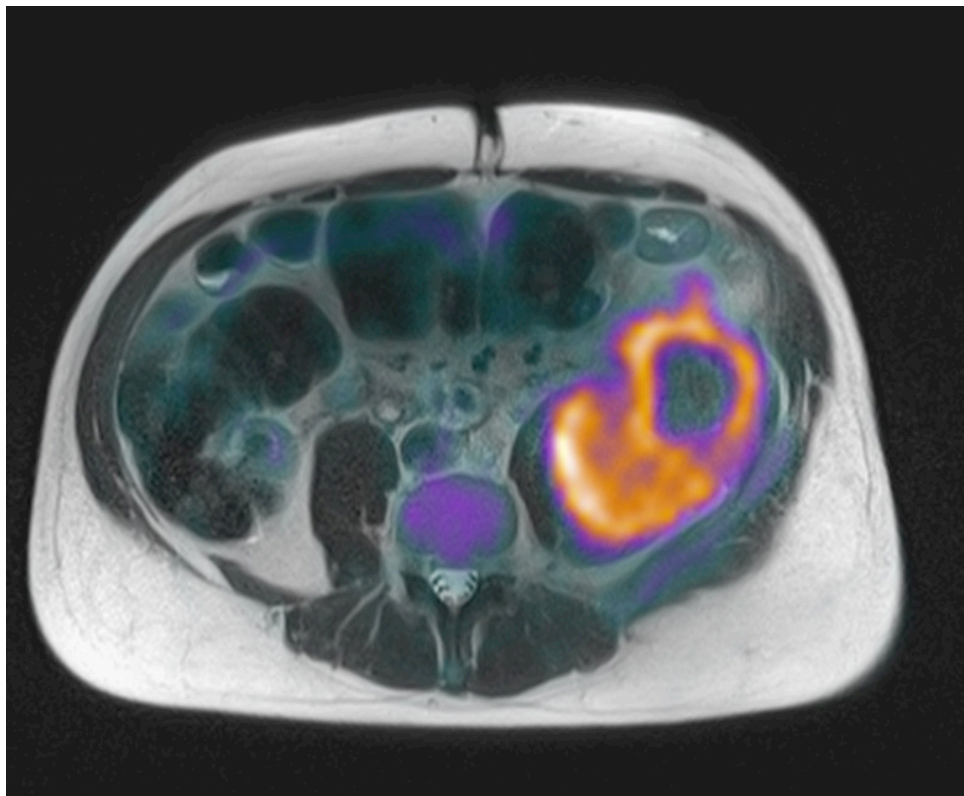


Figure 4.14 – the fused positron emission tomography/ magnetic resonance image.

Considering that PET/CT has an established role in identifying systemic metastases (Mainenti et al. 2011) and an emerging role as a definitive all in one cancer staging modality (Hicks, Ware, and Lau 2006) the ability to accurately establish tumour extent is paramount. This study highlights potential limitations in determining T2 and T3 stages with PET/CT, but also shows good accuracy rates with PET/MRI and CE-CT imaging of the colon. PET/MRI in our study was able to achieve high rates of T2 and T3 staging accuracy. These diagnostic accuracy rates were comparable to CE-CT, which is presently used in routine clinical practice for colon cancer staging. The finding of this study suggest PET/MRI may a role as a pre-operative imaging modality to plan complete surgical resection with a negative resection margin, in patients with localised tumours confined to the bowel wall.

Regarding N-staging this investigation showed that CE-CT had the highest overall diagnostic accuracy for staging regional lymph node metastases in patients with colon cancer. CE-CT had an overall N-staging accuracy of 65.3%, which was superior to both PET/CT and PET/MRI where best accuracies of 57.1% and 44.9% were achieved.

For PET/CT imaging, the diagnostic accuracy of the PET component of PET/CT and the CT component of PET/CT was assessed and compared in this study. In a similar fashion, for PET/MRI imaging the diagnostic accuracy of the PET component of PET/MRI and the MRI component of PET/MRI was also assessed. The criteria for consideration of FDG avid nodes with PET and positive nodes with each respective anatomical imaging component are further discussed in the methodology section of this chapter in section 2.2.8. The PET component of both PET/CT and PET/MRI achieved higher diagnostic accuracies for N-staging, as opposed to the CT and MRI components of PET/CT and PET/MRI respectively.

On sub-group analysis, the PET component of both PET/CT and PET/MRI showed diagnostic accuracies for individual N0 staging of 79% and 75% respectively. This was superior to CE-CT imaging where an accuracy of 63% for N0 staging was achieved. The PET component of PET/MRI imaging also showed a specificity of 75% for N-staging whilst the PET component of PET/CT showed 79.2% specificity, which were both superior to CE-CT where 62% was shown in this study.

Both the PET components of PET/CT and PET/MRI had relatively low sensitivity and high specificity for regional nodal staging in comparison to conventional imaging (CE-CT). Therefore from this study the PET components of PET/CT and PET/MRI imaging were able to improve the overall diagnostic accuracy of both imaging modalities and demonstrated superior accuracies for node negative than node positive tumours when compared to conventional imaging (CE-CT) for colon cancer N-staging.

In many specialist centres colo-rectal surgeons advocate the use of complete meso-colic excision (CME) or D3 excision, to improve oncological outcomes. The aim of this technique is to excise the affected colon, meso-colon and associated lympho-vascular supply in a complete envelope of visceral peritoneum followed by a central vascular tie. This procedure aims to excise paracolic, intermediate and central lymph nodes ensuring all lymph nodes are fully resected with the tumour (Dimitriou and Griniatsos 2015). Routine use of this technique is becoming more common due to an improved 4-year disease survival rate of 85.5% as opposed to that of 75.9% in patients undergoing elective colonic resections with conventional lymphadenopathy for stages 1 to 3-colon cancer (Bertelsen et al. 2015). However despite improved oncological outcomes CME has also been associated with a higher morbidity rates

resulting from sacral nerve damage, which may potentially result in bladder and bowel impairment as well as erectile dysfunction in men (Bertelsen et al. 2016). In comparison to conventional surgery, CME has been associated with an increased number of intra-operative associated injuries to adjacent organs, post-operative sepsis and respiratory complications (Bertelsen et al. 2016). In this study, high rates for N0 staging of 75% with PET/MRI and 79% with PET/CT were noted, which was higher than conventional imaging (CE-CT) where an accuracy of 63% for N0 tumours was observed. Also a specificity of 75% and 79.2% with PET/MRI and PET/CT respectively were noted which was considerably higher than conventional imaging where 62% was achieved. Due to the high rate of accuracy for N0 staging with PET/MRI and PET/CT, CME surgery may be avoided in high-risk patients who are at risk of increased peri-operative morbidity with no improved oncological survival advantage. Due to confidently being able to predict the lack of regional lymph node metastases and these patients may be subsequently managed with a limited resection.

In colon cancer patients, the presence and true extent of regional lymphadenopathy assists in guiding the appropriate post-operative management and long-term prognosis. This is because the number of lymph nodes examined per patient after surgical resection is positively correlated with improved survival rates in patients with stage two and three colon cancer (Chang et al. 2007). When fewer than 12 lymph nodes are examined, the risk of recurrence or progression to stage three disease is significantly higher and thus this is considered a high-risk feature for patients with stage two-colon cancer (Wells et al. 2017). Therefore the majority of international society guidelines recommend that a minimum of 12 lymph nodes should be sampled for adequate staging (Nelson et al. 2001) and this forms a

measure of quality for colon cancer resection (McGory, Shekelle, and Ko 2006). In patients where less than 12 lymph nodes are evaluated post-operatively, adjuvant chemotherapy is offered even to those patients where there is no demonstrable evidence of metastatic disease in the examined nodes (Kumar et al. 2015). In these patients PET/CT and PET/MRI may have a role in initial staging and preventing the potentially unnecessary administration of adjuvant chemotherapy with its associated side effects. This is because PET/CT and PET/MRI in this study was able to accurately predict the N0 stage in patients with colon cancer with high levels of specificity and therefore may be able to potentially select patients with an absence of nodal metastases, where further adjuvant treatment would not be beneficial.

A recent prospective study has suggested there is potential benefit from pre-operative chemotherapy for patients diagnosed with locally advanced colon cancer (Arredondo et al. 2013). In that study, the outcome and treatment related complications of neo-adjuvant oxaliplatin and capecitabine based chemotherapy agents prior to surgical resection in twenty-two patients with stage two and three colon cancers, of which 12 patients were staged as N0, were assessed (Arredondo et al. 2013). In our present study we found PET/MRI had a similar sensitivity and equivalent specificity of 83.3% to conventional imaging (CE-CT) for T-staging. Further studies in colon cancer patients have demonstrated T-staging accuracies for PET/CT of 94% (Mainenti et al. 2011) and 82% (Veit-Haibach et al. 2006). We found T-staging accuracies for both PET/CT and PET/MRI to both be 69.4%. Potential reasons for the differing accuracies were that Mainenti et al., 2011 used three independent readers, of which a consensus was then reached prior to discussion. This may have improved any potential post-test validation bias. The study by Veit-Haibach et al., 2006 used intestinal distension and pharmacological

bowel relaxation agents, so was slightly different in study design from our study. Both of these factors may have potentially increased the diagnostic accuracy of observed T staging in these studies. CE-CT studies have traditionally shown a lower diagnostic accuracy, which is attributed to poor sensitivities (Huh et al. 2011). The poor sensitivity is in part due to difficulties distinguishing tumour from normal tissue viscera due to poor attenuation (Tan and Iyer 2010). For N-staging we found that the PET of PET/MRI and PET/CT imaging modalities achieved comparable sensitivities of 48% and 52% and specificities of 75% and 79% respectively. This was directly comparable to a prospective study of 88 patients by Tsunoda et al., 2008 where a similar sensitivity of 51% and specificity of 85% for PET/CT was found (Tsunoda et al. 2008). Micro-metastatic deposits limit the observed diagnostic accuracy of N-staging in colon cancer with both PET/MRI and PET/CT. These local tumour deposits may be smaller than the inherent spatial resolution capable from the latest PET based imaging systems (Engelmann et al. 2014). Sub-centimetre positive nodes have also previously been found to contribute to false negative results in nodal staging with PET imaging (Mainenti et al. 2011). Alternatively FDG uptake may not be present in some lymph nodes with malignant potential. Together these may contribute to a high false negative rate found with PET imaging. In addition PET based imaging may also produce false positive findings attributed to local lymphoid reactions in node-negative colon cancers thus limiting the achievable N-staging accuracy (Engelmann et al. 2014). A further limitation from our study is that PET/MRI, PET/CT and CT imaging were compared from a single patient cohort where readers were blinded. There was no attempt at patient randomization; hence post-test validation bias must be considered in favour of PET/MRI. To negate this possibility, separate readers were used for PET/CT and PET/MRI image analysis.

The impact of the change in stage for colon cancer patients by PET/MRI was also not investigated, as this was not within the remit of this study. This would however provide further information as to the true impact PET/MRI has on colon cancer staging. Other factors that were not considered in the remit of this investigation include, patient satisfaction and intra-operative comfort, the duration of each scan and the associated expense incurred with a cost-benefit analysis. These are important factors when considering the advent of a new imaging modality and future studies should consider these.

This study has shown the potential benefits for PET/MRI over conventional imaging and the particular value for identifying T2/3N0 locally advanced colon cancers. These patients are at risk of developing post-operative local recurrence. Therefore they may be identified at a far earlier stage and then assessed for the appropriateness of neo-adjuvant chemotherapy prior to surgical resection. Hence accurate staging may have a direct impact on selecting appropriate therapeutic treatment modalities and therefore improving long-term survival rates in patients with locally advanced colon cancers. Also the surgical approach, extent of tumour resection and associated regional lymphadenectomy as well as the need for adjuvant chemotherapy, may be influenced by more accurate staging of localised colon cancers by PET/MRI thus improving long-term outcomes.

4.6 Conclusion

The most significant finding in this study was that, CE-CT showed the highest diagnostic accuracy for loco-regional staging of patients with primary colon cancer. From this study PET/MRI and PET/CT cannot be considered to be more accurate imaging modalities or recommended for routine clinical practice when compared to conventional imaging (CE-CT) for loco-regional staging in colon cancer.

However PET/MRI is still a valuable diagnostic imaging modality for the initial staging of patients with primary colon cancer and may also provide some added loco-regional staging information to a particular subgroup of patients with T2/3N0 tumours. This has a number of clinical implications, which include better selection of more appropriate patients who may benefit from for the administration of neo-adjuvant or adjuvant chemotherapy. Surgical resection remains the only curative treatment modality for localised colon cancers. PET/MRI may assist in altering the extent of tumour and lymph node resection and thus improve long-term patient outcomes after curative surgery. The results of this study may potentially help to evaluate the role of PET/MRI in loco-regional staging contributing to the developing role of PET/MRI as a single examination imaging technique for the complete staging in colon cancer.

CHAPTER 5

Loco-regional staging in rectal cancer with PET/MRI and PET/CT – an observational cohort study

5.1 Background

The lifetime incidence of colorectal cancer (CRC) in the United States is 4.2 to 4.6 percent, which equates to one person in twenty-two developing the disease during their lifetime (Siegal, Naishadham, and Jemal 2012). In 2015, in the United States, 140,250 new cases of CRC were diagnosed, of which 43,030 affected the rectum. Approximately 39% of newly diagnosed CRC patients have localised disease and 37% have node positive disease after initial assessment (Siegal, Naishadham, and Jemal 2012). Seventy to eighty percent of patients with a new diagnosis of loco-regional disease are found to be suitable for surgical excision with curative intent with an improvement in long-term survival (Meyerhardt and Mayer 2003). The standard of care for uncomplicated colon cancer is primary surgical excision. In contrast the rates of local recurrence after surgery for rectal cancer are higher than colon cancer. This is mainly due to difficulties in achieving complete surgical clearance of the tumour and radial resection margin. Adjuvant and neo adjuvant therapy is considered part of the standard treatment pathway after surgical resection of trans-mural (T3/4) or node positive rectal cancers or if there is invasion of the meso-rectal fascia suggesting a threatened or involved colorectal resection margin (CRM). The decision to pursue an initial course of radiotherapy or chemoradiotherapy as opposed to primary surgical excision is determined by loco-regional staging. Accurate pre-therapeutic assessment also determines the optimum operative approach and choice of procedure in those patients suitable for surgical excision of the tumour. Symptoms of tenesmus and pain on defecation may suggest the presence of a fixed tumour in the lower third of the rectum. In patients where these symptoms are present, a formal assessment of tumour localisation and extent is required to necessitate further treatment. This involves accurate preoperative

locoregional staging of the depth of transmural penetration (T-staging), the presence or absence of suspicious perirectal nodes (N-staging), and the likely status of the CRM. Pre-therapeutic loco-regional staging in patients with rectal cancer typically consists of physical examination, endoscopic endo-luminal evaluation of the tumour, magnetic resonance imaging (MRI) and in some cases trans-rectal endoscopic ultrasound (TEUS) (Fountzilas and Kaklamani 2017). After the assimilation of these results, patients with suspected rectal cancer are discussed at a multi-disciplinary team meeting (MDT) and often equivocal or conflicting results necessitate further investigations. The aim of this chapter is to assess if PET/MRI is a more accurate imaging modality than PET/CT, and if PET/MRI may be considered a complimentary or equivalent imaging modality to gold standard MRI for loco-regional staging of patients with rectal cancer.

5.2 Aims

The aims of this chapter are to prospectively evaluate if PET/MRI is a more accurate imaging modality than PET/CT, and if PET/MRI may be considered an equivalent imaging modality to gold standard MRI for loco-regional staging of patients with rectal cancer.

The objectives are,

- i) To compare the diagnostic accuracy of PET/MRI and PET/CT imaging using conventional imaging (MRI) as the gold standard for determining the precise location of tumour within the rectum in patients with primary rectal cancer
- ii) To compare the diagnostic accuracy of PET/MRI and PET/CT imaging using conventional imaging (MRI) as the gold standard for determining the depth of tumour invasion (T-staging) in patients with primary rectal cancer.
- iii) To compare the diagnostic accuracy of PET/MRI and PET/CT imaging using conventional imaging (MRI) as the gold standard for determining circumferential resection margin (CRM) involvement in patients with primary rectal cancer.
- iv) To compare the diagnostic accuracy of PET/MRI and PET/CT imaging using conventional imaging (MRI) as the gold standard for determining the presence of lymph node metastases (N-staging) in patients with primary rectal cancer.

5.3 Methods

5.3.1 Patient recruitment

Patients were recruited prospectively for this study with histological biopsy proven primary rectal cancer. The cohort of patients used for this chapter consisted of patients referred from the UCLH NHS trust and peripheral hospitals via their multidisciplinary teams. All patients were asked to give written informed consent following a full explanation of the procedure.

Institutional ethical review board approval, pre-scanning preparation details and patient informed consent details from this chapter can be found further detailed in Chapter 2.1.1, Methodology.

5.3.2 Patient population

A total of 114 patients were initially recruited in this study. However seventeen patients did not proceed to have PET/MRI imaging despite undergoing PET/CT and MRI imaging modalities and thus were excluded from this study. Therefore, a total of 97 patients with suspected malignant CRC lesions were successfully recruited in this study. All patients were imaged with MRI, PET/CT and PET/MRI imaging. Forty-four patients had a histology proven rectal cancer and 53 patients had colon cancer. The resultant 44 patients with 44 rectal cancer lesions were successfully analysed in this chapter and consisted of 31 men and 13 females. The median age of recruited patients was 68 years old and mean age 68.2 years old. The flow of patients in this study is shown below in Figure 5.1.

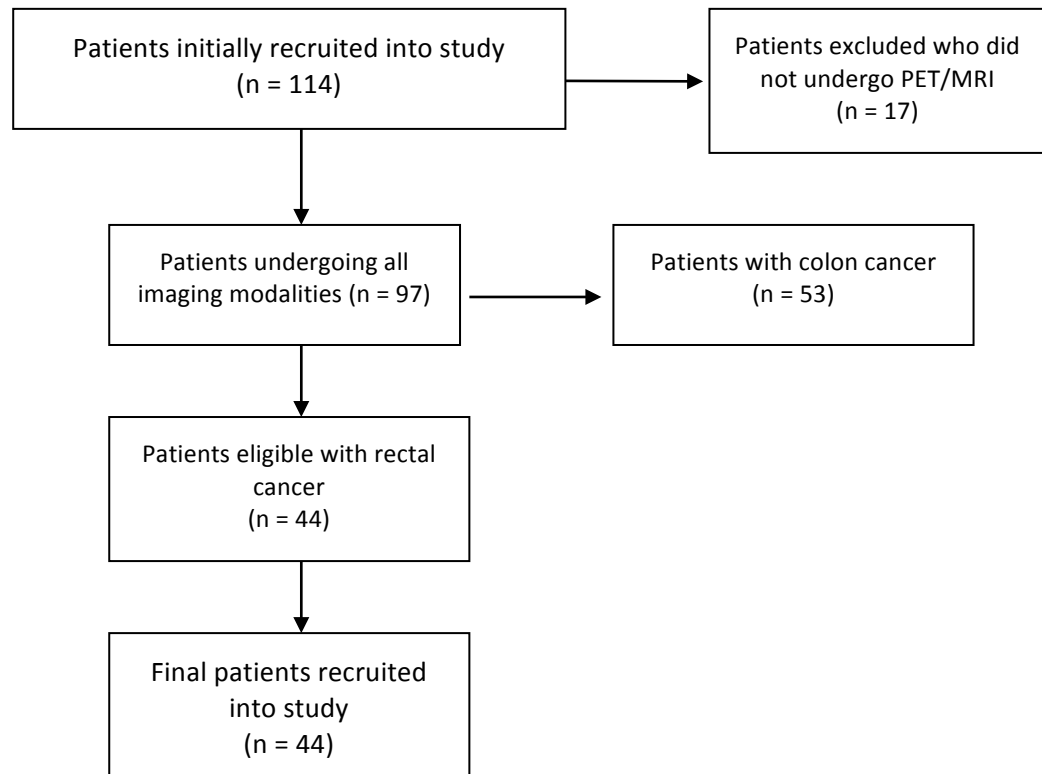


Figure 5.1 - Flow chart of patients in the study. n = number of patients in the study.

5.3.3 Imaging

Patients underwent whole body ^{18}F -FDG PET/CT and PET/MRI scans on the same day, as per the protocols in chapter 2, methodology. ^{18}F -FDG radio-tracer was prepared as described in chapter 2 with a mean administered dose of 250MBq or 370MBq for research or clinical scans respectively.

Visual analysis and standardised uptake values (SUVs) were obtained for each lesion using the methodology described in section 2.4.1. For each patient, regions of interest (ROI) were drawn over the tumour and normal tissue images.

5.3.4 Reference Standards

All patients underwent conventional imaging in the form of diagnostic MRI of the rectal tumour in-situ in the pelvis. These images were subsequently analysed and considered to be the reference standard in this chapter.

The initial intention in this investigation was to use the pre-therapeutic post-operative histo-pathological rectal tumour specimens as the reference standard. However, of the 44 patients in this investigation only 4 pre-therapeutic post-operative histopathological specimens were available. The remaining patients underwent neo-adjuvant chemotherapy and a course of radiotherapy prior to surgical resection. Therefore the lack of surgical specimens in addition to the potential for the tumour to be down staged prior to surgical resection meant that the conventional imaging modality (MRI) was used throughout this study as the reference standard for analysis.

5.3.5 Statistical analysis.

All data from this study are expressed as mean \pm two standard deviations or as a proportion as appropriate. The two commercial statistical software packages used were, Microsoft ExcelTM and SPSS software (version 25). All statistically significant levels were set at 5%, where a p value <0.05 was considered significant.

5.4 Results

5.4.1 Standard of reference

A total of 44 histo-pathological biopsy proven adenocarcinomas of the rectum were found in patients diagnosed with radiological features of rectal carcinoma with diagnostic MRI imaging. No patients with primary squamous rectal tumours or anal carcinomas were recruited or included in this study. No patients had any synchronous lesions or evidence of inflammatory bowel disease affecting the rectum or colon. Per-patient and per-lesion analyses were used and are further detailed below.

MRI analysis demonstrated, 0 out of 44 tumours as T1, 9 (20.5%) as stage T2, 24 (54.5%) as T3 and 11 (25%) as T4. Regarding regional lymph node metastases, 14 out of 44 nodes (31.8%) were classified as N0, 17 (38.6%) nodes as N1 and 13 (29.5%) as N2.

5.4.2 Tumour localisation and identification

The locations of the 44 tumours within the rectum were classified according to the distance from the anorectal ring to the distal tumour margin using diagnostic MRI as the gold standard. They were noted to be, upper rectum (n = 18), mid rectum (n = 20) and low rectum (n = 6). This is illustrated in Figure 5.2.

The CT and MRI components of PET/CT and PET/MRI respectively, were used to calculate the distance from the anorectal ring to the distal tumour margin.

This is because the PET component of PET/CT and PET/MRI did not have the anatomical resolution for this comparison, therefore only the CT component of PET/CT could be compared to the MRI component of PET/MRI for assessing the tumour location within the rectum.

Both imaging modalities correctly located all tumours within the rectum and no tumours were classified as being in the colon. PET/MRI correctly located the correct site of each tumour within the rectum, when compared to diagnostic MRI imaging. PET/CT showed concordance with diagnostic MRI for the precise tumour location within the rectum in 35/44 (79.5%) tumours. PET/CT incorrectly classed 3 high rectal tumours as mid rectal, two high rectal tumours as low and 4 further mid rectal tumours as low rectal leading to the lower percentage accuracy in comparison to PET/MRI.

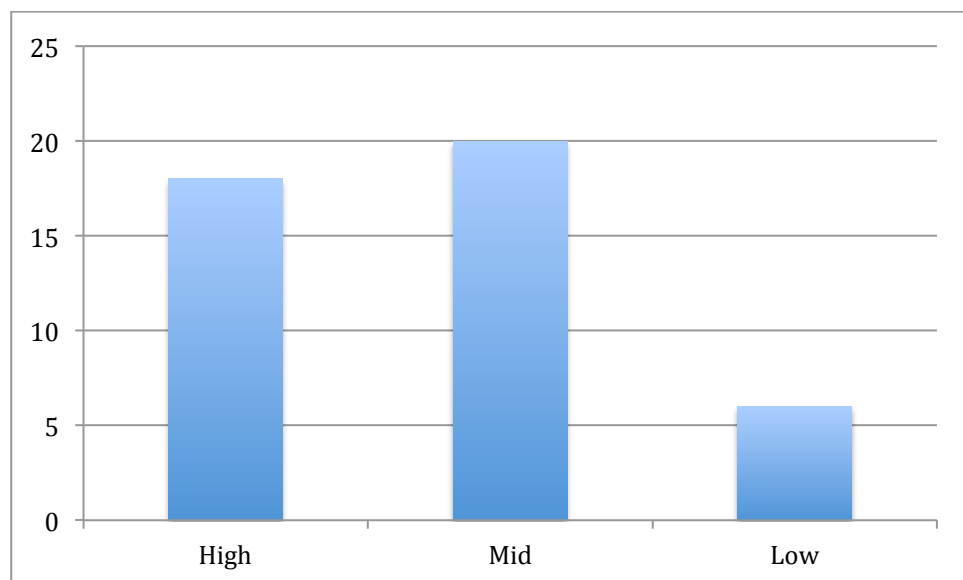


Figure 5.2 – A graphical representation of tumour distribution within the rectum showing the number of rectal tumours and the distance from the ano-rectal ring.

5.4.3 Rectal tumour T-staging accuracy

PET/MRI staged 31/44 (70.5%) tumours of the rectum concordantly when compared to gold standard MRI staging. PET/CT was marginally better than PET/MRI and showed concordance for T-staging in 33/44 (75%) of rectal tumours.

Table 5.1 shows the overall diagnostic accuracy for T-staging of rectal cancers with each imaging modality.

Imaging Modality	Accuracy	% Accuracy	P-Value (compared to MRI)
PET/MRI	31/44	70.45	0.38
PET/CT	33/44	75.00	0.63

Table 5.1 – T-staging overall diagnostic accuracy

A sub-group analysis was performed and individual diagnostic accuracies for T2, T3 and T4 tumours were calculated for each imaging modality investigated in this chapter, and are shown in Table 5.2.

Imaging Modality	Imaging modality T-stage	Number of patients correctly staged	Mean Accuracy (%)	95% CI low	95% CI high	p-value compared to MRI
PET/MRI	T2	6/9	66.67	33.67	99.67	1
	T3	23/24	95.83	87.63	104.03	0.63
	T4	2/11	18.18	-5.82	42.18	0.06
PET/CT	T2	5/9	55.56	21.56	89.56	
	T3	21/24	87.50	73.50	101.50	
	T4	7/11	63.64	33.64	93.64	

Table 5.2 – Individual diagnostic accuracies for T2, T3 and T4 rectal tumours for each imaging modality.

PET/MRI was concordant with diagnostic MRI stage in 31/44 of rectal tumours (Tables 5.2 and 5.3). The best concordance between PET/MRI and conventional imaging was with the staging of T3 rectal lesions. Only one T3 tumour was incorrectly staged as a T4 tumour. An accuracy of 95.83% (95% CI: 87.63%-104.03%) was achieved for T3 staging (Table 5.3). In contrast to T3 tumours, PET/MRI showed the lowest concordance for T4 tumours with only 2/11 tumours correctly staged as T4 and a corresponding accuracy of 18.2% (95% CI: -5.8%-42.2%). This is because nine T4 tumours were incorrectly down staged as T3 tumours by PET/MRI (Table 5.3).

Conventional Imaging (MRI)

		T2	T3	T4	Total
PET/MRI	T2	6	0	0	6
	T3	3	23	9	35
	T4	0	1	2	3
	Total	9	24	11	44

Table 5.3 – PET/MRI rectal cancer T- stage vs conventional imaging (MRI) T-stage

PET/CT was concordant with MRI stage in 33/44 of rectal tumours (Tables 5.2 and 5.4). PET/CT showed the highest concordancy for T3 tumours of the rectum where an accuracy of 87.50% (95% CI: 73.50%-101.50%) was noted. The lowest diagnostic accuracy by PET/CT was found to be for T2 rectal tumours with an accuracy of 55.56% (95% CI: 21.56%-89.56%). Only five T2 rectal tumours were concordantly identified with PET/CT imaging and a further four tumours were discordantly over staged as T3 tumours.

Conventional Imaging (MRI)

		T2	T3	T4	Total
PET/CT	T2	5	0	0	5
	T3	4	21	4	29
	T4	0	3	7	10
	Total	9	24	11	44

Table 5.4 – PET/CT colon cancer T- stage vs conventional imaging (MRI) T-stage

5.4.4 Rectal tumour N-staging accuracy

PET/MRI and PET/CT staged regional lymph node metastases according to PET tracer uptake to determine the number of lymph node deposits and nodal morphology when nodes $\geq 2\text{mm}$ were detected.

PET/MRI was concordant with diagnostic MRI for overall N-staging in 68.2% of cases and showed the greatest accuracy of both imaging modalities. PET/CT showed concordance with diagnostic MRI for overall N-staging in 59.1% of rectal cancer patients (Table 5.5).

Imaging Modality	Accuracy	% Accuracy	P-Value (compared to MRI)
PET/MRI	30/44	68.18	1.00
PET/CT	26/44	59.09	0.56

Table 5.5 – N-staging overall diagnostic accuracy

PET/MRI and PET/CT images were further evaluated by two different criteria. These were, nodal morphology on the MRI component of PET/MRI and CT component of PET/CT respectively and abnormal uptake on the PET component of the PET/CT and PET/MRI. This method of analysis has previously been validated by (Tsunoda et al. 2008) and was used in addition to comparing the overall diagnostic N-staging accuracy for each imaging modality.

PET/MRI imaging when analysed according to nodal morphology staged more regional lymph nodes concordantly to diagnostic MRI, than PET/MRI when analysed according to PET tracer uptake. PET/MRI when analysed according to nodal morphology also staged more lymph nodes concordantly in comparison to PET/CT imaging (Table 5.6).

Imaging Modality	Accuracy	Percentage Accuracy	P-Value
PET/MRI_morphology	30/44	68.2	
PET/MRI_PET	26/44	59.1	0.42
PET/CT_morphology	26/44	59.1	0.42
PET/CT_PET	26/44	59.1	0.50

Table 5.6 – N-stage imaging modality overall accuracy.

Both PET/MRI and PET/CT PET uptake imaging showed greater concordance with diagnostic MRI than all other imaging when assessing the N0 individual stage and thus excluding the presence of positive regional lymph nodes. However for detecting the presence of one or more lymph nodes, nodal morphology based PET/MRI imaging showed the best level of concordance (Table 5.7).

Imaging Modality	Imaging modaility N-stage	Number of patients correctly staged	Mean Accuracy (%)	95% CI low	95% CI high	p-value compared to MRI
PET/MRI (morphology)	N0	7/14	50	0.27	0.73	1
	N1	13/17	76	0.53	0.90	
	N2	10/13	77	0.50	0.92	
PET/MRI (PET)	N0	10/14	71	0.45	0.88	0.25
	N1	10/17	59	0.36	0.78	
	N2	6/13	46	0.23	0.71	
PET/CT (morphology)	N0	11/14	79	0.52	0.92	0.13
	N1	5/17	29	0.13	0.53	
	N2	10/13	77	0.50	0.92	
PET/CT (PET)	N0	13/14	93	0.69	0.99	0.03
	N1	5/17	29	0.13	0.53	
	N2	8/13	62	0.36	0.82	

Table 5.7 – N-stage imaging accuracy according to individual stage.

5.4.5 Imaging Sensitivities and Specificities

The T-staging and N-staging sensitivities and specificities for rectal cancer with both imaging modality are shown in Table 5.8 and Table 5.9 respectively.

PET/MRI showed equivalent sensitivity in comparison to PET/CT but superior specificity for T-staging.

Imaging Modality	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR(+)	LR(-)
PET/CT	97.10	55.60	89.50	83.30	2.19	0.052
PET/MRI	97.10	66.70	91.90	85.70	2.92	0.043

Table 5.8 – T-staging sensitivity and specificities for rectal cancers with PET/CT and PET/MRI.

Regarding regional lymph node metastases, the MRI component of PET/MRI then the CT component of PET/CT imaging showed the best sensitivities whilst the PET component of PET/CT then PET/MRI showed the best specificities.

Imaging Modality	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR(+)	LR(-)
PET/CT (CT)	86.70	78.60	90.00	73.30	4.05	0.17
PET/CT (PET)	66.70	92.90	95.20	56.50	9.39	0.36
PET/MRI (MRI)	96.70	50.00	80.60	87.50	1.93	0.066
PET/MRI (PET)	73.30	71.40	84.60	55.60	2.56	0.37

Table 5.9 – N-staging sensitivity and specificities for rectal cancers with PET/CT and PET/MRI.

5.4.6 Circumferential Resection Margin accuracy

A positive CRM was considered to be one where tumour invades the mesorectal fascia within 1mm of the CRM. This study found that PET/MRI predicted a positive CRM in 30/43 of rectal tumours whilst PET/CT showed a positive CRM in 27/43 (Table 5.10). By contrast diagnostic MRI was the gold standard imaging modality and showed a positive CRM in 23/43 patients.

Imaging Modality	Accuracy	Mean (%)	95% CI low	95% CI high	p-value compared to MRI
PET/CT	27/43	62.79	0.48	0.76	
PET/MRI	30/43	69.77	0.55	0.81	0.55

Table 5.10 – CRM imaging accuracy for rectal cancers with PET/CT and PET/MRI.

5.5 Discussion

Both PET/MRI and PET/CT used in this investigation were able to correctly localise all tumours of the rectum from the colon. In addition PET/MRI showed 100% concordance to gold standard MRI imaging when distinguishing the precise location of the tumour within the rectum. PET/CT only showed concordance in 35/44 (79.5%) of patients. Five high rectal tumours were classified as mid or low whilst 4 mid rectal tumours were classified, as low rectal tumours by PET/CT. PET/CT appeared to locate tumours closer to the anal verge in comparison to PET/MRI contributing to the lower rates of concordance. This observation has important clinical implications, as the surgical management and use of adjunctive therapies may be significantly impacted by this study finding and is further explained below.

The rectum extends from the recto-sigmoid junction to the anorectal ring, which is well defined on MRI imaging. The European Society of Gastrointestinal and Abdominal Radiology recommend measuring the distal tumour margin from the anorectal ring (Beets-Tan et al. 2013) as this may negate the variable length of the anal canal and therefore standardise rectal tumour location. The rectum has traditionally been divided into thirds from the anorectal ring (Goligher et al. 1965). The anorectal ring is considered to be roughly 3.5cm from the anal verge on rigid sigmoidoscopy and was used in this study. The upper third of the rectum is 12 to 16cm from the anorectal ring and is covered by peritoneum whilst the middle third of the rectum is 7.5 to 12 cm from the anorectal ring and only covered anteriorly by peritoneum. In contrast the lower rectum is 3.5 to 7.5 cm from the anorectal ring and is entirely extra-peritoneal (Lahaye et al. 2006). Upper third rectal cancers require

only partial mesorectal excision (Hermanek et al. 2003) whilst in middle and lower third rectal cancers a more cautious approach with total mesorectal excision (TME) is recommended for complete tumour excision (Heald, Husband, and Ryall 1982). Patients with locally advanced rectal cancers in the middle and lower rectum are commonly offered pre-operative neo-adjuvant therapy in order to reduce local recurrence rates and improve long-term survival (Valentini et al. 2005). This is because in the lower rectum, tumour may infiltrate the junction where the mesorectum ends and the levator ani muscles insert and tumour extension into the meso-rectal fat may then potentially involve the sphincter and pelvic floor muscles below this level. From this study PET/MRI was able to show equivalence to conventional imaging (MRI) in identifying the distance from the ano-rectal ring to the distal aspect of the rectal tumour. The clinical significance of this is that in patients with locally advanced rectal cancer PET/MRI may accurately locate middle and lower third rectal tumours. In turn this may aid in the early selection of patients suitable for neo-adjuvant therapy followed by TME surgical excision. PET/MRI may subsequently help to optimise the timing of surgical treatment and the surgical approach required to reduce local recurrence rates in patients with mid to low rectal tumours.

Curative surgery may be considered for localised rectal tumours where the ultimate aim is to firstly resect the tumour with histologically negative resection margins and secondly to maintain intestinal continuity. If this is not technically possible due to the tumour location or extent, then sphincter-sparing surgery is the next secondary aim to improve post-operative quality of life. To minimise local recurrence rates, it is recommended that a minimum proximal resection margin of 5 centimetres be surgically excised (Nelson et al. 2001). In order to select the most

appropriate surgical procedure, accurate measurement of the distal resection margin is essential. Traditionally a 5 cm distal resection margin was recommended, and where this was not achievable an abdomino-perineal resection (APR) was considered. The National Surgical Adjuvant Breast and Bowel Project (NSABP) R-01 trial has accepted a negative distal resection margin of 2 cm in cases where a sphincter-sparing procedure in conjunction with TME surgery is performed (Nelson et al. 2001). In patients where the distal margin was negative but less than 1 cm, local recurrence rates were reduced through TME surgery or radiation therapy (Fitzgerald, Brinkley, and Zervos 2011). PET/MRI showed equivalence to MRI in identifying the distance from the ano-rectal ring to the distal aspect of the rectal tumour. PET/CT located rectal tumours closer to the anal verge and showed discordance to MRI in 9/44 (20.5%). PET/MRI may subsequently help with estimating the appropriate resection margins required for effective surgical resection to reduce local recurrence rates. Therefore PET/MRI may be used as a potential imaging adjunct to aid in the pre-operative planning in patients deemed suitable for primary surgical resection in cases where MRI has been equivocal. PET/MRI may also be used as an alternative imaging modality to MRI to select a sphincter sparing surgical procedure in cases where uncertainty of the distal resection margin would result in an APR. In patients with distal rectal tumours PET/MRI may be especially helpful in predicting the appropriateness and effectiveness of sphincter sparing surgery and the need for adjuvant treatment. In these patients PET/MRI may predict a negative resection margin of less than 1 centimetre with sphincter preservation surgery and these patients would then be suitable for TME surgery in combination with radiation therapy to reduce local recurrence rates.

The pre-operative planning for rectal cancer surgery requires careful consideration of the circumferential radial margin (CRM). A CRM of less than 1mm is associated with high rates of local recurrence and reduced overall disease free survival (Park et al. 2014). This is because microscopic residual tumour may potentially remain in situ after surgical resection. The risk of a positive CRM is increased when tumour is noted within 2mm of the mesorectal fascia therefore in these patients neoadjuvant therapy is recommended prior to surgical resection. In standard clinical practice a CRM of more than 1mm is the minimum desired radial resection margin and in our study a positive CRM was considered to be one where tumour invades the mesorectal fascia within 1mm of the CRM and hence threatened or less than 1mm and therefore involved. Our study found that PET/MRI predicted a positive CRM in 30/43 (69.8%) rectal tumours whilst PET/CT showed a positive CRM in 27/43 (62.8%) of patients. By contrast MRI, which was the gold standard imaging modality, showed a positive CRM in 23/43 patients. PET/MRI incorrectly staged 7 (30.4%) additional rectal tumours as having a positive CRM whilst PET/CT incorrectly staged 4 (17.4%) tumours in comparison to MRI. PET/MRI over staged 5 rectal tumours as having a CRM that was threatened and hence positive when MRI imaging deemed the CRM to be not involved. Our study suggests the use of PET/MRI as a routine imaging modality for assessing CRM involvement may result in the over estimation of tumour invasion in relation to the CRM. This may potentially result in patients with low rectal cancers being deemed suitable for a more invasive AP resection with dissection through the levator ani muscle plane rather than through the sphincter complex, with no effect on the long-term recurrence rate. From this study, PET/MRI is not an equivalent imaging modality to MRI for predicting CRM involvement and hence poor at selecting patients who may

potentially benefit from sphincter sparing surgery. Routine use of PET/MRI in assessing the CRM may also result in patients being inappropriately considered for adjuvant therapy after surgery with no survival benefit. Therefore, PET/MRI should be used with caution when assessing the radial resection margin prior to consideration of adjuvant therapy and rectal cancer operative planning. Figures 5.3, 5.4, 5.5, 5.6 and 5.7 show the images used for analysis of an 84 year old patient diagnosed with a T2 adenocarcinoma of the rectum.

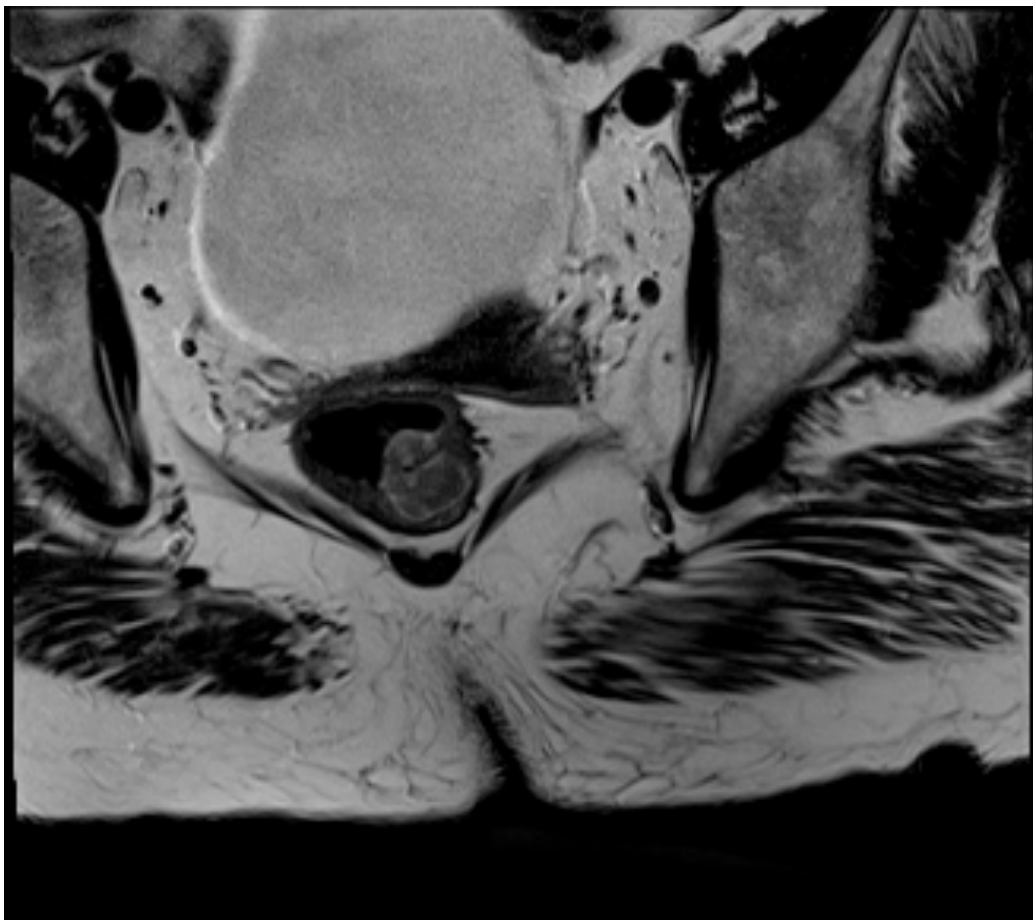


Figure 5.3 – the unenhanced magnetic resonance imaging small field of view image.

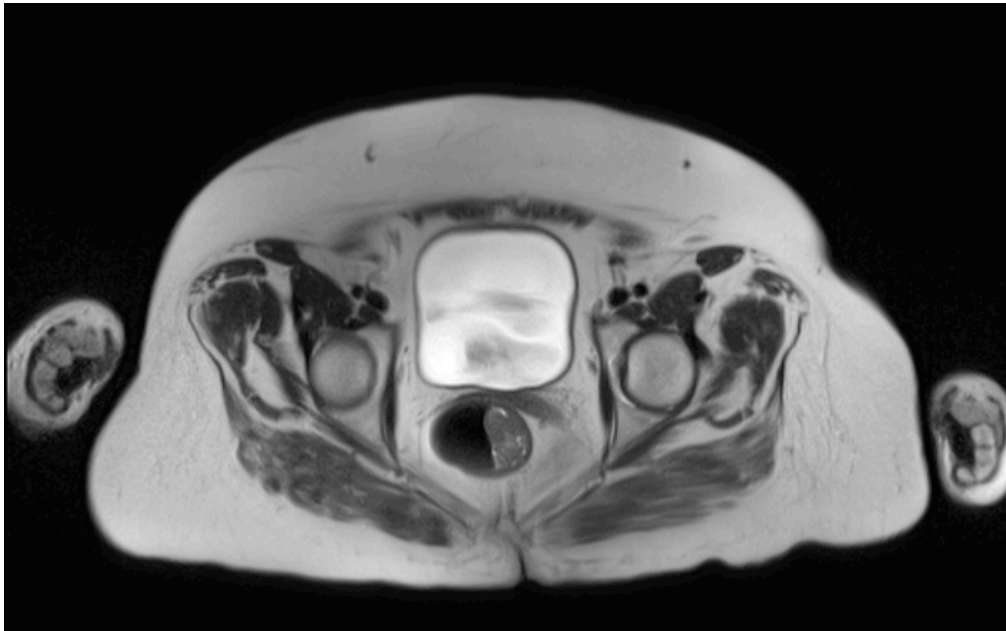


Figure 5.4 – the unenhanced magnetic resonance imaging axial view image.

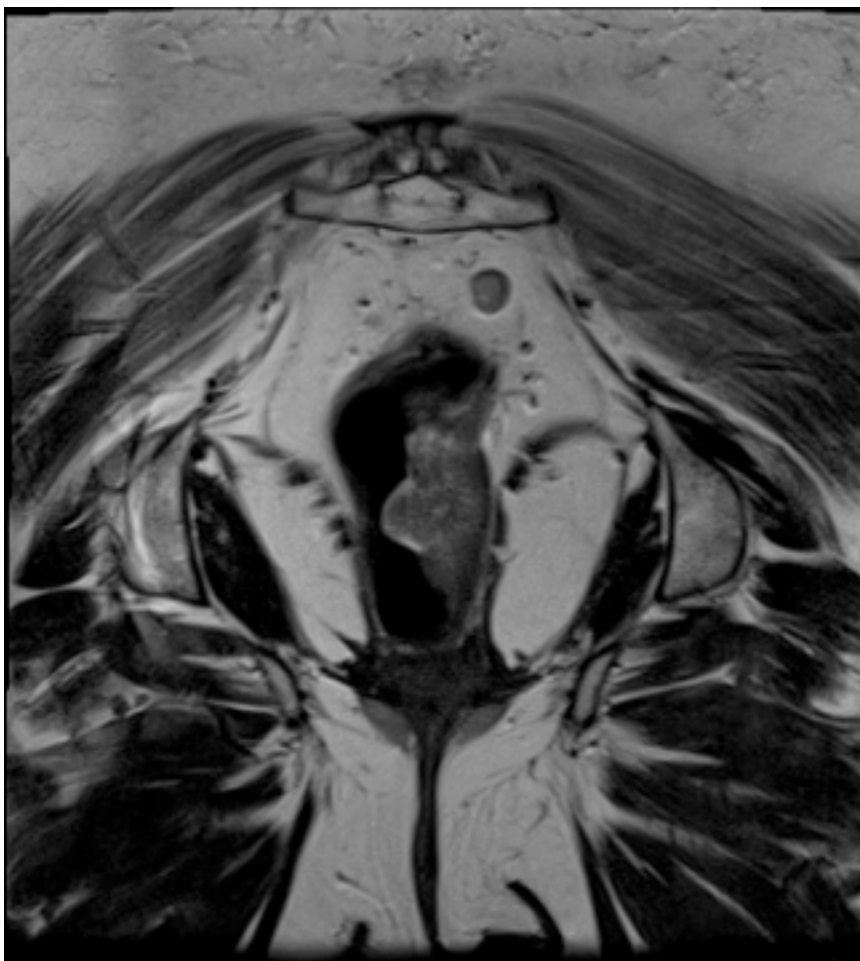


Figure 5.5 – the unenhanced magnetic resonance imaging coronal oblique view image.

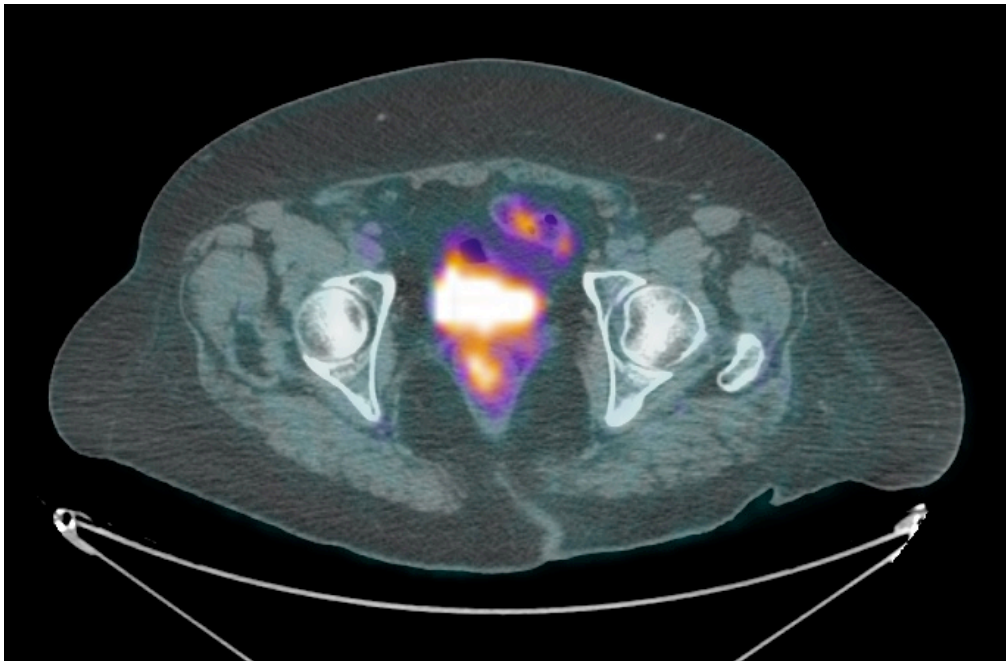


Figure 5.6 - the fused positron emission tomography/computed tomography.

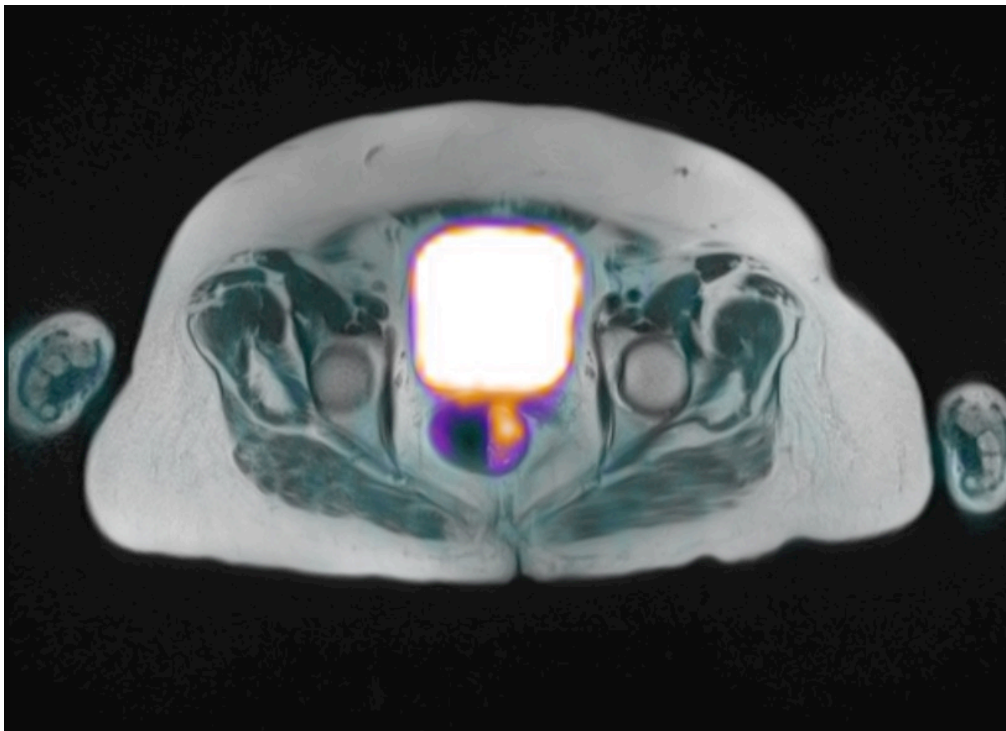


Figure 5.7 – the fused positron emission tomography/ magnetic resonance image.

In patients with rectal cancer, PET/MRI showed concordance with conventional imaging for T-staging in 31/44 (70.5%) of patients whilst PET/CT staged 33/44 (75%) of patients. The marginally superior overall T-staging accuracy shown by PET/CT may be explained by the superior concordance in staging T4 lesions. PET/CT had a higher diagnostic accuracy for staging T4 lesions where concordance with conventional imaging was shown in 7/11 (63.6%) of patients as opposed to PET/MRI where concordance in only 2/11 (18.2%) of patients was shown. However for T2 and T3 lesions, PET/MRI was more concordant with conventional imaging with accuracies in 6/9 (66.7%) and 23/24 (95.8%) respectively. PET/CT showed accuracies in 5/9 (55.6%) and 21/24 (87.5%) for T2 and T3 lesions respectively. PET/MRI only overstaged one T3 tumour, whilst PET/CT overstaged three T3 tumours. It was also demonstrated that the T-staging sensitivity of both PET/MRI and PET/CT were both 97.1% and essentially equivalent to that of conventional imaging. However the specificity of PET/MRI was 66.7%, which was superior to that of PET/CT, which was only 55.6%. Considering the superior diagnostic accuracy of PET/MRI over PET/CT for T2 and T3 rectal tumour staging and the high sensitivity and superior specificity, PET/MRI may have a number of clinical implications. PET/MRI may help to define the appropriate individual treatment pathway according to the patients T-stage. This is because by definition T2 tumours invade but do not extend beyond the muscularis propria whilst T3 tumours may extend through the muscularis propria into the subserosa or perirectal fat. Node negative T2 rectal tumours may be successfully managed by surgical excision whilst for T3 tumours pre-operative radiotherapy or chemotherapy is recommended. From this study PET/MRI may potentially provide accurate pre-treatment staging evaluation and distinguish between T2 and T3 tumours. PET/MRI

may help to decide on appropriate treatment strategies, which include initial surgical resection or neo-adjuvant long course chemo-radiotherapy or short course radiotherapy. For patients staged with T3 tumours by PET/MRI, they may benefit from neo-adjuvant therapy rather than initial surgical excision. This may result in a reduction in local recurrence and improved long-term treatment toxicity rates as opposed to post-operative chemotherapy (Ma et al. 2017).

When staging T4 lesions with PET/MRI, discordance was demonstrated in 9/11 (81.8%) tumours that were all staged as T3 tumours. This may be partially explained by the difficulty encountered with PET/MRI in differentiating tumour extension into the mesorectal fat suggestive of a T3 tumour or invasion into the mesorectal fascia suggesting a T4 tumour in the rectum. Unlike colon cancer staging there are inherent anatomical variations in the rectum, such that the peritoneal surface of the rectum varies along its course in relation to the peritoneal reflection. A peritoneal layer of serosa encloses the rectum at and above the peritoneal reflection anteriorly. As the rectum extends proximally this peritoneal layer extends laterally and it is difficult to distinguish this layer with modern imaging modalities. In some cases where the rectal tumour traverses above the peritoneal reflection, tumour within the serosa is indicative of T4 disease whilst tumour affecting the bare uncovered rectal surface is suggestive of T3 disease. The resolution of PET/MRI and PET/CT imaging used in this study were both 5mm slice thicknesses but PET/MRI was unable to differentiate this tumour within the serosa, hence the poor T4 staging concordance. Therefore caution should be taken when staging T4 tumours extending above the peritoneal reflection. In these cases, MRI imaging should be considered.

Regarding N-staging this investigation showed that PET/MRI had the highest overall diagnostic accuracy for staging regional lymph node metastases in patients

with rectal cancer. PET/MRI had an overall N-staging accuracy of 68.2%, which was superior to PET/CT where a best overall accuracy of 59.1% was achieved.

For PET/CT imaging, the diagnostic accuracy of the PET component of PET/CT and the CT component of PET/CT was assessed and compared in this study. In a similar fashion, for PET/MRI imaging the diagnostic accuracy of the PET component of PET/MRI and the MRI component of PET/MRI was also assessed. The criteria for consideration of FDG avid nodes with PET and positive nodes with each respective anatomical imaging component are further discussed in the methodology section of this chapter in section 5.4.4.

On sub-group analysis, the diagnostic accuracy for PET/MRI based on nodal morphological criteria staged 30/44 (68.2%) of nodes correctly whilst PET/MRI based on PET uptake, and PET/CT nodal morphology and PET/CT based on PET uptake all equally staged 26/44 (59.1%) of nodes concordantly. PET/MRI imaging based on morphology alone was able to successfully show concordance with MRI in four more nodal lesions than PET based imaging. On sub-group analysis, the PET component of PET/CT and PET/MRI showed diagnostic accuracies for individual N0 staging of 93% and 71% respectively. This was superior to morphological based imaging of PET/CT and PET/MRI where accuracies for N0 staging were 79% and 50% respectively. The PET component PET/CT and PET/MRI imaging also showed specificities of 92.9% and 71.4%, which were superior to morphological based PET/CT and PET/MRI where specificities of 78.6% and 50% respectively were achieved for N-staging. From our study both the PET components of PET/CT and PET/MRI had relatively low sensitivity and high specificities for regional nodal staging in comparison to morphological based imaging and MRI. Therefore from this study the PET component of PET/MRI and PET/CT was able to improve the overall

diagnostic accuracies of both imaging modalities for node negative tumours when compared to conventional imaging (diagnostic MRI) for rectal cancer N-staging.

Loco-regional staging in rectal cancer is dependent on the T-stage and the number of involved regional lymph nodes as well as any peri-rectal tumour deposits that may be present. Regional lymph nodes follow the corresponding lymphatic drainage course, which may be broadly classified as meso-rectal or internal iliac (Gabriel, Dukes, and Bussey 1935). Peri-rectal tumour deposits may potentially be present in the serosa, meso-rectal tissues or the mesentery and may also spare any regional lymph nodes. The presence of peri-rectal tumour deposits results in classification of a rectal tumour as N1c. Extra-regional lymph nodes are considered to be involved nodes that follow the course of the external iliac, inguinal and peri-aortic regions and are classed as distant metastases. The ability of an imaging modality to confidently and accurately predict lymph nodes with metastatic involvement and differentiate between the precise sites of these nodes is crucial to determine the optimum treatment pathway for patients. This is especially important in patients with low third rectal cancers, where the associated lymphatic drainage is to the para-aortic and inferior mesenteric nodes as well laterally to the internal iliac nodes (Miscusi, Masoni, and Montori 1987). Lateral or extended lymphadenectomy has an emerging role in the surgical treatment of rectal cancer. In Japanese patients with T3 or T4 low rectal cancers below the peritoneal reflection, 15-20% of patients were noted to have lateral pelvic lymph node metastases, which were considered to be regional lymph nodes (Akiyoshi et al. 2012). These lateral pelvic lymph nodes are not amenable to a standard TME alone surgical resection. In these patients the Japanese Society for Cancer of the Colon and Rectum recommend the use of a surgical approach incorporating lateral pelvic lymph node dissection (Watanabe et al.

2015). The outcomes of surgical resection with TME alone versus TME with lateral lymph node dissection were reviewed in pre-therapeutic patients with stage 2 or 3 low rectal cancer with clinically negative lateral lymph nodes (Fujita et al. 2017). The local recurrence rate was lower in the TME with lateral dissection group (7.4%) compared to the TME alone group (12.6%). The observed difference in overall local recurrence rates, were attributed to 57% more lateral recurrences in the TME alone group. Lateral pelvic lymph node dissection has also been found to be safe and a highly reproducible technique in patients with low rectal cancers below the peritoneal reflection (Kanemitsu et al. 2017). However lateral lymphadenectomy has also been associated with higher rates of urinary or sexual dysfunction in men when compared to standard TME alone surgery (Georgiou et al. 2009). In our study we noted high rates for N0 staging of 93% and 71% with the PET aspect of PET/CT and PET/MRI. These accuracy rates were higher than the corresponding accuracies of morphological based imaging with each respective imaging modality. Also the specificity of PET based imaging with PET/CT and PET/MRI was noted to be considerably higher than the corresponding morphological based imaging for N-staging. Therefore due to the high specificity and high rate of accuracy for N0 staging with PET based imaging, lateral lymphadenectomy may be avoided in patients with low rectal cancers below the peritoneal reflection with node negative disease, where there would be no improved survival advantage. This is especially important in patients with multiple medical co-morbidities or in younger patients where the potential lasting effects of sexual or urinary dysfunction may be avoided. PET based imaging may also have a potential role in being used in addition to conventional imaging to identify patients with clinically node positive disease, who may benefit from TME surgery with lateral lymph node dissection.

In rectal cancer patients undergoing surgical treatment, the number of lymph nodes examined per patient after surgical resection is positively correlated with improved survival rates (Chang et al. 2007). This is because the presence and true extent of regional lymphadenopathy guides the appropriate further adjuvant treatment and the long-term prognosis of the patient. The National Comprehensive Cancer Network recommends that 12 lymph nodes should be sampled in the post-operative surgical specimen for accurate N-staging in rectal cancer (Rajput et al. 2010). The presence of fewer than 12 lymph nodes in the post-operative specimen suggests an inferior quality of rectal cancer resection (Tepper et al. 2001). In this study a number of patients were misclassified as node negative due to incomplete lymph node sampling and subsequently were not offered further adjuvant therapy (Tepper et al. 2001). In contrast for locally advanced rectal cancer patients undergoing neo-adjuvant chemoradiation therapy a reduction in the number of lymph nodes sampled in the resected specimen has been observed (de Campos-Lobato et al. 2013). Therefore it is difficult to differentiate if the absence of 12 post-operative lymph nodes in the resected specimen is due to poor surgical technique or good response to neoadjuvant treatment. The implications of both of these findings may have very different effects on long-term survival rates and the next appropriate course of treatment. In patients with trans-mural rectal tumours PET/MRI may have a role in the initial nodal staging and help to determine if further adjuvant chemotherapy or clinical follow up alone is required. PET/MRI may also potentially prevent the unnecessary administration of adjuvant chemotherapy with its associated side effects with limited long-term survival benefits. This is because PET/MRI in this study was able to accurately predicting the N0 stage in patients with rectal cancer with high levels of specificity and therefore may be able to potentially select

patients with an absence of nodal metastases when less than 12 lymph nodes are sampled, where further adjuvant treatment would not be beneficial.

Due to the increased local recurrence rates, patients with transmural rectal adenocarcinomas or node positive disease are offered neoadjuvant treatment in the form of short course radiotherapy or long-course chemoradiotherapy prior to surgical resection. Neoadjuvant therapy in patients with resectable T3N0 rectal tumours have been shown to be associated with an improved long-term toxicity profile and a reduction in the local recurrence rate as opposed to adjuvant chemoradiotherapy (Sauer et al. 2004). However in patients with T3N0 upper rectal tumours low rates of local recurrence have been observed after TME surgery alone (Kapiteijn et al. 2001). In these patients the benefit from neoadjuvant therapy and the potential side effects incurred prior to TME surgery has been questioned. From our study PET imaging achieved a high specificity for N staging and the addition of PET to PET/MRI morphological imaging improved the diagnostic accuracy for N0 staging. Therefore PET/MRI may potentially be used as an alternative to MRI imaging in selecting patients with upper rectal trans-mural node negative tumours who may undergo TME surgery and not require neoadjuvant therapy. This may be especially useful in patients with multiple medical co-morbidities or poor pre-operative performance status, thus reducing their length of stay and potentially improving their 30-day morbidity and mortality rates and eventual outcomes.

There were a number of limitations from this study that must be taken into consideration when the value of PET/MRI is evaluated as a potential imaging modality for loco-regional staging in patients with rectal cancer. The most apparent limitation was that diagnostic MRI was used as the gold standard imaging modality in our study. This was unfortunately unavoidable due to the lack of primary surgical

resection specimens available in patients who had not undergone neo-adjuvant therapy. Specifically from the 44 patients recruited with rectal tumours, 26 patients had mid or low rectal tumours after endoscopic evaluation with histological confirmation or were node positive with conventional imaging. A further 14 patients had a CRM that was involved or threatened. Subsequently all of these patients were offered and underwent neoadjuvant chemoradiotherapy or radiotherapy prior to surgical resection. Therefore although consideration was taken to use the post-operative resected rectal specimen as the gold standard for assessing the loco-regional stage. However in view of the potential effects of neoadjuvant therapy with the aim of tumour regression in these 40 patients there was concern that the tumour grade would be down staged. Consequently, despite rectal cancer prognosis being closely related to the post therapy pathological stage, an assessment of concordance or accuracy of PET/MRI and PET/CT would potentially overestimate the true loco-regional stage. There were only 4 patients who underwent primary rectal resection without any neo-adjuvant treatment where histology was available. Therefore diagnostic MRI was used as the most appropriate gold standard in this study. As such this adds bias to the study findings since the value of PET/MRI and PET/CT imaging in rectal cancer loco-regional staging could only be shown at best to be equivalent to diagnostic MRI as opposed to showing superior accuracies within the remit of our study. A further limitation of our study was that T3 tumours were not further subdivided in relation to the depth of spread from the muscularis propria and hence an assessment of the depth of extra mural invasion was not made. Patients with T3 tumours with more than 5mm of extra mural invasion beyond the muscularis propria have been shown to have higher rates of peri-rectal nodal involvement and poorer long-term survival rates (Merkel et al. 2001). It has been suggested that if there is no

levator ani tumour extension and the mesorectal fascia is not threatened then these patients may be suitable for immediate surgical resection rather than neoadjuvant therapy (Glynne-Jones et al. 2017). Therefore further subdivision of T3 tumours and the true extent of extra mural invasion may be more beneficial to assessing a change in rectal cancer management than distinguishing between T2 and T3 rectal cancers in our study. Another limitation of this study was that no attempt to assess the imaging response to therapy was made. This would have involved a change in our methodology with longer-term follow up and further interval imaging. Despite the correlation of tumour regression grade with prognosis being an important clinical consideration, this was not within the aims of our study and further studies are required to address the role of PET/MRI in assessing complete tumour response.

5.6 Conclusion

In this study the emerging role for PET/MRI in staging T2/3N0 locally advanced rectal cancers has been evaluated. In this very specific patient subset, PET/MRI was most beneficial as a complimentary imaging modality to conventional imaging (MRI). PET/MRI was able to show equivalent rates of T2, T3 and N0 staging accuracy in comparison to conventional imaging and therefore may be considered a complimentary or alternative imaging modality in tumour identification and location within the rectum as well as for staging T2/3N0 rectal cancers. This study has also demonstrated superior accuracy rates for loco-regional staging in rectal cancer in comparison to PET/CT. In these patients with a localised tumour confined to the rectal wall with no systemic metastases, PET/MRI imaging may be used as a complimentary or alternative imaging modality to help achieve a negative resection margin, by ensuring complete surgical resection. Therefore more accurate loco-regional staging by PET/MRI may result in curative surgery being a realistic option for an increasing number of patients with or without neo-adjuvant therapy.

Based on the study imaging protocols and findings in this chapter, it is difficult to recommend routine use of PET/MRI over the current standard of diagnostic MRI for the loco-regional staging of rectal cancer. The use of PET/MRI in distant staging is considered in Chapter 6. At the same time, future directions may include specific use of PET/MRI focusing at the pelvis, to assess if such an approach could enhance loco-regional staging accuracy over and above simple routine structural diagnostic MRI.

CHAPTER 6

**Metastatic staging in colon and rectal
cancers with PET/MRI and PET/CT – an
observational cohort study**

6.1 Background

In the United States in 2015, one hundred and forty thousand, two hundred and fifty (140,250) new cases of CRC were diagnosed. The 5-year survival rate of patients with CRC has been reported to be as low as 55% and metastases to the liver have been apportioned to poor survival in these patients (Wiering et al. 2005). Twenty percent of patients with newly diagnosed CRC have distant metastases on initial presentation (Siegel 2012). CRC commonly infiltrates regional lymph nodes, solid organs (such as the lungs or liver and the peritoneum) via haematogenous and lymphatic spread. Patients with distal metastases have stage 4 disease. Symptoms and signs of distant metastatic disease vary according to the site and extent of disease progression.

Metastatic spread to the liver is the most common site of CRC metastases, with an incidence of 50-60% in patients diagnosed with primary CRC (Ismaili 2011). Liver metastases may be treated by curative segmental resection, targeted ablation or palliative chemotherapy. Liver resection due to metastatic colorectal disease has an improved 5-year survival of 25-40% when compared to treatment with only palliative chemotherapy (Choti et al. 2002). However, fifteen to twenty five per cent of patients with resectable disease on pre-operative conventional imaging are subsequently found at the time of surgery to have unresectable disease (Takahashi et al. 2003). Therefore, accurate assessment of the location and extent of disease with consideration of resultant resectability is essential for deciding on the most appropriate treatment algorithm for each patient.

In standard clinical practice contrast enhanced CT (CE-CT) is considered the gold standard for the identification of metastatic disease in patients with CRC. MRI has shown an improved sensitivity for M-staging when compared to CT and is the

preferred imaging modality for liver metastasis (Floriani et al. 2010), Intra-operative US has shown good sensitivity but results vary due to being operator dependent as well as being an invasive imaging modality limiting its practical application for the pre-operative staging of patients with CRC (Choti et al. 2002). PET/CT when used for M-staging has been shown to significantly reduce the number of inappropriate liver resections (Ruers et al. 2009). However, more recently it has been argued that PET/CT has resulted in poor patient selection prior to resection of liver metastases (Moulton et al. 2014). The role for PET/MRI in M-staging has not been fully evaluated in patients with CRC. In this chapter the study aims to evaluate the diagnostic accuracy of PET/CT and PET/MRI in identifying and staging metastatic disease in patients with primary CRC and assess if PET/CT and PET/MRI may be considered equivalent to the conventional current CRC staging imaging modality, which is primarily CE-CT.

6.2 Aims

The aim of this chapter is to prospectively evaluate if PET/CT and PET/MRI may be considered equivalent imaging modalities to current conventional imaging (CE-CT) for the identification and staging of metastases (M-staging) in pre-therapeutic patients with primary colon and rectal cancers.

The objective is,

- i) To compare the diagnostic accuracy of PET/CT and PET/MRI imaging using conventional imaging (CE-CT) as the reference standard for determining the presence and site of distant metastatic disease (M-staging) in pre-therapeutic patients with primary colon and rectal cancer.

6.3 Methods

6.3.1 Patient recruitment

Patients were recruited prospectively for this study with histological biopsy proven primary colon cancer. All patients were asked to give written informed consent following a full explanation of the procedure.

Institutional ethical review board approval, pre-scanning preparation details and patient informed consent details from this chapter can be found further detailed in Chapter 2.1.1, Methodology.

6.3.2 Patient population

A total of 114 patients with CRC were prospectively recruited into this study. Fifteen patients were excluded that did not all undergo CE-CT, PET/CT and PET/MRI imaging, leaving 99 patients in total. This was because some patients were unable to tolerate all three imaging modality investigations due to patient discomfort or for logistical reasons. These included, scanner and isotope failure or all imaging modalities not being able to be performed prior to the date of surgery. The resultant 99 patients all underwent CE-CT, PET/CT and PET/MRI imaging. However as PET/MRI was a new imaging modality and imaging protocols were still being developed, whole body PET/CT was used to validate the sequences for whole body PET/MRI imaging. The first 50 patients were used to successfully validate the whole body PET/MRI sequences.

The resultant 49 patients with 49 CRC lesions all underwent whole body CE-CT as part of their standard clinical management, and research whole body PET/CT and whole body PET/MRI imaging on the same day. The PET/CT and PET/MRI imaging was performed within 2 weeks of the staging CE-CT scans. The cohort of patients used in this chapter consisted of 34 men and 15 females. The median age of all recruited patients was 68 years old and average age 68.4 years old. The 49 patients successfully analysed in this chapter consisted of 25 patients with histologically proven colon cancer and 24 patients with rectal cancer. The flow of patients in this study is shown below in Figure 6.1.

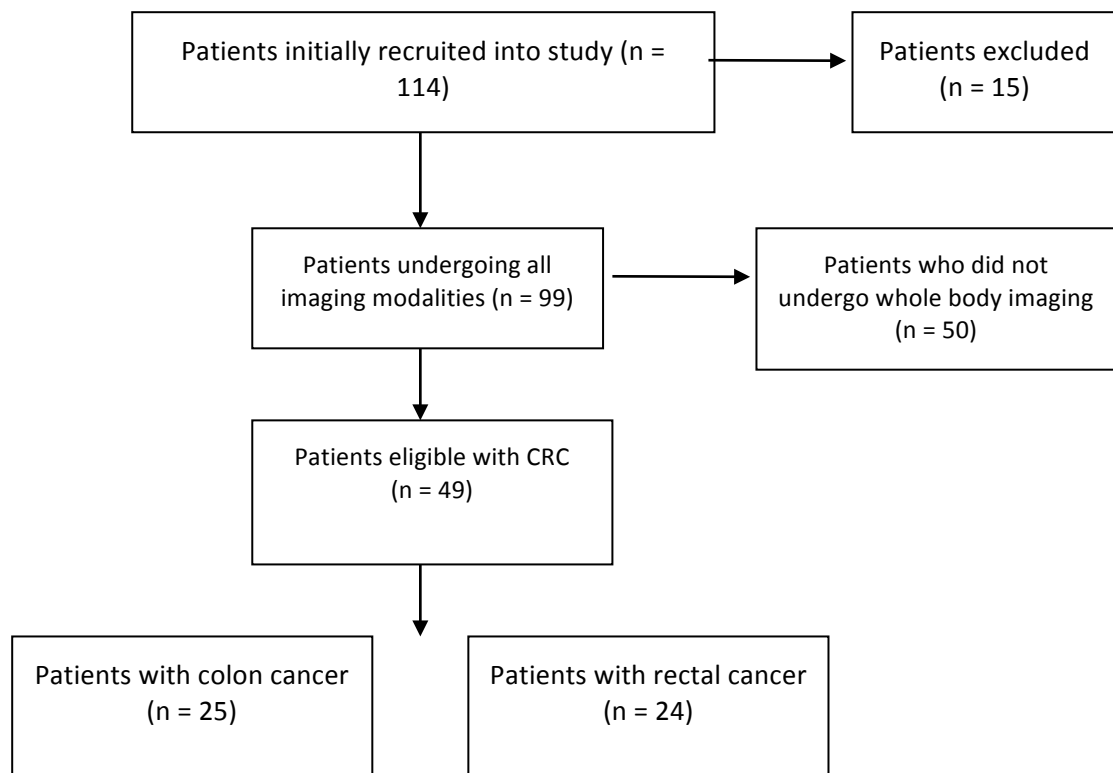


Figure 6.1 - Flow chart of patients in the study. n = number of patients in the study.

6.3.3 Imaging

Patients underwent whole body ¹⁸F-FDG PET/CT and PET/MRI scans on the same day, as per the protocols in chapter 2, methodology. ¹⁸F-FDG radio-tracer was prepared as described in chapter 2 with a mean administered dose of 250MBq or 370MBq for research or clinical scans respectively.

Visual analysis and standardised uptake values (SUVs) were obtained for each lesion using the methodology described in section 2.4.1. For each patient, regions of interest (ROI) were drawn over the tumour and normal tissue images.

6.3.4 Reference Standards

From the 49 patients recruited with CRC, all patients underwent conventional imaging in the form of contrast enhanced CT (CE-CT) of the tumour in-situ in the pelvis, abdomen, and chest. These images were subsequently analysed and considered to be the reference standard in this chapter.

All liver metastasis were either biopsied, which confirmed histologically liver metastases secondary to CRC or showed characteristic radiological features on cross sectional CE-CT imaging. All patients with suspected liver metastases on CE-CT went on to have an MRI liver scan.

6.3.5 Statistical analysis.

All data from this study are expressed as mean \pm two standard deviations or as a proportion as appropriate. The two commercial statistical software packages used were, Microsoft ExcelTM and SPSS software (version 25). All statistically significant levels were set at 5%, where a p value <0.05 was considered significant.

6.4 Results

6.4.1 Standard of reference

A total of 49 patients were prospectively recruited and consented to this study with 25 histo-pathological biopsy proven adenocarcinomas of the colon and 24 of the rectum. These patients were all diagnosed with radiological features of colon and rectal carcinoma respectively on conventional imaging. All patients underwent whole body CE-CT, PET/CT and PET/MRI imaging. Per-patient and per-lesion analyses were used and are further detailed below.

For patients with colon cancer, CE-CT staged 11 patients with metastasis. 8 patients were staged as M1a consisting of, 6 metastases in the liver, 1 in the lung and 1 non-regional lymph node. One patient was staged as M1b with metastases to the liver and lung and 2 patients were staged as M1c with metastases to the peritoneum (Table 6.1). All patients with suspected liver metastases on CE-CT went on to have an MRI liver scan for further confirmation, according to standard clinical practice.

M0	M1a	M1b	M1c
14	8	1	2

Table 6.1 – M-staging for colon cancer patients with CE-CT.

For patients with rectal cancer, CE-CT staged 7 patients with metastasis. Seven patients were staged as M1a consisting of, 5 metastases in the liver and 2 non-regional lymph nodes (Table 6.2.). As with colon cancer patients, all rectal cancer patients with suspected liver metastases on CE-CT went on to have a further MRI liver scan.

M0	M1a	M1b	M1c
17	7	0	0

Table 6.2 – M-staging for rectal cancer patients with CE-CT.

6.4.2 Colon tumour M-staging accuracy

PET/MRI staged 23/25 (92%) tumours of the colon concordantly when compared to reference standard CE-CT staging. PET/MRI incorrectly staged 2 peritoneal metastases (M1c) as M0. PET/CT was superior to PET/MRI and showed concordance for M-staging in 25/25 (100%) of colon tumours.

Table 6.3 shows the overall diagnostic accuracy for M-staging of colon cancers with PET/MRI and PET/CT.

Imaging Modality	Accuracy	% Accuracy
PET/MRI	23/25	92
PET/CT	25/25	100

Table 6.3 – M-staging overall diagnostic accuracy for colon tumours.

6.4.3 Colon tumour imaging Sensitivity and Specificity

The M-staging sensitivity and specificity for metastatic colon cancers with PET/CT and PET/MRI are shown in Table 6.4 below.

PET/MRI showed inferior sensitivity (9/11) but equivalent specificity (14/14) to PET/CT for M-staging.

Imaging Modality	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR(+)	LR(-)
PET/MRI	81.82	100	100	87.50	n/a	0.18
PET/CT	100	100	100	100	n/a	n/a

Table 6.4 – M-staging sensitivity and specificity for colon cancers with PET/MRI and PET/CT.

6.4.4 Rectal tumour M-staging accuracy

PET/MRI staged 24/24 (100%) tumours of the rectum concordantly when compared to reference standard CE-CT staging. PET/CT was inferior to PET/MRI and showed concordance for M-staging in 22/24 (91.7%) of rectal tumours. One non-regional node (M1a) was incorrectly staged as M0 by PET/CT; false negative, whilst 1 patient with no metastasis was incorrectly staged as having a non-regional node (M1a); false positive.

Table 6.5 shows the overall diagnostic accuracy for M-staging of rectal cancers with PET/MRI and PET/CT.

Imaging Modality	Accuracy	% Accuracy
PET/MRI	24/24	100
PET/CT	22/24	91.7

Table 6.5 – M-staging overall diagnostic accuracy for rectal tumours.

6.4.5 Rectal tumour imaging Sensitivity and Specificity

The M-staging sensitivity and specificity for metastatic rectal cancers with PET/CT and PET/MRI are shown in Table 6.6 below.

PET/CT showed inferior sensitivity (6/7) and inferior specificity (16/17) to PET/MRI for M-staging in patients with primary rectal cancer.

Imaging Modality	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR(+)	LR(-)
PET/MRI	100	100	100	100	n/a	n/a
PET/CT	85.70	94.12	85.71	94.12	14.57	0.15

Table 6.6 – M-staging sensitivity and specificity for rectal cancers with PET/MRI and PET/CT.

6.5 Discussion

Distal metastatic spread to the liver is the most common site of CRC metastases and an incidence of 50 to 60%, has been reported in patients diagnosed with primary CRC (Ismaili 2011). In our study we found isolated liver metastasis in 24% (6/25) patients with colon cancer and 20.8% (5/24) patients with rectal cancer. This observed percentage occurrence of liver metastases at initial presentation, may be partially explained by considering the anatomical blood supply to the liver. The liver receives blood from the systemic and portal circulation as well as via the fenestrations in the sinusoidal epithelium (Kew 1998). Therefore the liver is unique with regards to potential sites for malignant cells to infiltrate normal hepatic tissue (Kew 1998) and the high-observed rates of liver metastasis within our cohorts of colon and rectal cancer patients may have been expected.

In this thesis, PET/CT and PET/MRI both showed 100% concordance with CE-CT in the identification of liver metastases in patients with colon and rectal cancers. Both PET/CT and PET/MRI were also concordant with CE-CT in determining the number of metastatic deposits to the liver in both cohorts of patients with colon and rectal cancers. For CRC patients with liver metastasis an accurate assessment of the number and location of liver metastases are essential to decide if these patients would be potentially candidates for curative resections. Also the surgical approach and extent of resection is dependent upon these factors in order to achieve complete excision and reduced long term recurrence rates. The five and ten year survival after hepatic resection with curative intent of colorectal liver metastasis have been reported to be 47% and 28% respectively(Wei et al. 2006) and a post-operative mortality rate of 1.5% has also been reported (Rees et al. 2008). This improved survival benefit with relatively low post-operative mortality rates have

made surgical resection with curative intent in selected patients with CRC liver metastases the optimal treatment modality. From our study PET/CT and PET/MRI may be considered equivalent imaging modalities to CE-CT for assessing resectability in patients with liver metastases and in assisting in the pre-operative surgical planning and approach in patient with resectable metastases.

A significant number of patients have hepatic metastases, which are not amenable to initial surgical resection. In the vast majority of cases this is due to the presence of extensive tumour deposits affecting a single lobe or multi-focal disease, an inability to achieve adequate resection margins to enable an R0 resection or in some cases tumour may involve the porta hepatis making resectability challenging. In these patients with initially unresectable disease, a course of neo-adjuvant chemotherapy may be considered appropriate, followed by reassessment of suitability for resection. Twelve and a half percent of patients with initially unresectable liver metastases, after undergoing neo-adjuvant therapy were considered appropriate candidates for surgical resection (Adam et al. 2004). In our study PET/CT and PET/MRI were both able to show concordance with CE-CT in identifying the presence of liver metastasis and also the number of metastatic deposits when present. PET/CT and PET/MRI may both have a future role in identifying patients who are suitable for hepatic metastasectomy with curative intent or who may benefit from neo-adjuvant chemotherapy then surgical resection. In cases where conventional imaging (CE-CT) is equivocal or has deemed patients to have initially unresectable hepatic metastases, PET/CT and PET/MRI may be used as an alternative imaging modality to verify the optimum treatment pathway to improve long term survival. The gold standard imaging modality in clinical practice is MRI of the liver for confirmation of liver metastasis after identification on staging CE-CT.

However PET/CT and PET/MRI may provide a single examination, whole body staging scan for patients with CRC for staging of the primary tumour and liver metastases due to the high rates of identification of liver metastasis in this study. There is also the added advantage of reduced radiation dose exposure to patients with PET/CT and PET/MRI imaging as opposed to sequential CE-CT of the primary tumour then a potential further staging CE-CT for patients with suspected metastases.

Figure 6.2 shows a CE-CT axial image of a 72-year old patient who was diagnosed with a low rectal primary cancer and a single liver metastasis. Figures 6.3 and 6.4 show the corresponding PET/CT and PET/MRI axial images.



Figure 6.2 – the CE-CT of a 72-year old patient diagnosed with a rectal cancer primary tumour and a liver metastasis.

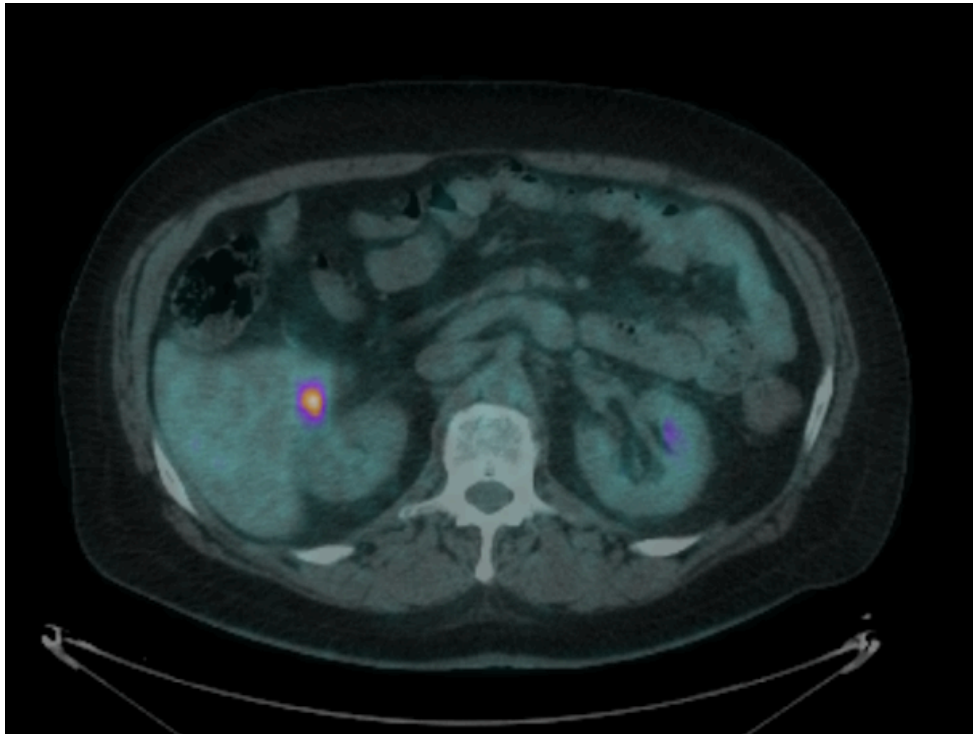


Figure 6.3 – the PET/CT of a 72 year old patient diagnosed with a rectal cancer primary tumour and a liver metastasis.

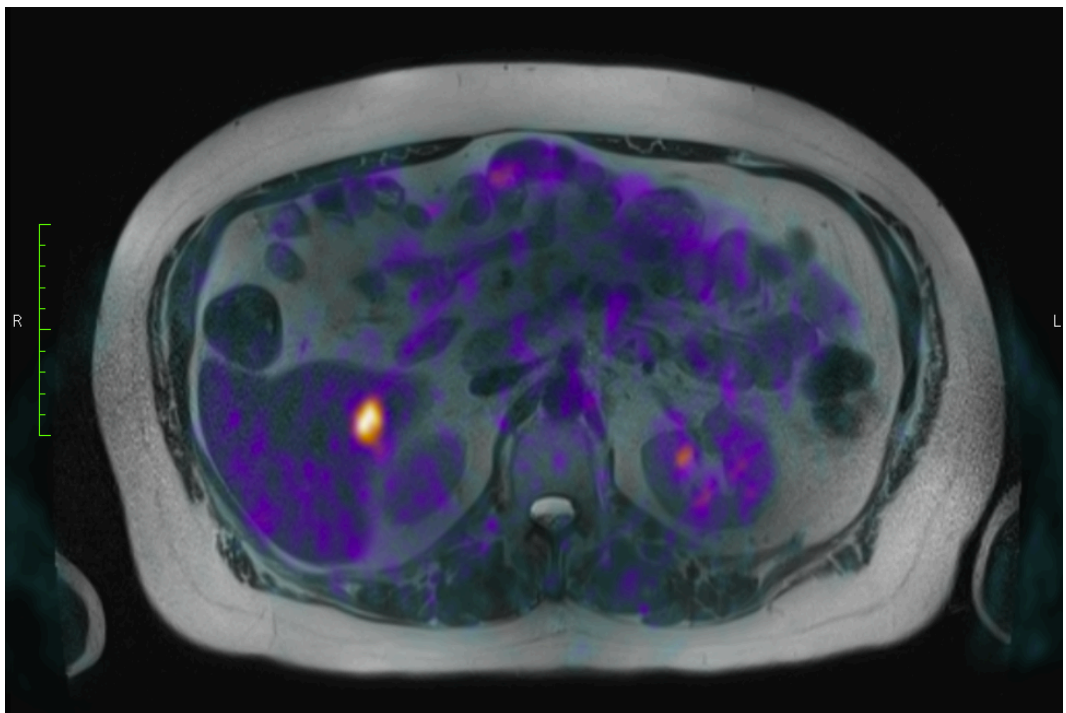


Figure 6.4 – the PET/MRI of a 72-year old patient diagnosed with a rectal cancer primary tumour and a liver metastasis.

In this study for colon cancer patients, PET/CT demonstrated a 100% (25/25) concordance rate with CE-CT for M-staging whilst PET/MRI showed concordance in 92% (23/25). PET/CT has a subsequent sensitivity and specificity of 100%, whilst PET/MRI had a sensitivity of 82.8% and specificity of 100%. PET/MRI correctly staged all metastases to the liver, lung as well as any non-regional lymph nodes. However two peritoneal metastases (M1c) were incorrectly staged by PET/MRI as M0, which contributed to the inferior M-staging accuracy and reduced sensitivity when compared to PET/CT. Approximately 10% of patients with metastatic CRC initially present with peritoneal carcinomatosis as the only site of metastasis at the time of diagnosis (Verwaal et al. 2005). This study found a rate of 18.1% (2/11) in the cohort of colon cancer patients. Metastasis confined to the peritoneum at initial diagnosis was traditionally treated with palliative chemotherapy due to the poor long-term outcomes. However peritoneal carcinomatosis is now considered to be part of initial disease dissemination as opposed to generalised systemic disease (Koppe et al. 2006). Therefore a loco-regional treatment approach with complete cytoreductive surgery (CCCS) then subsequent hyperthermic intra-peritoneal chemotherapy (HIPEC) has been suggested in a multi-centre prospective phase two clinical study to improve long-term survival (Hompes et al. 2012). From the PET/MRI findings in this study, due to the inferior accuracy and sensitivity observed in detecting metastasis confined to the peritoneum PET/MRI should be used with caution in the M-staging of colon cancer patients when compared to PET/CT and CE-CT. PET/MRI may be limited in detecting peritoneal carcinomatosis and therefore a poor imaging modality for potentially selecting patients who may benefit from CCCS followed by HIPEC. Therefore when considering treatment options of systemic

chemotherapy or cytoreductive surgery and intra-peritoneal chemotherapy, PET/CT and CE-CT could be considered to be the most appropriate imaging modalities.

In rectal cancer patients, PET/CT showed a 91.7% (22/24) concordance rate with CE-CT for M-staging whilst PET/MRI showed concordance in 100% (24/24). PET/CT has a subsequent sensitivity of 85.7% and specificity of 94.2% whilst PET/MRI had a sensitivity and specificity of 100%. PET/MRI correctly staged the location of all 7 patients with metastatic rectal cancer. PET/CT correctly staged all metastases to the liver (5/7), however incorrectly staged one non-regional lymph node as M0 and staged one patient without any systemic metastasis as having a non-regional lymph node. This contributed to the inferior M-staging accuracy and reduced sensitivity of PET/CT when compared to PET/MRI. Extra-regional lymph nodes are considered to be involved nodes that follow the course of the external iliac, inguinal and peri-aortic regions and are classed as distant metastases. Rectal cancer patients with extra-regional lymph node involvement may be suitable for lateral lymphadenectomy. Therefore due to observed limitations of PET/CT in this study in identifying extra-regional lymph nodes, care and consideration should be taken in assessing the suitability of patients considered appropriate for a surgical approach incorporating lateral pelvic lymph node dissection. This may subsequently contribute to a higher rate of local recurrence in these patients. Therefore when considering non-regional lymph node involvement and suitability for TME surgery with extended lymph node dissection, PET/MRI and CE-CT may be considered the most appropriate imaging modalities.

A systematic review of PET imaging in patients with CRC has shown a pooled sensitivity and specificity for PET in the detection of extra hepatic disease to be 91.5% and 95.4% respectively (Wiering et al. 2005). In a further meta-analysis

and systematic review of PET/CT in the detection of liver metastasis, on a per-patient basis the pooled sensitivity and specificity was noted to be 93% and 86% whilst for MRI was 100% and 81% respectively (Maffione et al. 2015). By comparison for colon cancers, we found the sensitivity and specificity of PET/CT for M-staging to be 100% and 100% and for PET/MRI to be 81.82% and 100% respectively. For rectal cancers we found the sensitivity and specificity of PET/CT for M-staging to be 85.7% and 94.2% and for PET/MRI to be 100% and 100% respectively when compared to CE-CT. Our sensitivity and specificity rates observed in our study for both colon and rectal cancers with PET/CT and PET/MRI are comparable to other imaging modalities in the existing literature. Therefore PET/CT and PET/MRI may have diagnostic value in the staging of extra-hepatic and hepatic lesions in patients with CRC. The detection of extra-hepatic disease may potentially change patient management regarding suitability for liver resection whilst the detection of additional liver lesions may result in a change in the surgical approach or a course of chemotherapy prior to surgical resection.

An important consideration not addressed within this study is the subsequent M-staging with PET/CT or PET/MRI after neo-adjuvant therapy. This was not within the scope of the study or outlined in our aims but has important therapeutic implications with regard to suitability for surgical resection or a palliative treatment approach. Presently with PET/CT imaging the sensitivity is reduced for the detection of liver metastases, due to the inhibitory effects of chemotherapy on cellular metabolic activity (Glazer et al. 2010). However there is a lack of clinical controlled trials assessing the potential benefits of PET/CT and PET/MRI in assessing the response after neo-adjuvant therapy and future studies should be considered. A further consideration was the lack of available histology, which meant that

conventional imaging (CE-CT) was used as the reference standard in this investigation. All liver metastases had histological confirmation in the form of biopsy proven metastatic lesions in addition to CE-CT images suggestive of liver metastasis. However histological confirmation of the other sites of metastasis, such as the lung, peritoneum and non-regional lymph nodes were not performed clinically and thus were not available to be used as a reference standard in this study. Therefore as CE-CT is considered the gold standard imaging modality in clinical practice, it was also used in this study.

6.6 Conclusion

In this chapter both PET/CT and PET/MRI showed concordance to CE-CT in identifying colon and rectal cancer patients with liver metastasis and assessing the number of liver metastases. Both PET/CT and PET/MRI may provide valuable information and be used as additional imaging modalities to conventional imaging (CE-CT) when assessing suitability for curative hepatic metastasectomy.

For the staging of extra-hepatic metastases in colon cancer patients PET/CT showed equivalence to CE-CT. PET/CT may potentially identify peritoneal metastasis and help select patients who would benefit from early cytoreductive surgery with intra-peritoneal chemotherapy to improve long-term disease free survival.

For the staging of extra-hepatic metastases in rectal cancer patients PET/MRI showed equivalence to CE-CT. PET/MRI may potentially identify non-regional lymph node metastasis and help select patients who would benefit from TME surgery with extended lymph node dissection to reduce recurrence rates and improve long-term outcomes.

The role of PET/CT in identifying systemic colorectal metastases is well established (Maffione et al. 2015) and has a developing role as an all in one cancer staging modality (Hicks, Ware, and Lau 2006). PET/MRI has an evolving role in M-staging. The results of this study may potentially help to evaluate the role of PET/MRI in metastatic staging contributing to the developing role of PET/MRI as a single tailored imaging technique for the complete staging in colon and rectal cancer.

CHAPTER 7

Quantitative tumour perfusion assessment with dynamic contrast enhanced CT (DCE-CT) – to what extent does inter-observer agreement have on metabolic vascular parameters.

7.1 Background

Colorectal cancer (CRC) is the third most common malignancy in men with 746,000 new cases and second most common malignancy in women with 614,000 new cases in 2012 (Siegal, Naishadham, and Jemal 2012). The worldwide estimate for both sexes of new cases of colorectal cancer in 2012 was 1.36 million and the estimated number of resulting deaths was 694,000. Due to recent improvements in screening and neo-adjuvant therapy, the overall five-year survival rate has improved from 51% to 66% from 1975 to 2006 respectively. In 2010, the five-year survival for localised disease was 90.4% (Altekruse 2009). The Dutch Total Mesorectal Excision (TME) trial has shown short course pre-operative radiotherapy has reduced the 10-year incidence of local recurrence from 11% in rectal cancer patients undergoing surgical excision alone to 5% in patients receiving radiotherapy treatment prior to surgical resection (Peeters et al. 2007; van Gijn et al. 2011). In patients with advanced colon cancer, neo-adjuvant chemotherapy has been considered to improve the rates of R0 surgical resection and resultant reduced local recurrence rates (Nilsson et al. 2013). Therefore accurate tumour assessment with appropriate pre-operative imaging is essential to plan the most suitable treatment for the individual patient to improve long-term survival.

It is well established that the blood supply of a tumour develops via the process of neovascularization, also known as angiogenesis. This development of an additional blood supply allows the tumour to further develop and metastasise, a feature which is associated with a poorer long-term prognosis (Brawer et al. 1994; Fontanini et al. 1997). High glucose metabolism by hypoxic tumours has also been associated with aggressive tumour sub-classes, which have been shown to exhibit treatment resistance (Padhani and Miles 2010). The micro-vascular changes in a

tumour formed via angiogenesis form the principles behind dynamic contrast-enhanced computed tomography (DCE-CT), otherwise known commercially as CT perfusion. Tumour perfusion *in vivo* has been shown to increase in comparison to normal tissue, when imaged with DCE-CT (Miles et al. 2000). DCE-CT has also been shown to provide information regarding improved tumour staging, prognosis and monitoring of therapy (Miles and Griffiths 2003). Commercial software packages have subsequently been developed to reliably quantify these CT perfusion parameters (Purdie, Henderson, and Lee 2001; Gillard et al. 2001). Commercial software analyses a rapid sequential series of acquired CT images produced by temporal changes in attenuation in tissues and blood vessels after the administration of intravenous iodinated contrast media (Miles and Griffiths 2003).

Assuming the concentration of iodine within tissues and blood vessels is proportional to the resultant increase in attenuation, the temporal attenuation changes of the tumour captured on the series of images acquired in DCE-CT can be analysed using standard kinetic modelling methods. Therefore, quantitative markers reflecting aspects of tumour perfusion may be derived. In practice, the range of physiological parameters maybe derived through pixel-by-pixel calculations and displayed as parametric maps. These physiological parameters include, blood volume, tissue blood flow, mean transit time and capillary permeability. These individual DCE-CT measurements have all been shown to vary as a direct consequence of anti-angiogenic therapy (Willett et al. 2004). DCE-CT may potentially provide a bespoke pre-operative imaging modality, to tailor the most appropriate treatment pathway for each individual patient.

7.2 Aims

The aim of this chapter is to prospectively determine the level of agreement for tumour vascular parameters obtained by a surgical trainee and a Consultant radiologist, with a commercially available dynamic contrast-enhanced CT perfusion (DCE-CT) software package. These results were assessed and the inter-observer variability for this software package was compared.

The objectives are,

- i) To compare the level of agreement between a surgical trainee and Consultant radiologist, for measuring tumour blood volume with dynamic contrast-enhanced CT perfusion (DCE-CT) in pre-therapeutic patients with primary colon and rectal cancer.
- ii) To compare the level of agreement between a surgical trainee and Consultant radiologist, for measuring tumour permeability with dynamic contrast-enhanced CT perfusion (DCE-CT) in pre-therapeutic patients with primary colon and rectal cancer.

7.3 Methods

7.3.1 Patient recruitment

Patients were recruited prospectively for this study with histological biopsy proven primary rectal cancer. The cohort of patients used for this chapter consisted of patients referred from the UCLH NHS trust and peripheral hospitals via their multidisciplinary teams. All patients were asked to give written informed consent following a full explanation of the procedure.

Institutional ethical review board approval, pre-scanning preparation details and patient informed consent details from this chapter can be found further detailed in Chapter 2.1.1, Methodology.

7.3.2 Patient population

A total of 62 patients with CRC were prospectively recruited into this study. Six patients were excluded that did not undergo complete DCE-CT imaging, leaving 56 patients in total. In three of the six excluded patients, images were acquired but were not evaluable and this was classed as a technical failure. A further two of the six excluded patients, experienced extreme discomfort and were unable to tolerate the DCE-CT scan whilst in one patient extreme involuntary motion resulted in poor image quality, which could not be used for subsequent assessment. The resultant 56 patients all underwent DCE- imaging.

The patients used in this chapter consisted of 32 men and 24 females. The median age of all recruited patients was 68.2 years old and mean age 68.6 years old. The 56 patients successfully analysed in this chapter consisted of 30 patients with histologically proven colon cancer and 26 patients with rectal cancer. All participants underwent DCE-CT perfusion imaging and subsequent analysis with a commercial software package provided by, GE Healthcare Technologies (Waukesha). The flow of patients in this study is shown below in Figure 7.1.

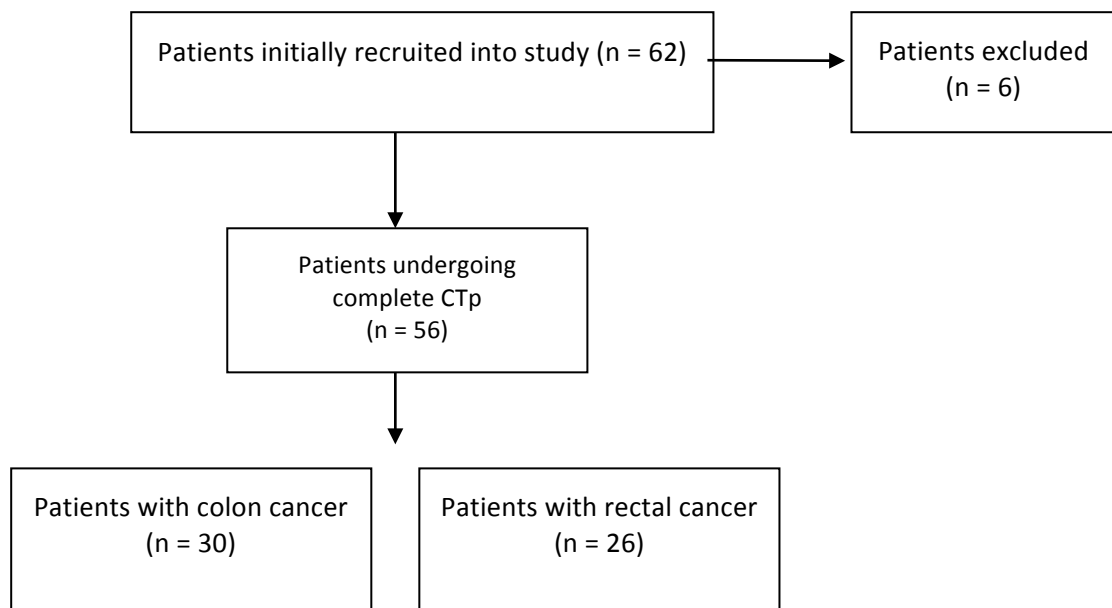


Figure 7.1 - Flow chart of patients in the study. n = number of patients in the study.

7.3.3 DCE-CT perfusion Technique

All participants underwent a whole body PET/CT scan for tumour localisation to a specific body region, followed by CT perfusion imaging of the tumour. A 64 slice discovery VCT dual modality integrated CT scanner (GE Healthcare, Waukesha, WI, USA) was used in 2D mode with an emission scan of 8 min/bed position, for CT perfusion imaging. A whole body CT was performed for localization and attenuation correction was used to identify the tumour location on the Z-axis. The CT perfusion protocol consisted of a non-enhanced 4cm localiser in order to confirm that optimum tumour coverage could be achieved. Unless contra-indicated an anti-peristaltic agent (intra-venous Buscopan) and an abdominal wall restraint was used to reduce potential gross patient involuntary movement which included excess respiratory or bowel motion.

The CT perfusion protocol selected varied according to the patient's Body Mass Index (BMI). Accordingly a BMI < 20, 120kV and 60mA, BMI of 20 to 25, 120kV and 80mA and for a BMI > 30, 120kV and 100mA perfusion parameters were used (50cm scan field of view, 512 x 512mm matrix). The entire detector width used was 64x0.25 with a Z-coverage of 4cm reconstituted to 5mm thick slices. The total scan time was 97.5 seconds, post contrast injection. The sampling frequency for the initial 30 bursts was 1.5 seconds, increasing to a 5 second inter-scan delay for the second pass measurements.

7.3.4 Image analysis and reference standard

All CT perfusion studies used in this chapter were transferred to a GE Healthcare Technologies workstation with deconvolution-based software. Two independent observers, who were blinded to the location of the tumour and each other's perfusion analysis measurements, performed image analysis. This consisted of one Consultant Radiologist (G.A) of at least 5 years of specific experience in tumour CT perfusion measurement and one higher surgical trainee (S.D). The Consultant Radiologist (G.A) was considered to be the reference standard in this chapter. The results of tumour perfusion analysis by S.D was compared to that of G.A and the inter-observer agreement calculated. All perfusion slices were viewed and whole tumour analysis approach was taken rather than selecting the largest cross sectional area of the tumour for analysis.

7.3.5 Distributed parameter analysis

All image analysis was initially performed with commercial perfusion software based on the kinetic model method adiabatic approximation of distributed parameter analysis (Perfusion 3.0; GE Healthcare Technologies, body protocol setting). To optimise soft tissue visualization, a processing threshold of 0 to 120 HU was chosen. The arterial input was localised, by placing a circular region of interest (mean size 10mm²) with an electronic mouse within the closest visualised artery supplying the tumour (Figure 7.2). This was typically the aorta, iliac or femoral artery as mesenteric vessels were typically difficult to locate within the limitations of 4cm scan coverage in addition to bowel motion. The software and resulting parametric maps were able to generate a resulting arterial time-enhancement curve

automatically. A mouse and electronic cursor were used to draw a freehand region of interest around the tumour margins on the blood volume and permeability maps that best demonstrated these tumours. Mean tumour blood volume (measured in milliliters per 100g of tissue) and mean permeability (measured in milliliters per 100g of tissue per minute) measurements were automatically generated and recorded by the computer software package for each tumour. These values were converted to values per unit volume using a tissue density measurement of 1.05 g/mL (the default setting of the software manufacturer) to enable comparison of these two measurements. This process produced resulting units of measurement of milliliters per 100mL and milliliters per 100mL per minute for blood volume and permeability respectively. To increase the reliability, repeatability and consistency of these results, surrounding peri-colic and peri-rectal fat and intra-luminal gas was omitted when a free hand region of interest was drawn.



Figure 7.2 – a DCE-CT axial image with a region of interest and tumour outlined.

7.3.6 Statistical Analysis

For blood volume and permeability values, for each individual reader, the mean difference, standard deviation of the difference and 95% limits of agreement were calculated. The intra-class correlation (ICC) with 95% confidence intervals was calculated for each vascular parameter for each observer by using analysis of variance (Bland and Altman 1986; Dewitte et al. 2002). All statistical analysis was calculated with commercial statistical software package (MedCalc[®] and SPSS version 25 software).

7.4 Results

7.4.1 Standard of reference

A total of 56 patients were prospectively recruited and consented to this study with 30 histo-pathological biopsy proven adenocarcinomas of the colon and 26 of the rectum. These patients were all diagnosed with radiological features of colon and rectal carcinoma respectively on conventional imaging. All patients underwent DCE-CT perfusion imaging and all perfusion studies were analyzed using a single software package. The mean and standard deviation of blood volume and permeability parameters for each observer and the inter-observer agreement are further detailed below.

7.4.2 Mean Values

The mean blood volume and permeability values calculated with the GE software package with the distributed parameter analysis by reader S.D were 6.47+-2.88 (standard deviation) and 12.47+-7.86 (standard deviation) respectively and by reader G.A 6.72+-3.48 (standard deviation) and 12.23+-7.18 standard deviation) respectively. For comparison the full results are further shown in Table 7.1.

Perfusion Measurement	Reader S.D	Reader G.A
Blood Volume (mL.100mL ⁻¹ .min ⁻¹)	6.47+-2.88	6.72+-3.48
Permeability (mL/100mL)	12.47+-7.86	12.23+-7.18

Table 7.1 – the mean values for blood flow and permeability calculated via distributed parameter analysis with GE software for observers S.D and G.A.

7.4.3 Inter-observer agreement

The intra-class correlation parameters of the blood volume measurements calculated by S.D, as compared to the reference standard reader G.A. with the GE software package by distributed parameter analysis is shown in Table 7.2. The mean difference and 95% limits of agreement values were 0.7 and 11.7 respectively. This indicated good to moderate agreement between the individual sets of measurements for the blood volume parameters. Excellent agreement was defined by an intra-class correlation (ICC) value of 0.8 and above. The intra-class correlation (ICC) value was 0.84 indicating excellent agreement.

	Cronbachs'	ICC	Lower CI	Upper CI	Mean of Difference	Width of 95% CI
SD vs GA	0.84	0.84	0.73	0.90	0.70	11.70

Table 7.2 – GE software analysis of Blood Volume physiological parameter.

The permeability measurements calculated by S.D and compared to the reference standard reader G.A. with the GE software package by distributed parameter analysis is shown in Table 7.3. The mean difference and 95% limits of agreement values were -0.3 and 24.8 respectively. This indicated good to moderate agreement between the individual sets of measurements for the permeability parameters. The intra-class correlation (ICC) value was 0.81 indicating excellent agreement.

	Cronbachs'	ICC	Lower CI	Upper CI	Mean of Difference	Width of 95% CI
SD vs GA	0.81	0.81	0.68	0.88	-0.3	24.80

Table 7.3 – GE software analysis of Permeability physiological parameter.

7.5 Discussion

Contrast enhanced CT perfusion (DCE-CT) is an experimental imaging modality, which is not routinely used in clinical practice. However in experimental studies DCE-CT has been considered a reliable means for assessing tumour vascularity due to the predictable and linear pharmacodynamics (Blomley et al. 1993). There are two main potential sources of variability errors associated with this imaging modality, which contribute to the limited clinical application of DCE-CT (Goh, Halligan, and Bartram 2007). These are extrinsic error caused by observer differences in image interpretation and intrinsic error caused by inherent measurement variability, attributable to limitations of the perfusion software used (Goh, Halligan, and Bartram 2007). An assessment of intrinsic error was not within the remit of this study and hence not investigated within this chapter.

From this study the agreement between S.D for both physiological parameters, using the same software package, and the reference standard G.A was excellent. This is because ICC values of 0.80 and 0.81 were achieved for blood volume and permeability respectively. For blood volume measurements calculated by S.D and compared to reference standard using distributed parameter analysis, the mean difference and 95% limits of agreement values were 0.7 and 11.7 respectively. This indicated good agreement between the individual sets of measurements by each observer for the blood volume parameters. In a similar fashion, permeability measurements calculated by S.D and compared to reference standard using distributed parameter analysis; the mean difference and 95% limits of agreement values were -0.3 and 24.8 respectively. As with blood volume measurements by each observer, this also indicated good agreement between the individual sets of measurements by each observer. Despite the excellent observed agreement between

S.D and reference standard G.A, there are a number of factors that may have still adversely affected agreement. These include common limiting factors related to the anatomical region being imaged and extrinsic errors due to observer differences. Figures 7.3, 7.4 and 7.5 show images that were used for analysis from an 80 year old patient with a T2N1 adenocarcinoma of the sigmoid.

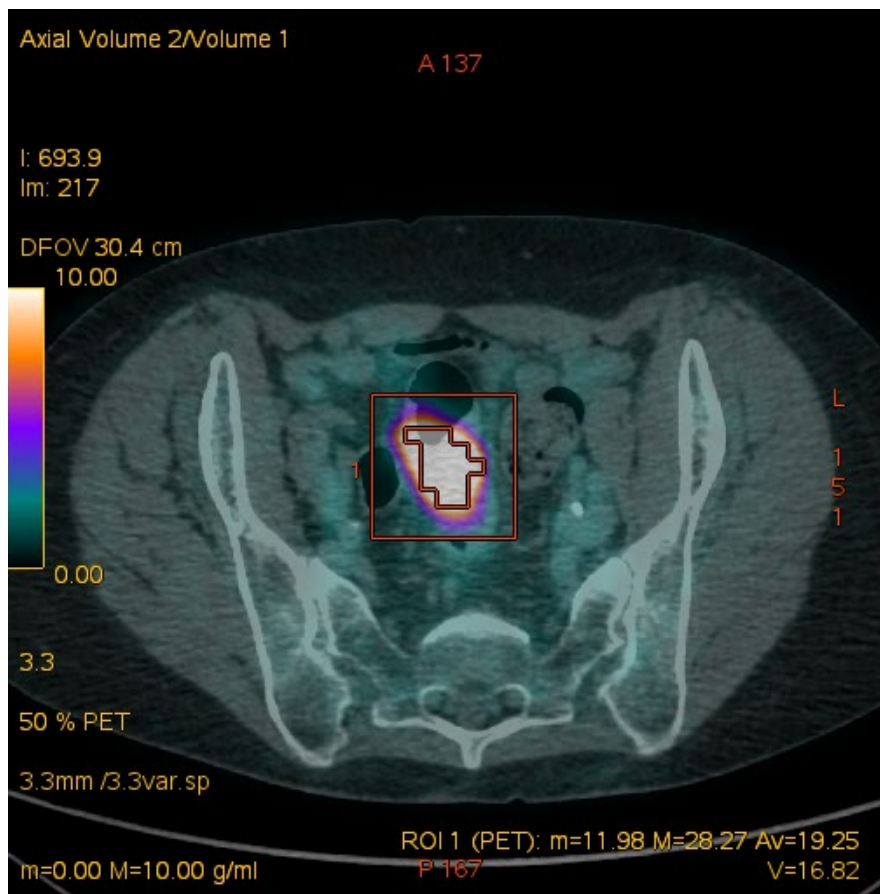


Figure 7.3 – the PET/CT axial image used for tumour localization, with an associated region of interest outlined.

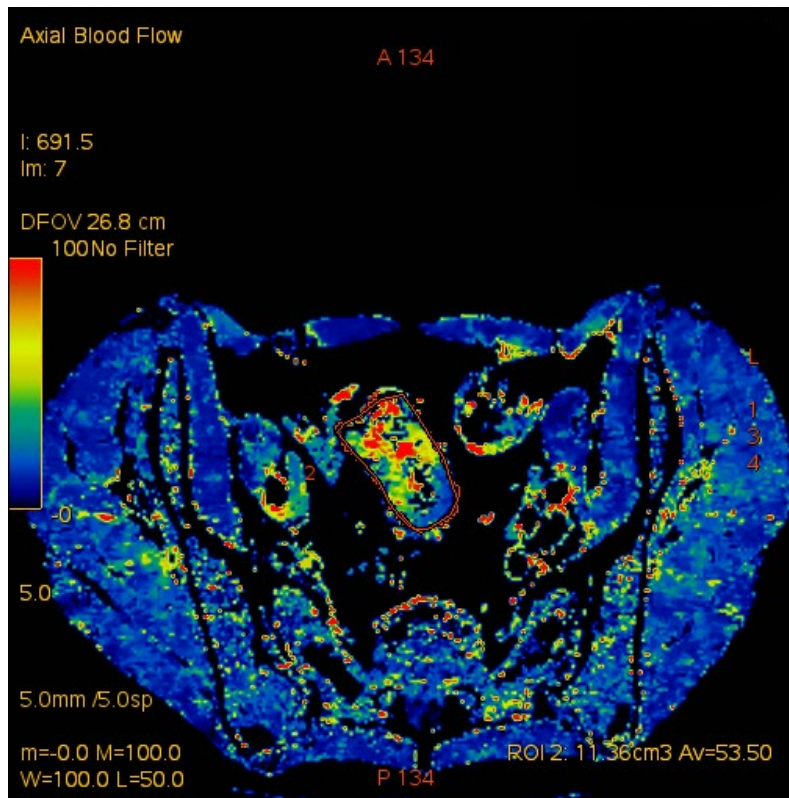


Figure 7.4 - the DCE-CT axial image with a region of interest located around the tumour and blood flow metabolic vascular parameter filter.

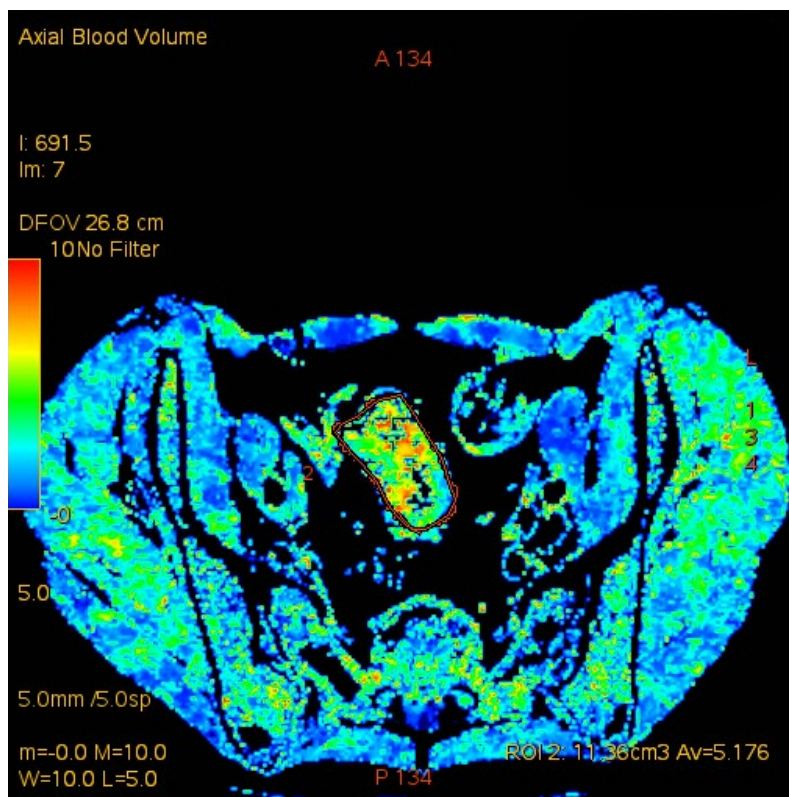


Figure 7.5 - the DCE-CT axial image with a region of interest located around the tumour and blood perfusion metabolic vascular parameter filter.

Common limiting factors related to the anatomical region being imaged may have potentially adversely affected the results in this chapter, despite excellent agreement being achieved. Khan et al., 2011 assessed the vascular quantification of the bowel wall for different anatomical segments of the colon and rectum. This group found that the assessment of bowel wall perfusion was feasible but challenging with quantification only possible in 77% of patients (Khan et al. 2012). These limitations were due to difficulties applying kinetic modeling to a mobile structure with a relatively thin wall, typically <5mm (Khan et al. 2012). There were also other technical limitations to this study such as bowel peristalsis, respiratory motion, inadvertent patient motion and slice misalignment, which may have influenced our results. These were minimised by the use of an anti-peristaltic agent and an abdominal wall restraint, however the use of motion corrective algorithms was not available with the chosen software package in this study.

The position and size of tumour regions of interest (ROI) drawn with a software package has been shown to influence the final perfusion values obtained (Goh et al. 2008). For this reason in our study we outlined a ROI for the entire tumour as opposed to outlining only the largest cross sectional area of the tumour. Newer advances in software packages facilitate whole tumour analysis by combining automated processing with an extrapolation function. These packages enable an initial tumour ROI to be drawn for the first few slices, then subsequently the software package is able to interpret and predict further tumour ROIs without the need for repeated manual outlining. In this study the GE Healthcare software package required a manual ROI to be outlined by hand for each tumour slice to allow vascular parameters to be quantified. This was a potential source of error and may

have potentially adversely affected our levels of achieved agreement between observers.

Different observers as opposed to a single observer are more likely to have a wider variation when outlining their ROI (Goh, Halligan, and Bartram 2007). Subsequently measurement variations between observers will result in an increase in the extrinsic error and thus a less clinically relevant study, which is of paramount importance when assessing the effect of anti-angiogenic therapy (Bland and Altman 1986). In the cerebral circulation, blood volume, blood flow and mean transit time values were assessed from ROIs placed by three different observers (Fiorella et al. 2004). The authors found that there was a high level of correlation with and between observers for all three parameters, although the level of agreement was not sufficient to be applied to clinical practice. Further studies in the extra-cerebral circulation have shown for liver perfusion (Blomley et al. 1995) and splenic perfusion (Miles and Griffiths 2003) good inter-observer agreement with correlation co-efficient values of 0.96 and 0.94 respectively. However the conclusions from these studies should be interpreted with caution as in both studies linear regression analysis was used to assess each of the results. Simple linear correlation and regression has been shown previously to be an incorrect method for accurately assessing agreement (Bland and Altman 1986; Bland and Altman 1999). This is because correlation is a measurement of linear association therefore high levels of correlation may still be present when true agreement is poor (Bland and Altman 1986; Bland and Altman 1999). The inter- and intra-observer agreement has been previously quantitatively assessed in 31 colorectal cancer patients imaged with DCE-CT (Goh et al. 2008). Excellent correlation was noted for tumour blood volume, blood flow, and mean transit time and permeability results. Intra class correlation was used to divide the

variability into two groups, that attributed to variability between observers and that attributed to variability between repeat measurement by the same observer taken 3 months apart. Unsurprisingly there was less variability between two measurements by the same observer than between those from different observers. Therefore this study concluded the inter-observer agreement was superior to intra-observer agreement for all four CT vascular perfusion measurements in primary colorectal cancer. Particular limitations in this study were that only two observers both of whom were Nuclear Medicine physicians and only repeat measurements of each value were analyzed. This means that the results of this ICC in this study must be considered with caution.

In this study permeability measurements and the interchangeability of blood volume measurements were investigated. Permeability in this study represents one-way free diffusion from the intra-vascular compartment to the extra-vascular compartment across capillary endothelium (Goh, Halligan, and Bartram 2007). Blood volume represents the total volume of blood circulating in all vessels in our tissue of interest (Goh, Halligan, and Bartram 2007). Both technical parameters represent important features of tumour angiogenesis. There are further features of angiogenesis such as blood flow and transit time which were not quantified in our study. This was because these acquisition parameters were suboptimal for analysis with one software programme, hence could not be used for direct comparison between both software packages.

In this study, two readers of varying clinical and technical background were used for tumour analysis with the same software package. This study aimed to help quantify differences in perceived measurements by each observer with the same software package and hence any extrinsic errors. However due to the excellent

agreement between both observers in this study, extrinsic errors may be considered to be very minimal. The clinical translation of this finding is that a higher surgical trainee with limited radiological training and experience of image analysis may produce comparable agreement to that of a Consultant Radiologist for the assessment of tumour blood volume and permeability measurements with DCE-CT. This may enable DCE-CT perfusion to be more widely available and clinically used by both surgeons and radiologist, to enable the assessment of tumour perfusion and resultant metastatic potential in colon and rectal cancer patients. This may have a profound impact on patient management when considering the potential for surgical resection or adjuvant therapy prior to discussion at MDT meetings. Further to this DCE-CT may have a clinical role with regard to assessing therapeutic response in patients treated with a watch and wait pathway after neo-adjuvant therapy.

7.6 Conclusion

DCE-CT is a functional imaging technique that allows the quantification of tumour vascularization. However there are limited clinical studies, which quantify extrinsic error in DCE-CT measurements caused by observer differences in image interpretation. This study has shown that a higher surgical trainee may obtain high levels of agreement for tumour blood volume and permeability measurements to that of a Consultant radiologist with extensive pre-existing radiological staging experience in pre-therapeutic patients with primary colon and rectal cancer. By being able to better phenotype colon and rectal tumours with DCE-CT, this may potentially help to guide more appropriate selection of patients who would benefit from neo-adjuvant therapy. The use of DCE-CT may also potentially be translated into clinical practice by surgeons in training.

CHAPTER 8

Conclusion

8.1 Summary of thesis findings

The principle aim of this thesis was to prospectively evaluate if PET/MRI may be considered to be a more accurate imaging modality than PET/CT or an equivalent or complimentary imaging modality to conventional imaging (CE-CT or diagnostic MRI) for the complete staging of patients with primary colon and rectal cancers. I wanted to conduct investigations to enable me to evaluate the diagnostic accuracy of PET/MRI and PET/CT for T, N and M colon and rectal cancer staging in a clinical setting.

Chapter 3: The impact of PET/CT on loco-regional staging in patients with primary colo-rectal cancer – a systematic review and meta-analysis.

A systematic review with meta-analysis was performed to evaluate the diagnostic accuracy of FDG PET/CT in the preoperative and pretherapeutic assessment of patients with colon and rectal cancers with specific reference to T and N-staging.

Twelve studies containing 1,643 patients were eligible for analysis. I found, patients with rectal cancers would particularly benefit from PET/CT imaging, due to more accurate loco-regional staging resulting in more appropriate pre-therapeutic management options prior to surgery, thus improving long-term survival and prognosis.

Chapter 4: Loco-regional staging in colon cancer with PET/CT and PET/MRI – an observational cohort study.

An observational cohort study was performed to assess if PET/MRI could be considered to be a more accurate imaging modality than PET/CT or conventional imaging (CE-CT) for T and N-staging in patients with primary colon cancer.

From this study CE-CT was the best overall imaging modality for T and N-staging. However, the PET component of PET/CT and PET/MRI imaging improved the overall diagnostic accuracy in assessing N0 stage. PET/MRI also demonstrated superior accuracy for transmural node negative (T2/T3N0) tumours when compared to PET/CT and conventional imaging for loco-regional staging in patients with colon cancer.

Chapter 5: Loco-regional staging in rectal cancer with PET/CT and PET/MRI – an observational cohort study.

An observational cohort study was performed to assess if PET/MRI could be considered to be an equivalent imaging modality to conventional imaging (diagnostic MRI) for T and N-staging in patients with primary rectal cancer.

From this study PET/CT was the most accurate imaging modality for T-staging and in predicting CRM involvement, whilst PET/MRI was the best overall imaging modality for N-staging in rectal cancer patients. However, PET/MRI demonstrated superior accuracy for transmural node negative (T2/T3N0) tumours when compared to PET/CT for loco-regional staging in patients with rectal cancer.

Chapter 6: Metastatic staging in colon and rectal cancers with PET/CT and PET/MRI – an observational cohort study.

An observational cohort study was performed to assess if PET/MRI could be considered a more accurate imaging modality than PET/CT and equivalent imaging modality to conventional imaging (CE-CT) for M-staging in patients with colon and rectal cancers.

PET/CT showed equivalence to CE-CT in colon cancer patients, whilst PET/MRI showed equivalence to CE-CT in patients with rectal cancer, in the staging of extra-hepatic metastases. PET/CT may potentially identify peritoneal metastasis in colon cancer patients and PET/MRI may potentially identify non-regional lymph node metastasis in rectal cancer patients. Both imaging modalities may help reduce recurrence rates and improve long-term disease free survival.

Chapter 7: Quantitative tumour perfusion assessment with CT in patients with CRC – to what extent does inter-observer agreement have on metabolic vascular parameters.

A prospective study to determine the level of agreement for tumour vascular parameters (blood volume and permeability measurements) by a Consultant radiologist and surgical trainee with DCE-CT was performed.

The agreement between the surgical trainee and Consultant radiologist, for both physiological parameters was excellent. This study showed a higher surgical trainee may obtain high levels of agreement for tumour blood flow and permeability measurements in pre-therapeutic patients with primary colon and rectal cancer with DCE-CT.

8.2 Strength and limitations of work

There is a lack of quantitative evidence for the use of PET/CT imaging in patients with primary CRC. There have been several studies performed, however they vary extensively regarding primary outcomes, the range of patients enrolled and reference standards used. PET/MRI imaging is a relatively new imaging modality and its use has evolved at a rate directly related to the development of imaging protocols and appropriate patient selection. A clear outlined algorithm regarding the optimum use of PET/CT and PET/MRI as imaging modalities in the initial staging and assessment of pre-therapeutic patients with CRC has not yet been fully evaluated.

Work in this thesis has demonstrated an optimum role for PET/MRI and PET/CT in patients with CRC where they may be both used as a single examination imaging modality for the complete staging of patients with primary colon and rectal cancers. PET/CT and PET/MRI have value in accelerating the CRC pathway by providing an all in one complete oncological imaging algorithm.

In this thesis, the diagnostic accuracy of PET/MRI and PET/CT for complete T, N and M colon and rectal cancer staging in a clinical setting has been evaluated. The value of both complete staging imaging modalities are that they may be initiated relatively early from confirmation of invasive adenocarcinoma, resulting in a reduction in the total number of investigations required prior to MDT discussion and the earlier initiation of more appropriate treatment pathways tailored to the patient disease status. This may ultimately result in improved 5-year disease free survival rates, an improvement in the long-term quality of life, and patient satisfaction.

There are a number of limitations in this thesis. A significant limitation throughout each chapter was that PET/MRI and PET/CT imaging were compared from a single patient cohort where readers were blinded. There was no attempt at patient randomization; hence post-test validation bias must be considered. To negate this possibility, two independent separate readers were each used for PET/MRI and PET/CT image analysis. Two dual accredited Nuclear Medicine Radiologists, who subsequently shared and discussed their findings, reviewed the PET/MRI studies. This enabled a single diagnostic accuracy to be determined by consensus. The PET/CT studies were reviewed in a similar fashion. Separate reading sessions were organised at independent times for PET/MRI and PET/CT image analysis and no clinical information except for the clinical indication of the patient was disclosed to each reader. A further limitation within chapter 5 was the use of diagnostic MRI as the reference standard, due to a lack of surgical pathology specimens in these patients, to which PET/MRI and PET/CT were compared. A better reference standard would have been a “consensus read” with multiple readers considering all available imaging data to formulate a reference standard T and N stage for the patients with rectal cancers. Alternatively the 5-year local or distant recurrent rates and disease free overall survival would have provided the best measures of rectal cancer staging. However due to limitations in the practicality of having multiple readers and the time frame of the study in chapter 5 of this thesis, both of these options were not feasible.

There were a number of patient related factors that limited the use of PET/MRI in this thesis. These may subsequently limit the clinical application of PET/MRI as a single examination imaging modality for the complete staging of CRC. For example, patients who are pregnant, have limited mobility or are diabetic,

may not be appropriate for PET/MRI examination. This is because prior to imaging patients must be fasted for 4-6 hours and minimal movement after FDG are essential to prevent excess skeletal muscle uptake away from the tumour of interest. For diabetic patients, aside from the clinical implications of impaired glucose tolerance whilst in the fasting state prior to scanning, those patients taking metformin medications are susceptible to false negative cancer detection due to this particular medication diffusely increasing bowel activity (Steenkamp, McDonnell, and Meibom 2014). Therefore in these diabetic patients, the use of alternative medications or consideration of the necessity and benefits of PET/MRI over conventional imaging modalities should be carefully considered.

There were also a number of imaging related factors that limited the use of PET/MRI in my thesis. These include the associated risks encountered with a static strong magnetic field. As such, patients with cardiac pacemakers or metallic implants are contra-indicated with this imaging modality due to the significant risk of device malfunction caused by localised heating effects or movement. Patient comfort prior to and during the scan was also limited in some patients. This is because in each chapter of my thesis, the radiotracer FDG was injected 60-90 minutes prior to PET/CT and PET/MRI imaging being undertaken. In conjunction with patients lying in a prone position for 45 minutes whilst relatively long PET/MRI acquisitions were performed which may often have been claustrophobic due to the scan design. In addition PET/MRI examination also has a far larger signal to noise ratio in comparison to PET/CT. Together all of these factors contribute to excess patient discomfort and may restrict the clinical use of PET/MRI.

A basic PET/MRI protocol includes only AC and anatomic localisation with 2-point Dixon VIBE and takes 20 minutes (Drzezga et al. 2012). In contrast a typical

whole body PET/MRI imaging study may take at least 60 minutes whilst PET/CT takes 15 to 30 minutes (Bashir et al. 2015). The PET/MRI acquisitions used within each study of this thesis were in effect a variation of “ultra-fast” PET/MRI protocol. The PET/MRI protocol used in this thesis consisted of T2 HASTE and T1 Dixon large field of view images over the five bed positions to cover the whole body. From the five sections imaged with PET/MRI, the pelvic region containing the rectum had the DWI sequences added. Considering the maximum scan time a patient can comfortably tolerate is 1 hour, the choice of protocol used in this thesis was to aim for whole body PET/MRI large field of view images as opposed to sequential small field of view images, which would have inevitably increased the scan time and potentially any patient discomfort. In effect the study in chapter 5 has compared if PET with fast but low resolution whole body MRI sequences may potentially produce comparable diagnostic accuracy for T and N staging of the rectum when compared to the clinical standard of high resolution MRI. However when considering the true value of PET/MRI as a diagnostic imaging modality in rectal cancer, the results from chapter 6 which include distant staging of any potential metastases must be taken into consideration, which high resolution whole body small field of view MRI is not capable of producing within an acceptable scanning time-frame.

The financial feasibility of PET/MRI has not been reviewed in this thesis. In order to consider the effectiveness of a new imaging modality a cost benefit analysis must be performed. Consideration must be made of the cost of the associated scan and trained personnel with comparison to the cost saving potential of a single examination with reduced radiation risk and improved patient satisfaction from potentially a faster time to diagnosis and treatment.

8.3 Suggestions for future work

The development of PET/CT and PET/MRI as single imaging modalities for the complete staging of patients with primary colon and rectal cancers has led to a range of various potential clinical uses. Hybrid PET/MRI scanners combine a highly sensitive PET system with the high contrast resolution of a 3-tesla MRI, as an integrated imaging system. The major limitation of PET/MRI has traditionally been adequate integration of PET and MRI systems to improve subsequent image quality, which has traditionally been susceptible to poor attenuation correction. As engineering advances continue to improve and PET/MRI evolves from a research tool to a clinically relevant imaging modality, it is likely that better image quality will subsequently result in improved staging accuracy in patients with CRC (Vandenberghe and Marsden 2015).

Specifically from this thesis there are a number of considerations for future work. Consideration of imaging protocols for PET/MRI as with loco-regional MRI functional sequences should be explored. In the future these may include dynamic contrast enhanced MRI, diffusion weighted MRI and blood oxygenation level dependent MRI and their incorporation into PET/MRI imaging systems. This may potentially result in a more extensive evaluation of tumour physiology and biology and thus a more detailed description of the tumour and disease stage, resulting in more timely and effective treatment options.

Throughout this thesis and all of the subsequent chapters the radionuclide tracer used has been fluorine-18 2-fluoro-2-deoxy-D-glucose (^{18}F -FDG). However there are a number of various other radionuclide tracers that in the future may be used to provide more accurate information as a non-invasive *in vivo* assessment of

different aspects of the cell cycle in patients with CRC. Future work from this thesis may concentrate on assessing cellular proliferation rates and hence clinically how aggressive in nature the tumour is through the use of the radionuclide FLT. Hypoxia may be measured through further work with the radionuclide FMISO, somatostatin receptors may be assessed with 68-GA-Dotatate and tumour angiogenesis may be measured through integrin concentration.

PET/MRI has developed from a research tool to a clinically important imaging modality and the more widespread availability of PET/CT make both imaging modalities good candidates for the initial staging of patients with CRC. However future studies could be developed to utilise the high contrast and spatial resolution of both imaging modalities for re-staging of patients with CRC. In patients with rectal cancers this would potentially enable an accurate assessment of complete clinical response to neo-adjuvant therapy. This may translate to clinical practice by patients considered high-risk undergoing neo-adjuvant therapy alone and avoiding an operative procedure. Instead these patients may be sequentially followed up with interval imaging and PET/CT and PET/MRI may be used to monitor the response to chemoradiation therapy. For patient with trans-mural or node positive colon cancers, the need for adjuvant treatment may also be assessed after an R1 surgical resection.

Work in this thesis has demonstrated that PET/CT as an established imaging modality and PET/MRI as an evolving imaging modality can be used as a non-invasive single examination for the complete staging of patients with primary CRC. Future studies from the principles of this thesis should assess the impact of a change in stage on the subsequent management of patients with CRC. This because a change in tumour stage from PET/CT or PET/MRI imaging will not necessarily result in a

change in the clinical management of the patient and improved patient outcomes. Therefore the true clinical translation and impact of PET/CT and PET/MRI may be assessed from further studies. The long-term benefits of PET/CT and PET/MRI should also be assessed by further studies concentrating on patient outcomes and ultimately survival. This could give a true reflection of the value of PET/CT and PET/MRI in assessing patients with primary colon and rectal tumours and the effect on the future pathological disease process.

Another factor that was not considered in the remit of this investigation but requires future investigation is the associated expense incurred with a cost-benefit analysis of PET/CT and PET/MRI imaging. This is an important factor when considering the advent of a new imaging modality and its availability to the general population with CRC. In future studies when considering a cost benefit analysis, the cost saving financial implications of improved tumour identification and disease extent resulting in more efficient patient stratification must be balanced against the direct costs incurred from imaging and the associated costs of the highly trained technical and medical staff.

8.4 Thesis conclusions

The value of PET/MRI and PET/CT in oncological imaging is based on the fundamental principle that abnormal alterations in intra-cellular biochemical reactions result in the development of malignancy. Positron-emitting analogue tracers may be synthesised from organic matter and utilised to demonstrate these intra-cellular sequential processes. The role of PET/CT and PET/MRI in combination with the glucose analogue FDG has been shown to be an effective and established imaging modality in evaluating tumour stage in patients with primary CRC.

Hybrid PET/MRI is able to provide high-resolution anatomical, molecular and functional information, which in combination allow the comprehensive assessment of tumour location and stage in a single imaging examination. PET/MRI is also able to provide loco-regional and systemic staging of CRC disease. Through incorporation into CRC protocols, patient pathways may be streamlined and provide an effective algorithm for more appropriate and timely treatment. PET/MRI has the benefits of superior soft tissue contrast resolution of MRI with multi-parametric MRI data, which make it a more advantageous imaging modality over PET/CT. In patients with primary CRC, tumour stage, potential resection margins, surgical approach, likelihood of local recurrence, appropriateness and timing of neo-adjuvant and adjuvant therapy may be effectively assessed with PET/MRI. This will ultimately result in an improved patient satisfaction, prognosis and long-term survival in comparison to conventional imaging modalities. From the work in this thesis, PET/MRI may have a potential role as a complimentary or alternative diagnostic imaging modality for selected patients with primary CRC.

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