Staging and management of primary and recurrent rectal cancer

Thesis submitted in accordance with the regulations of Imperial College

for the degree of

DOCTOR OF MEDICINE (Research), MD (Res)

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February 2019

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Dedication

I dedicate this thesis to my wife Maria and our son, Antonios, to my parents Antonios and Demetra, and my brother Charalambos.

Declarations

The work has not already been accepted in substance for any other degree and is not being concurrently submitted in candidature for any other degree.

I declare that this thesis is my work and that everything else is appropriately referenced.

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Acknowledgements

This work was carried out during my appointment as a Clinical Research Fellow in the Department of Colorectal Surgery between 2008 and 2012 at The Royal Marsden NHS Trust. I obtained grant funding from the Pelican Cancer Foundation and the Bowel Diseases Research Foundation (BDRF) to support the work reported in this thesis (Chapters: 5, 6, 7 and 9).

The design of the radiological and histopathology reporting proformas for the diagnostic studies in this thesis were undertaken by me with some guidance from my supervisors; the follow-up database was maintained by Professor Tekkis and myself; the data were collected by myself and Professor Tekkis. The data analysis and interpretation were performed by myself, following advice and discussion from my supervisors and statistician Suzanne St Rose.

I would like to thank Professor R John Nicholls for his significant contribution and critical judgement that enabled the completion of this project. I would also like to acknowledge and thank Mr Vasilis Constantinides, Mr Emile Tan, Mr Anthony Antoniou, Mr Shahnawaz Rasheed, Dr Sue Chua, Dr Muh Koh, Dr Uday Patel and Dr Gary Cook for their project contributions and advice.

Finally, I would like to thank my supervisors Professor Gina Brown and Professor Paris Tekkis, to whom I am greatly indebted for their expert guidance and encouragement throughout the past years.

Publications related to the thesis

1. Georgiou PA, Mohammed Ali S, Brown G, Rasheed S, Tekkis PP. Extended lymphadenectomy for locally advanced and recurrent rectal cancer. Accepted for publication. *Int J Colorectal Dis. 2017 Jan 27. doi: 10.1007/s00384-016-2711-6. [Epub ahead of print]*

2. Georgiou PA, Bhangu A, Brown G, Rasheed S, Nicholls RJ, Tekkis PP. Learning Curve for the Management of Locally Advanced Primary and Recurrent Rectal Cancer: a single team's experience. *Colorectal Dis. 2015 Jan;17(1):57-65. doi: 10.1111/codi.12772. PMID: 25204543*

3. Georgiou PA, Tekkis PP, Constantinides VA, Patel U, Goldin RD, Darzi AW, John Nicholls R, Brown G. Diagnostic accuracy and value of magnetic resonance imaging (MRI) in planning exenterative pelvic surgery for advanced colorectal cancer. *Eur J Cancer. 2013 Jan;49(1):72-81. doi: 10.1016/j.ejca.2012.06.025. Epub 2012 Oct 1. PMID: 23036847.*

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5. Panagiotis Georgiou, Emile Tan, Nikolaos Gouvas, Anthony Antoniou, Gina Brown, R John Nicholls, Paris Tekkis. Extended Lymphadenectomy versus Conventional Surgery for Rectal Cancer: a Meta-Analysis. *Lancet Oncology. 2009 Nov;10(11):1053-62.*

Presentations related to the thesis

International Oral Presentations

1. SC Chua, PA Georgiou, G Brown, GJ Cook, B Drake, A Antoniou, P Tekkis. "The added value of combined 18F-FDG-PET-MRI in the preoperative assessment of local tumour invasion in recurrent and locally advanced primary rectal cancer using pelvic compartmental analysis." *European Association of Nuclear Medicine 2011, Birmingham, UK.*

2. P. A. Georgiou, G. Brown, A. Antoniou, M. Akmal, R. J. Nicholls, P. P. Tekkis. "Learning Curve for the Management of Locally Advanced Primary and Recurrent Rectal Cancer: a single team's experience." *(LP). European Society of Coloproctology (ESCP) 2010, Sorrento, Italy.*

3. P. A. Georgiou, P. P. Tekkis, S. Chua, G. Cook, V. A. Constantinides, A. Antoniou, G. Brown. "Accuracy of ^{18}F-FDG-PET/CT and MRI in predicting local tumour invasion within different pelvic compartments in recurrent and locally advanced primary rectal cancer." *(LP). ESCP 2010, Sorrento, Italy.*

4. P. Georgiou, S. Ali, G. Brown, A. Antoniou, A. Darzi, R. Nicholls, P. Tekkis. "Extended Lymphadenectomy For Recurrent And Locally Advanced Primary Rectal Cancer." (*LP). ESCP 2010, Sorrento, Italy.*

5. S. Ali, V. Constantinides, P. Georgiou, G. Brown, R. Goldin, A. Antoniou, P. Tekkis. "Survival And Metastatic Patterns Of Signet Cell And Mucinous Carcinoma Vs Adenocarcinoma Of The Colon And Rectum." (*LP). ESCP 2010, Sorrento, Italy.*

6. M. Alfa-Wali, P. A. Georgiou, A. Antoniou, R. J. Nicholls, P. P. Tekkis**.** "Inflammatory bowel disease (IBD) and colorectal cancer (CRC): a meta-analysis." (*LP). ESCP 2010, Sorrento, Italy.*

7. Georgiou Panagiotis, Gouvas Nikolaos, Tan Emile, Antoniou Anthony, Brown Gina, Tekkis Paris P. "Extended versus Non-Extended Lymphadenectomy for

Rectal Cancer: A meta-analysis." (*LP). ESCP September 2009, Prague, Czech Republic.*

8. Georgiou P, Brown G, Constantinides V, Antoniou A, Nicholls R. J., Tekkis P. P. "Diagnostic accuracy of MRI in assessing tumor invasion within pelvic compartments in recurrent and locally advanced rectal cancer." *American Society of Colon and Rectal Surgeons (ASCRS) May 2009, Florida, USA*

International Poster Presentations

1. P. A. Georgiou, P. P. Tekkis, U. Patel, A. Antoniou, A. W. Darzi, D. Cunningham, D. Koh, G. Brown. "The added value of Diffusion Weighted MRI in the local staging in advanced colorectal pelvic cancer." *Association of Clinical Oncology of America (ASCO), 2010.*

2. P. P. Tekkis, P. A. Georgiou, V. A. Constantinides, U. Patel, A. Antoniou, R. D. Goldin, A. W. Darzi, D. Cunningham, R. Nicholls, G. Brown. "Diagnostic accuracy and value of magnetic resonance imaging (MRI) in planning exenterative pelvic surgery for advanced colorectal pelvic cancer*." Association of Clinical Oncology of America, 2010.*

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5. Georgiou Panagiotis, Gouvas Nikolaos, Tan Emile, Antoniou Anthony, Brown Gina, Tekkis Paris P. "Extended versus Non-Extended Lymphadenectomy for Rectal Cancer: A meta-analysis."
   i. *ESCP September 2009, Prague, Czech Republic.*
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6. Georgiou Panagiotis, Brown Gina, Constantinides Vasilis, Antoniou Anthony, Nicholls R. J., Tekkis Paris P. "Diagnostic accuracy of MRI in assessing tumour invasion within pelvic compartments in recurrent and locally advanced rectal cancer. "
   i. *ESCP September 2009, Prague, Czech Republic.*
   ii. *ASCRS, May 2009, Florida, USA.*

National Oral Presentations

1. P. Georgiou, S. Ali, G. Brown, A. Antoniou, A. Darzi, R. Nicholls, P. Tekkis. "Extended Lymphadenectomy For Recurrent And Locally Advanced Primary Rectal Cancer." *ACPGBI 2010, Bournemouth, UK.* ***Best 15 posters; chosen for oral presentation.***

2. Georgiou Panagiotis, Gouvas Nikolaos, Tan Emile, Antoniou Anthony, Brown Gina, Tekkis Paris P. "Extended versus Non-Extended Lymphadenectomy for Rectal Cancer: A meta-analysis." *BASO November 2009, London, UK.*

3. Georgiou Panagiotis, Tan Emile, Chua Sue, Purkayastha Sanjay, Brown Gina, Tekkis Paris P. "Diagnostic Precision of Positron Emission Tomography Compared to Conventional Diagnostic Investigation in Managing Recurrent Rectal Cancer." ACPGBI June 2009, Harrogate, UK

National Poster Presentations

1. P. Georgiou, S. Ali, G. Brown, A. Antoniou, A. Darzi, R. Nicholls, P. Tekkis. "Extended Lymphadenectomy For Recurrent And Locally Advanced Primary Rectal Cancer." *ACPGBI 2010, Bournemouth, UK.* **Best 15 posters; chosen for oral presentation.**

2. P. A. Georgiou, G. Brown, A. Antoniou, M. Akmal, R. J. Nicholls, P. P. Tekkis. "Learning Curve for the Management of Locally Advanced Primary and Recurrent Rectal Cancer: a single team's experience. "
   i. *BASO 2010, London, UK*
   ii. *ACPGBI 2010, Bournemouth, UK;*

3. Georgiou Panagiotis, Tan Emile, Chua Sue, Purkayastha Sanjay, Brown Gina, Tekkis Paris P. "Diagnostic Precision of Positron Emission Tomography Compared to Conventional Diagnostic Investigation in Managing Recurrent Rectal Cancer." *BASO November 2009, London, UK*

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Abstract

Introduction: Currently in the UK, 11-14000 patients are diagnosed with rectal cancer each year sixteen percent of whom will have a locally advanced primary rectal cancer requiring exenterative pelvic surgery (extending beyond the conventional anatomic boundaries of anterior resection surgery). A further 10-20% of patients suffer local recurrence that may be amenable to exenterative surgery. The surgical management, the radiological assessment and clinical outcomes have been poorly understood and largely limited to self-reported personal series. The aim of this thesis was to evaluate surgical optimisation and staging assessment in this group of patients.

Methods: The role of lateral pelvic sidewall lymphadenectomy in optimising outcomes for patients with locally advanced and recurrent rectal cancer was examined through a meta-analysis of the literature and a prospective database of patients undergoing exenterative surgery at the Royal Marsden. The safety and feasibility of exenterative surgery were evaluated using as endpoint the diagnostic accuracy of modern imaging techniques (PET-MRI fusion, diffusion weighted MRI and high resolution MRI) in this patient undergoing exenterative surgery compared to histopathology. The learning curve of exenterative surgery was evaluated using a Risk Adjusted Cumulative Sum (RA-CUSUM).

Results: Extended lymphadenectomy showed no significant benefit. MRI was overall very accurate in predicting tumour invasion within the pelvic compartments (ROC≥0.877). Patients with invasion of the anterior above the peritoneal reflection compartment were shown to have poorer prognosis (HR=4.621, p=0.012). Diffusion weighted MRI did not improve overall accuracy. PET MR image fusion was feasible with very good diagnostic accuracy for all the compartments. Finally, a colorectal

surgeon required a minimum of 14 cases under supervision to improve the morbidity following exenterative pelvic surgery for locally advanced primary and recurrent rectal cancer.

Future studies: The findings need to be tested prospectively in multicentre studies to validate the results of the learning curve, staging and lymphadenectomy.

CHAPTER 1: Introduction and literature Review

1.1 History and prevalence of primary and recurrent rectal cancer surgery

1.1.1 History of primary rectal cancer surgery

The first attempts to surgically treat rectal cancer took place during the 18th century when Giovanni Morgagni was the first to suggest that resection of the rectum could be used as a treatment of rectal carcinoma. Operating at that time was performed without general anaesthesia and haemostasis, carrying a significant risk for mortality and morbidity. The first two reported resections were unsuccessful with the patients not surviving the operation (1).

The first attempt to resect the rectum was performed by accident in 1739 by Jean Faget, when he was aiming to drain an ischio-anal abscess but instead found a perforated rectal cancer (1). The patient died following the operation as he was left with an "uncontrollable anus." The second recorded attempt to resect an annular obstructing lesion had also resulted to the patient not surviving the operation. (2)

It was not until 1826 when the first “successful” resection of the rectum was performed by LisFranc (3). This success was followed by five more successful operations from a total of nine that LisFranc performed over the following seven years. These procedures were performed without anaesthesia and haemostasis and carried significant risks of postoperative morbidity. Severe pain, sepsis and major bleeding were the most prevalent complications. The oncological outcomes were poor with any patients that survived the initial operation, ultimately succumbing to

recurrence and death. During that era of surgery, the operation was considered successful if the patient could be discharged home following the procedure (4).

The application of the aseptic technique and the introduction of general anaesthesia enabled the performance of more advanced procedures, with Theodor Kocher proposing the transacral resection of the rectum which was further developed by Paul Kraske aiming to improve operative exposure (5, 6). Carl Gussenbauer followed on this work by using an abdominal approach to resect the tumour (7) and Hochenegg (8) used a ‘‘pull-through’’ (duerchzug) technique to perform a recto-anal anastomosis.

1.1.2 Abdomino-perineal resection of the rectum

Vincent Czerny in 1884 was most likely the first surgeon to introduce the abdominoperineal resection when he recognised that the tumour could not be removed perineally and turned the patient supine completing the procedure through the abdomen. The patient did not survive surgery. It was Ernest Miles who recognised that the tumour could spread not just by direct extension, but also the venous and lymphatic systems. Taking advantage of the larger operating field when combining the abdominal and perineal approach, he was the first to perform an "anatomically correct" resection of the rectum by also including in the resection specimen the draining lymph nodes (9).

Using this technique, Miles reported a reduction in recurrence rates to 29.5% (10). The most common complications were sepsis and blood loss resulting in a mortality rate of 31% as blood transfusion and antibiotics were not yet available. However, many surgeons suggested that the Miles procedure was too radical, carrying

significant risks of genitourinary and bowel dysfunction with adverse psychosocial implications. This led Cuthbert Dukes to further investigate the resected specimens following the Miles procedure and demonstrated that Miles overestimated tumour spread within the regional lymph nodes and that the majority of lymph nodes were much closer to the level of the primary tumour (11).

1.1.3 Anterior resection of the rectum

The poor functional outcomes, led surgeons to focus their efforts in evolving their surgical technique to reduce the insult with less radical resection. Donald Balfour described the technique of the anterior resection with the performance of an end-to-end anastomosis (12). Dukes' findings that Miles' overestimation of tumour spread, led other surgeons to investigate the further potential of anterior resection as an alternative for cure, with the advantage of maintaining the bowel continuity. Anterior resection was not widely adopted until 1948 when Claude Dixon demonstrated that it was safe to perform (13). In a series of 426 patients, the mortality and five year survival rate was shown to be improved to 5.9% and 67.7% respectively (13). Anterior resection was only performed for tumours that were more than 5 cm above the anal verge as it was believed at the time that 5 cm distal margins were essential to achieve a curative resection. The possibilities for further development of the anterior resection were realised after a published study demonstrated that up to 2 cm distal margins from the tumour do not compromise the oncological result in terms of survival and local control (14). Subsequently sphincter preservation procedures were introduced as the standard in cases when the tumour did not directly involve the sphincter. In 1986 the creation of a colonic pouch combined with colo-anal anastomosis was proposed (15, 16) improving the bowel functional outcomes (17).

This study demonstrated that the daily frequency of bowel movements, the ability to defer defaecation and the degree of incontinence were significantly improved with colonic pouch. These results were evident during the first two months following surgery.

1.1.4 Total Mesorectal Excision

In 1982, Heald proposed the existence and role of the “mesorectum” as a fatty envelope containing all the local disease spread from the primary tumour with its origins derived from the embryological hindgut (18). This led him to further investigate the "holy plane" around the embryologic hindgut (mesorectum) and propose a standardised oncological approach that required sharp dissection of the mesorectum to remove the primary, and all localised disease. The operation became popularised as total mesorectal excision surgery (19). Adherence to the mesorectal planes could potentially improve the oncological outcomes while preserving the sphincter and maintain a good quality of life. In 1992, he successfully demonstrated that total mesorectal excision significantly reduced the local recurrence rate especially for patients with Dukes' B and C' stage cancers (20). These findings along with the findings that the distance of 2 cm from the distal surgical margins is safe, (14) have probably been the most significant milestones in rectal cancer surgery and have led rectal cancer surgeons to widely adopt the technique of total mesorectal excision, welcoming the option to preserve the sphincter and bowel function without compromising the oncological outcome.

1.1.5 Extended lateral pelvic sidewall lymphadenectomy

Between 30-40% of patients treated for rectal cancer present with lymph node metastases. These can occur either along the mesorectal nodal chain along the inferior mesenteric artery nodes in around 40 percent of patients, and/or to the lateral pelvic lymph nodes (along the obturator, internal iliac and medial aspect of the external iliac artery) in 10-25 percent of patients. (55, 56, 57) The presence of lateral lymph node metastasis in rectal cancer was first reported in the 1950s (21) and nodal involvement has subsequently been shown to be associated with a poorer prognosis, (22-27) higher incidence of local recurrence and reduced survival (22, 23, 25, 26).

In Western countries total mesorectal excision (TME) has become the operation of choice for low rectal cancer (18). The technique is associated with a low incidence of local recurrence and facilitates sparing of the pelvic autonomic nerve plexuses (19, 20, 28, 29). With the introduction of neo-adjuvant radiotherapy combined with TME local recurrence rates of less than 10 per cent have been achieved (30). Western surgeons do not utilise extended lymphadenectomy regularly and this may pose a risk of local recurrence in the pelvic sidewall in patients who have undergone potentially curative surgery, without pre-operative radiotherapy. Whether pelvic sidewall lymph nodes should be considered metastatic disease or part of the regional lymphatics remains a contentious issue.

Based on the above, Japanese surgeons have adopted the technique of extended lymphadenectomy (EL) to supplement the total mesorectal excision aiming to minimize local recurrence and improve survival (31-33). The disadvantages of extended lymphadenectomy may include increased rates of autonomic nerve

dysfunction such as urinary and sexual impairment and intra-operative adverse events (33, 34). There has also been interest in neo-adjuvant radiotherapy in addition to TME and Nagawa *et al* (35) showed that the addition of extended lymphadenectomy to surgery, when neo-adjuvant radiotherapy had been previously applied, did not significantly alter the local recurrence and survival rates.

Even though there have been a number of published studies assessing the added value of extended lymphadenectomy to traditional rectal cancer surgery (TME). The findings have been contradictory without clear evidence of its value, and therefore there is a need for a meta-analysis to include the findings of published studies to provide an answer to this question.

In addition, the value of extended lymphadenectomy has not been assessed in patients with locally advanced primary and recurrent rectal cancer.

All the efforts of these great surgeons have significantly changed the management of these patients, improving the oncological outcomes and their quality of life. However, the recurrence rates following curative resection of the primary tumour are still considered high, necessitating more radical resection (exenterative procedures) such as abdominosacral resection of the rectum and total pelvic exenteration, which involves the removal of the adjacent pelvic organs and structures.

1.2 History of recurrent rectal cancer surgery

The development of the above techniques and the knowledge acquired from the "mistakes" of the past have resulted in the progressive reduction of the local recurrence rates. The recurrence rates remain high though, necessitating drastic measures to resect the cancer and improve the oncological outcome. The extensive lymphatic system of the mesorectum increases the likelihood a local failure to occur within the pelvis. Local recurrence can be either isolated to the anastomosis or more extensive invading adjacent organs and structures.

The patterns of recurrence significantly vary and therefore the management plan should be made on an individual basis. A surgical plan can be made with the help of radiological modalities such as MRI and CT scan, modalities that were significantly improved in the recent years enabling better detection rates and earlier identification of recurrences. Isolated anastomotic recurrences may be dealt with local resection, but more extensive disease needs to be addressed with more radical resection. Pelvic exenteration when the tumour invades adjacent structures, with lateral extended lymphadenectomy when the tumour invades the lateral pelvic structures. When the tumour invades the sacrum, removal of the tumour along with the sacrum is required, a procedure called abdominosacral resection.

The absence of decent diagnostic tools, lack of knowledge and the anatomical/surgical challenges, have resulted in a delay in the attempts to resect recurrent rectal tumours. Thus, advanced pelvic exenterative surgery for locally advanced primary and recurrent colorectal cancer was not considered as an option for cure, until the mid-90s. Brunschwig (36) was the first to describe a pelvic exenterative

procedure in 1948. He performed the procedure in 22 patients and reported high mortality and morbidity rates. Numerous studies have been published since with a significant variation in the reported mortality and morbidity rates. This is mainly due to the differences in the patient selection. Wanebo (37) was the first to report in 1981 on the performance of abdominosacral resection in 11 patients with locally advanced primary (1) and recurrent colorectal pelvic cancer (10). The procedure was performed following radiotherapy and reconstruction was performed to close the pelvic and perineal defect. The reported mortality and morbidity rates were also high. The development of the technology and the knowledge acquired from performing these procedures had led to the improvement of the patient selection, surgical technique and medical therapy. Studies from various tertiary centres in the world have been published showing an improvement of results with time but with mortality and morbidity rates remaining high.

1.3 Incidence of primary and recurrent rectal cancer

Colorectal cancer is a major health problem with an annual incidence of more than a million new cases worldwide, with up to 50% mortality (38). It is estimated that about 2.8 million persons are alive with colorectal cancer worldwide (38). Despite significant developments in surgery and neo-adjuvant and adjuvant medical therapy, up to 40% of patients develop local recurrence and / or distant metastases (39-42). Local recurrence rates have been reported as low as 2.5% (43) but can range up to 30%, with distant hepatic or lung metastases developing in up to 20% and 9% of patients respectively (42). It has been reported that 85% of the recurrences occur within the first three years following surgery (44). A third of the patients operated for primary rectal cancer will be free of distant metastases and may be eligible for a

curative resection. For this group of patients, radical resection is the only potentially curative treatment as chemotherapy and radiotherapy are unlikely to result in cure and are used for palliation when used alone. Curative resection is possible in less than 33% of cases, amounting to approximately 150-250 new cases per year in the UK (45).

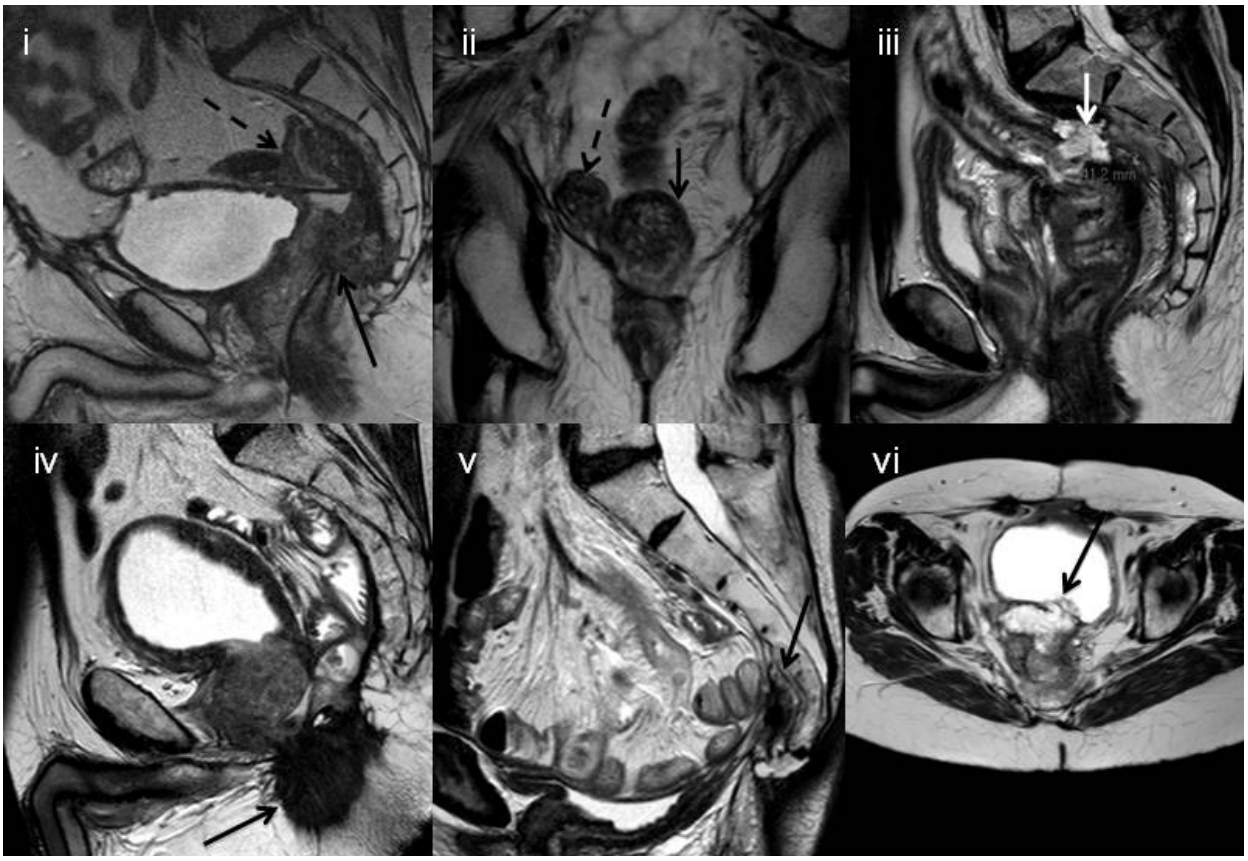
Currently in the UK, there are approximately 11 - 14 000 newly diagnosed patients with rectal cancer each year (46). Up to sixteen percent will have a locally advanced primary rectal cancer requiring exenterative pelvic surgery similar to the surgery performed for recurrent rectal cancer.

1.4 Patterns of recurrence

Tumour recurrence may invade any of the intrapelvic structures. It may be progressing anteriorly, posteriorly, laterally or inferiorly. In some occasions it may be isolated at the anastomosis or invading the peritoneum and/or large and small bowel. Published data suggest that the posterior intrapelvic compartment (figure 1) that includes the presacral fascia, retrosacral space and sacrum, is the most common site of local recurrence, representing up to 56.6% of local recurrences (47-51). Anterior below the peritoneal reflection compartment has been shown to be the second most commonest site of recurrence, ranging up to 50.9% of local recurrence (48). This includes the genitourinary system. Invasion of the lateral compartment structures has been demonstrated to be up to 26.7% of local recurrence (49). Lateral compartment structures include the ureters, iliac vessels, lateral pelvic sidewall lymph nodes, fascia and bone as well as the roots of the sciatic nerve. Anastomotic (central compartment) recurrence has been shown to range up to 33.9% of local recurrences (47, 52-54).

Involvement of the perineum and perineal scar (inferior compartment) following abdominoperineal excision of rectum (APER) has been shown to be up to 14% of all recurrences. (55) Extent of tumour within a bowel loop has been also reported at the range of 14% (55).

Figure 1. Patterns of recurrence



MRI images showing tumour invasion within different pelvic compartments.

i: Sagittal MRI image showing tumour invasion at the peritoneal reflection anterior above and below the peritoneal reflection.

ii: Coronal MRI image demonstrating a central and lateral compartment invasion

iii: Sagittal MRI image showing a mucinous central recurrence fistulating towards the posterior compartment

iv: Sagittal MRI image demonstrating an inferior compartment recurrence that invades at the anterior below the peritoneal reflection compartment

v: Sagittal MRI image demonstrating a posterior compartment recurrence

vi: Axial MRI image demonstrating a central recurrence invading the anterior below the peritoneal reflection compartment

1.5 Local preoperative staging for locally advanced primary and recurrent rectal cancer

Accurate local staging is critical for the management of this group of patients. It can provide information about the extent of the disease, the type of surgery that would be required to achieve a complete removal of the tumour and the likelihood of a complete tumour resection. It also allows a detailed discussion within a multidisciplinary team to plan neo-adjuvant, adjuvant and palliative therapy.

1.5.1 Endorectal Ultrasound

Endorectal ultrasound (EUS) has been used to diagnose recurrent disease with adequate sensitivity and specificity, (56, 57) facilitating at the same time the performance of biopsies. A meta-analysis demonstrated that EUS is very accurate in staging advanced (T4) rectal cancer with 95% sensitivity and 98% specificity (58). However, it provides limited information on the extent of the disease within the adjacent structures and cannot safely assess the tumour resectability. USS has limited field of view and cannot be performed when there is significant stenosis caused by intra-luminal tumour or extra-luminal pressure by tumour (59). It has limited value following APER when it can only be used transvaginally in female patients to assess tumour invasion in the anterior structures. Therefore, its value is very limited in the preoperative assessment and staging of this group of patients; and is gradually abandoned. It may be used for the detection of the recurrence when there is an anastomosis.

1.5.2 CT

Computer tomography (CT) is the most commonly used radiological modality for staging primary and recurrent rectal cancer. CT has been demonstrated to have a sensitivity up to 95% in detecting local recurrence (60, 61). However, it may often have difficulties distinguishing disease recurrence from tissue fibrosis (62, 63) and has the tendency to overstage bladder involvement (64). This becomes even more difficult if radiotherapy had previously been applied or there was previous pelvic sepsis from an anastomotic dehiscence (65). Blomqvist *et al* demonstrated that the sensitivity of CT was low in diagnosing tumour invasion within the anterior structures (bladder and uterus; 50%) and loco-regional lymph nodes (33%) (66). The sensitivity was further reduced to 25% and increased to 50% respectively following radiotherapy. One study assessed the ability of CT scan to determine the extent of the pelvic disease, demonstrating an overall accuracy of 87% (77.5% - 93%) (64). CT scan for tumours confined in the pelvis was higher (89%) than the tumours that were extending into the abdomen (80%) (64).

1.5.3 Magnetic Resonance Imaging

Magnetic Resonance Imaging has been shown to be of high value in the pre-operative staging of locally advanced primary and recurrent colorectal intrapelvic cancer, providing significant anatomical details that enable the planning of neoadjuvant therapy and surgery (67, 68). In the institutions that this study took place, the patient selection is performed by employing a number of radiological modalities such as CT, MRI and PET scan in order to better facilitate the decision-making process. MRI has a fundamental role when surgery is considered as an option for treatment as it

accurately depicts the pelvic anatomical structures and compartments relevant to surgery (67, 68). Previous studies had shown MRI to be highly accurate in detecting colorectal tumour invasion into pelvic structures such as the prostate, seminal vesicles and the sacrum (69, 70). A more recent study reported that MRI is accurate in predicting the absence of disease to non-resected organs/structures (71). Messiou *et al* (69) demonstrated that the MRI was highly accurate in diagnosing tumour invasion into individual adjacent to the rectum anatomical structures but proved to be problematic when assessing the pelvic sidewalls (sensitivity= 70%) and the female reproductive organs (specificity= 33%). Compared with CT, MRI can more accurately differentiate recurrent cancer within a presacral scar, based on differences in signal intensity between tumour and fibrosis using T2-weighted sequences or contrast-enhanced imaging techniques (72).

Several studies have been performed assessing the value of MRI in predicting tumour invasion within the different intrapelvic organs. However, no study at the start of this thesis has evaluated its accuracy in predicting tumour invasion in the different pelvic compartments, this is of greater surgical relevance as it would dictate the type of surgery required to remove the tumour. Similarly, no study has been performed to assess the value of MRI in predicting the oncological outcome based on its findings.

1.5.4 Diffusion weighted Magnetic Resonance Imaging

Diffusion-weighted MR imaging is a functional radiological modality that can provide indirect information about the water proton mobility within biologic tissue, (73, 74) without the need of a contrast agent (75-77). Thus, a few studies have been

performed aiming to exploit the features of diffusion-weighted imaging and try to characterise the cellular composition of different tissues. Diffusion weighted MR imaging has since found widespread application in the management of acute cerebral ischemia as it has been demonstrated to be highly accurate in its early detection (78-80).

Consequently, there has been a rising interest about the diagnostic value of diffusion weighted MRI in oncology. Findings of recent studies suggested that the management of patients with different cancers could be benefitted from the additional information DW-MRI can provide (81-86). In colorectal cancer, there have been a number of studies investigating the DW-MRI's efficacy in the management and prediction of oncological outcomes. In a series of 33 patients Ichikawa et al (87) showed that DW-MRI is highly accurate in detecting colorectal cancer. Sun et al (88) investigated its value in a series of 37 patients with locally advanced primary rectal cancer, concluding that it can be used to predict tumour response to chemoradiotherapy. Another study compared it with Positron Emission Tomography (PET) in a series of twenty-five patients with colorectal cancer and reported it to be inferior in the detection of primary lesions but superior to PET in the detection of lymph nodes metastases. Lambregts *et al* (89) however, demonstrated that it is not reliable to stage local lymph nodes following radiotherapy if used alone. The main benefit of adding DW-MRI in the same study was the increased number of detected lymph nodes and the improved positive predictive value for the identification of metastatic lymph nodes. Kim et al (90) demonstrated that there is a role for DW-MRI as it can improve the diagnostic accuracy of MRI in the evaluation of the tumours' response to neoadjuvant chemoradiotherapy.

Diffusion-weighted MRI has been evaluated in colorectal cancer, mainly in assessing the presence of a recurrence or the tumour response to chemoradiotherapy. No study has been performed investigating its value in predicting tumour invasion in the different intrapelvic compartments.

1.5.5 PET and PET/CT

Positron Emission Tomography (PET) scan is an accurate diagnostic tool and may have advantages over CT and MRI in discriminating fibrosis from cancer (91). Exploiting the enhanced uptake of FDP-glucose by tumour cells, PET is able to detect both local recurrence and distant metastases. A meta-analysis demonstrated a PET sensitivity and specificity of 94% for detecting local recurrences (92) with high accuracy in detecting pelvic recurrence in patients who had previously been irradiated (93). However, limitations of PET scan include the inability to identify small volume disease and a relatively low sensitivity for detecting lymph node metastases (94). Mucinous adenocarcinomas have poorer FDG uptake and therefore can be easily missed by PET scan (95). In an effort to increase the confidence in diagnosing recurrence, PET with CT (PET/CT) image fusion was performed. Sapir *et al* investigated the role of PET/CT in 62 patients demonstrated that PET/CT was more accurate than PET alone for detecting local recurrence (96) but is not very helpful in evaluating anatomical tumour changes following chemoradiotherapy (97). It might be useful in predicting pathological tumour response though (97-99).

1.5.6 Summary of strengths and weaknesses of CT, MRI and PET

CT and MRI have demonstrated high sensitivity in detecting local and distant recurrence and can provide detailed anatomical information of the affected organ and tumour extension into surrounding tissues (64, 100). One study evaluating the diagnostic precision of abdominal CT, has reported a 95% sensitivity for detecting local recurrence (60) and 78 - 90% for liver metastasis (101). However, CT may often have difficulties determining if a suspected pelvic mass represents disease recurrence or tissue fibrosis. This becomes even more difficult if radiotherapy had previously been applied or there was previous pelvic sepsis from an anastomotic dehiscence (65).

PET scan is an accurate diagnostic tool and may have advantages over CT and MRI in differentiating scar tissue from cancer (91). Exploiting the enhanced uptake of FDP-glucose by tumour cells, PET can detect both local recurrence and distant metastases. One study (93) showed that PET correctly identified pelvic recurrence in 16 out of 19 patients (87%) who had previously been irradiated. However, limitations of PET scan include the inability in identifying small volume disease (94) and a relatively low sensitivity for detecting lymph node metastases (94). Mucinous adenocarcinomas have poor FDG uptake (95) and therefore can be easily missed by PET scan.

There is a need for a meta-analysis comparing the above radiological modalities in detecting local and distant metastases.

1.5.7 PET/MRI

In a need to eliminate the limitations of CT that brought into PET/CT, researchers in started fusing the images of PET and MRI for different conditions, using software.

The published results were promising and sparked a growing interest in the development and potential value of a new radiological modality, PET/MRI, which can be used in the management of different cancers and other non-malignant conditions. At the time of the writing of this study there has not been any published study documenting the industrial production and value of a PET/MRI scanner for humans. There are studies though investigating smaller versions of this type of scanners for research purposes reporting that there might be a diagnostic value but more research is still required to reduce the errors and artefacts introduced from the combination of these two modalities (102-104). A number of studies evaluated the potential benefit of this new modality in oncology and non-oncology pathologies, using different fusing techniques and demonstrated very encouraging initial results (105-109).

There has been no study evaluating the value of fusion PET/MRI in the management of locally advanced primary and recurrent rectal cancer.

1.6 Classifications of locally advanced primary and recurrent rectal cancer

In the effort to establish criteria that would enable better prediction of tumour resectability and outcome, several classifications have been proposed. The Mayo clinic classified local recurrence according to the points of tumour fixation and pathological findings (110) while Yamada *and al* described local recurrence by the pattern of pelvic fixation into localised, sacral, or lateral (111). Other proposed classification systems (48) are based on the UICC TNM system (112). The Memorial Sloan Kettering group have categorised local recurrence based on the anatomical site of invasion by the tumour (113-115).

None of the existing classifications provides all the information required for the surgeon to plan the extent of the surgery required to achieve a complete oncological resection of the tumour. Therefore a new classification needs to be developed based on the fascial boundaries and planes of dissection between intra-pelvic organs (116).

Table 1. Local staging Classifications for locally advanced primary and recurrent rectal cancer

Study-Group	Classification	Definitions		Outcomes
Mayo Clinic (110)	Symptoms	S0	Asymptomatic	Pain free patients had better survival
		S1	Symptomatic without pain	
		S2	Symptomatic with pain	
	Degree and site of Fixation	F0	No fixation	More points of fixation resulted in more complications and worse survival.
		F1	Fixation to one point	
		F2	Fixation to two points	
		F3	Fixation to > 2 points	
Yamada (111)	Pattern of pelvic fixation	Localised	Invasion to adjacent pelvic organs or tissue	5-year survival of 38%
		Sacral	Invasion to lower sacrum (S3, S4, S5), coccyx, periosteum	5-year survival of 10%
		Lateral	Invasion to Sciatic nerve, greater sciatic foramen, lateral pelvic wall, upper sacrum (S1, S2)	5-year survival of 0%
RWC (48)	Five Stages	TR1	Limited invasion of the muscularis	
		TR2	Full thickness penetration of muscularis propria	
		TR3	Anastomotic recurrences with full thickness penetration beyond the bowel wall and into the perirectal soft tissue	
		TR4	Invasion into adjacent organs without fixation	

		TR5	Invasion of the bony ligamentous pelvis including sacrum, low pelvic/side walls, or sacrotuberous/ischial ligaments	
MSK (113-115)	Anatomical region involved	Axial Anterior Posterior Lateral	Anastomotic, mesorectal, perirectal soft tissue, perineum (APER) Genitourinary tract Sacrum and presacral fascia Soft tissues of the pelvic sidewall and lateral bony pelvis	Axial only recurrence has 90% likelihood of R0; Lateral recurrence is associated with 36% likelihood of R0.

Abbreviations: RWC= Roger Williams Medical Centre USA, MSK= Memorial Sloan-Kettering, RMH= Royal Marsden Hospital Group as proposed by the present thesis, APER= abdominoperineal excision of the rectum, PR= peritoneal reflection, AA PR= anterior compartment above the peritoneal reflection, AB PR= anterior compartment below the peritoneal reflection, R0= complete tumour clearance.

1.6.1 The Mayo Clinic Classification

The Mayo Clinic (110) classified recurrences according to symptoms and the degree and site of fixation. Asymptomatic patients were classified as S0 whereas symptomatic patients without or with pain were classified as S1 and S2 respectively. F0 was used to describe the absence of fixation; F1-2 corresponding to one and two points of fixation respectively; F3 corresponding to three or more sites of fixation. The degree of fixation was also described in terms of the site of fixation (anterior, sacral, right, or left) or invasion of adjacent structures. The patients that were presented without pain had better three (68.4% vs 31.6%) and five (37.3% vs 26.3%) year survival compared to the patients that were symptomatic with pain ($p=0.065$). They demonstrated that patients with more points of fixation (F1-3) had more complications following surgery and had worse three (35.7% vs 61.3%) and five (31.2% vs 50%) year survival compared to the patients with an F0 stage ($p=0.384$).

1.6.2 Kagoshima, Japan

Yamada *et al.* (111) classified local recurrence according to the pattern of pelvic fixation. They described the recurrence that is localised to adjacent pelvic organs or tissue as "Localised"; the recurrent tumour that invades the lower sacrum (S3, S4, S5), coccyx or periosteum as "Sacral invasive type"; and the recurrent tumour that invades the sciatic nerve, greater sciatic foramen, lateral pelvic wall or upper sacrum (S1, S2) as "Lateral invasive type". They demonstrated that the pattern of recurrence was a predictive factor for five-year survival following surgery ($p<0.001$). The five-year survival rate was 38%,

10% and 0% for patients with localised, sacral invasive and lateral invasive type of recurrence respectively.

1.6.3 Roger Williams Medical Centre, USA

Wanebo *et al*. (48) proposed a five stages classification system. They described intraluminal local recurrence at the anastomotic site as TR 1 or 2 corresponding to limited invasion of the muscularis and full thickness penetration of muscularis propria respectively. TR3 was to describe the anastomotic recurrences with full thickness penetration beyond the bowel wall and into the perirectal soft tissue. Invasion into adjacent structures/organs including vagina, uterus, prostate, bladder, seminal vesicles or presacral tissues with tethering but not fixation was described as TR4. Invasion of the bony ligamentous pelvis including sacrum, low pelvic/side walls, or sacrotuberous/ischial ligaments was described as TR5.

1.6.4 The Memorial Sloan Kettering Classification

The Memorial Sloan Kettering (MSK) group (113-115) have described a classification based on the anatomical region of the pelvis that is involved. They defined local recurrence as either axial, anterior, posterior or lateral. Axial recurrence was subdivided into anastomotic, mesorectal or perirectal soft tissue, or perineum if an APER was previously performed. Anterior recurrence involves the genitourinary tract including bladder, vagina, uterus, seminal vesicles and prostate whereas a posterior recurrence involves the sacrum and presacral fascia. Lateral recurrence involves the soft tissues of the pelvic sidewall and lateral bony pelvis. Moore et al from the MSK group (114)

demonstrated that axial only or axial/anterior only recurrences the likelihood for a complete resection was high (90% vs 43%, $p<0.001$ and 72% vs 42%, $p= 0.003$ respectively). The likelihood for a complete resection was significantly reduced though when there was a lateral recurrence (36% vs 65%, $p= 0.002$).

1.7 Imaging to exclude distant metastases

Accurate identification of extrapelvic disease is key for the decision to operate a patient. CT and MRI have demonstrated high sensitivity in detecting distant recurrence providing detailed anatomical information of the affected organ and tumour extension into surrounding tissues (64, 100). The accuracy of CT in detecting abdominal disease has been demonstrated to be over 85% (64) with the MRI appearing to have similar accuracy (67, 68).

A meta-analysis investigating the value of US, CT, MRI and PET in detecting liver metastases, demonstrated a sensitivity of 63%, 74.8%, 81.1% and 97.2% respectively and specificities of more than 93.8%, with MRI being significantly more sensitive than CT ($p= 0.05$) and equally sensitive to PET ($p= 0.02$) (117). There was no significant difference in the sensitivity of PET and CT ($p>0.05$) and neither between CT and US ($p= 0.45$) (117).

Positron emission tomography (PET) has been demonstrated to be highly accurate in the detection of disseminated disease (118-121) and to have significant impact on the management of patients with suspected recurrent colorectal cancer (122, 123). A meta-

analysis reported a PET sensitivity of 91% and specificity of 83% for the diagnosis of distant metastases (92). However the authors admitted that only 8/27 (29.6%) studies were of high quality fulfilling their quality criteria at least by 80%. Another study showed that the overall added value of PET in the management of patients with local and/or distant recurrent colorectal cancer is 8% and suggested that PET should be used when findings remain equivocal after serial imaging review (124). In the authors practice, all patients considered for a potentially curative surgical resection undergo a PET scan to exclude disseminated disease.

1.8 Selection Criteria for surgery

Decision for surgery is made after extensive discussions at the local multidisciplinary meeting and relies on the findings of the available diagnostic modalities. It is the radiological findings that will determine the tumour resectability. Therefore accurate preoperative staging can help to establish the extent of local disease and the presence or absence of distant metastases, which is imperative when considering patients for exenterative surgery for locally advanced primary or recurrent rectal cancer.

1.8.1 Distant Recurrence

The presence of distant metastases is normally considered as a contraindication for exenterative surgery for locally advanced primary or recurrent rectal cancer (125). However, a number of centres have demonstrated that synchronous or staged resection of locoregional recurrence and distant metastases can have acceptable results in highly

selected patients (126-128). It is generally contraindicated though, due to the significant morbidity that is may be associated with this type of procedures (48, 111, 129-131).

1.8.2 Resectable local recurrence

In the absence of distant disease, surgical resection of the primary cancer or the locoregional recurrence is the only potentially curative option. Surgery for advanced primary or recurrent rectal cancer includes a range of different procedures that depend on the extent of the disease and the specific organs/structures that are involved. Surgery has to be performed *en bloc* and is considered curative when the resection margins are free of microscopic disease (R0 resection). The presence of microscopic or macroscopic residual disease at the resection margins is defined as R1 and R2 resection respectively. It has been previously demonstrated that R1 or R2 resection can result in poorer survival (110, 132-134) and it should be consequently considered as palliative resection. This type of surgery carries considerable mortality and morbidity. Therefore the identification of patients that an R0 resection can be potentially achieved is crucial and extremely difficult. Preoperative imaging with PET, CT and MRI and clinical assessment are utilised in an effort to optimise the selection of patients in whom curative resection is considered possible as well as those in whom curative resection is an unlike scenario.

1.8.3 Contraindications for surgical resection

One of the key factors that guide patient management is the patient's fitness for surgery. It is essential to assess it prior to any discussion for surgical options since the lack of fitness is often considered a contraindication when undergoing such a major procedure,

due to the significant risk of death and complications. Operation is contraindicated in the presence of circumferential or extensive lateral pelvic sidewall involvement, involvement of the iliac vessels, bilateral ureteric obstruction, sciatic nerve involvement and para-aortic lymph node metastases (125, 126, 135-137). Involvement of the external iliac vessels may present with lower limp oedema whereas ureteric obstruction with hydronephrosis. Tumour invasion of the sciatic nerve may present with lower limp pain and weakness. Limited tumour invasion to the lateral pelvic sidewall and invasion of the sacrum above the S2 vertebrae are considered relative contraindications since there are surgical options in both cases (48, 129, 138) but the likelihood of a complete resection is considerably low while the perioperative risk of mortality and morbidity is higher.

1.8.4 Irresectable local recurrence

Surgical resection and chemoradiotherapy can be used for palliation, alleviating the patients' symptoms that are related to the organs/structure that are invaded by tumour. It has been suggested that palliative resection can have an improvement in quality of life and pain relief (139, 140). However its use can be usually unsuitable considering the co-morbidities related with this type of surgery (141). It is therefore important that the patients are carefully selected for palliative procedures taking into consideration possible co-morbidities and their social circumstances, as the benefits from these procedures are short term. The symptomatic relief can last up to 17 months with median symptom free interval of 4 months compared with 23 months for non-palliative procedures ($p<0.001$) (142).

1.9 Exenterative surgery for locally advanced primary and recurrent rectal cancer

The introduction of total mesorectal excision has significantly improved the local recurrence rates and survival, with the lateral pelvic sidewall lymphadenectomy still not to be widely accepted. However, local recurrence rates are still considered to be relatively high with significant variation between centres and among surgeons, ranging between 2.5 and 15% (43, 143-146). The only potential cure for these patients is radical surgery, in the form of exenterative pelvic surgery, including total pelvic exenteration and abdominosacral resection.

Patients with locally advanced primary rectal cancer requiring surgery beyond the boundaries of TME requires similar aggressive approach by performing exenterative pelvic surgery and abdominosacral resection when the tumour invades the sacrum. At the writing if this thesis, there have not been published data reporting the incidence of this group of patients.

1.9.1 Abdominosacral resection

Abdominosacral resection of the rectum was initially used to treat primary rectal cancers (147-151). Surgeons were using it as it provides good exposure of the rectum and tumour, allowing its wide resection, safe surgical margins and anastomosis. This procedure was used without the disruption of the anal sphincters and their innervation. One centre has suggested the use of abdominosacral resection for the surgical management of low rectal cancers, demonstrating similar oncological and functional results to the patients treated

with conventional abdominoperineal excision of the rectum (152-154). The high morbidity rates and the introduction of total mesorectal excision had led the surgeons to abandon it as treatment for non-advanced primary rectal cancer. Wanebo (37) was the first to perform abdominosacral resection for patients with locally advanced primary and recurrent rectal cancers. The results of operating on the first 11 patients were published in 1981, showing high rates of mortality and morbidity.

In the modern era of colorectal surgery, abdominosacral resection is used to treat locally advanced primary and recurrent rectal cancer when the cancer progresses posteriorly and breaches the retro-sacral fascia, therefore potentially threatening the posterior margins. Numerous studies (table 2) have reported their results of performing abdominosacral resections in patients with locally advanced primary and/or recurrent rectal cancer. The colorectal group of Mayo clinic (155) used intraoperative radiotherapy to supplement the abdominosacral resection and reported high rates of complete resections (R0= 87%) associated with morbidity (50%) and poor survival. The results of another published series of 12 patients (all with complete tumour clearance (R0)) (156) that underwent abdominosacral resection for recurrent rectal cancer showed the lowest morbidity at 42% but 3 year survival as low as 17%.

Results from studies that followed were more promising though. A study (137) where composite abdominosacral resection was performed in patients with locally advanced primary (n = 13) and locally recurrent rectal cancer (n = 37), demonstrated a 61% overall local control and 41% disease free 3 year survival. Yamada et al (157) used the

abdominosacral approach to treat patients with locally advanced primary (n=15/22; 68.18%) and recurrent (n=21/42; 50%) rectal cancer achieving overall curative resection of 79.69% and 23% overall 5-year survival. The Memorial Sloan Kettering Cancer Group demonstrated in a series of 29 patients a 62% complete tumour resection and 20% 5-year survival with significant morbidity though at the range of 59%. (158) Moriya et al (129) reported similar complete clearance rates at 84%. More studies have been recently performed and reported similar results as demonstrated in table (133, 153, 159, 160). One recent study has investigated the feasibility of laparoscopic abdominosacral resection in three patients with locally advanced primary rectal cancer and demonstrated that it is feasible providing an acceptable cosmetic result without compromising the oncological outcome (all patients had a complete tumour resection) (161).

Table 2. Studies reporting on abdominosacral resection for locally advanced primary and recurrent rectal cancer

Author	Year	Curative intent	R0 (n)	R0 (%)	R1 (n)	R1 (%)	R2 (n)	R2 (%)	Mortality (%)	Morbidity (%)	5 year Survival
Sagar (133)	2009	40	20	50	19	47.5	1	2.5	2.5	60	-
Ferenschild (159)	2009	25	19	76	4	16	2	8	0	68	30.00%
Williams (161)*	2008	3	3	100	0	0	0	0	0	100	-
Akasu (160)	2007	44	24	54.54545	13	29.55	7	15.90	2	61	34.00%
Melton (158)	2006	29	18	62.06897	10	34.48	1	3.44	3.4	59	43.00%
Moriya (129)	2004	57	48	84.21053	9	15.79	0	0	3.5	58	42.00%
Gonzalez (162)	2003	45	33	73.33333	12	26.67	0	0	4	56	32
Yamada (157)	2002	64	51	79.6875	13	20.31	0	0	1.6	56	-
Mannaerts (137)	2001	50	26	52	18	36	6	12	0	82	-
Weber (163)	2000	23	21	91.30435	2 **	8.70	0	0	0	43	-
Zacherl (156)	1999	12	12	100	0	0	0	0	0	42	-
Wanebo (48)	1999	53	45	84.90566	8 **	15.09	0	0	8	-	31
Magrini (155)	1996	16	14	87.5	2	12.5	0	0	0	50	-
Wanebo (164)	1994	47	40	85.10638	7 **	14.89	0	0	8.5	-	33

* this is a study reporting the feasibility of laparoscopic abdominosacral resection for locally advanced primary rectal cancer.

** these studies did not clarify between R1 and R2.

1.9.2 Total pelvic exenteration

Total pelvic exenteration involves the removal of the rectum with all the anterior structures, including the bladder, prostate and seminal vesicles (male patients) and vagina and uterus (female patients). It is performed when the primary or recurrent tumour invades the anterior structures of the pelvis. Ceulemans reported five cases in 1959 that performed a total pelvic exenteration to resect advanced rectal cancer (165). The perioperative risk associated with this group of patients was high at the time mainly because of their malnutrition and consequent hypoproteinaemia. The main operative challenge was the diversion of the urinary system as it was proved to carry a high risk for the development of a fistula (165). The first case was after a tumour was identified to invade the bladder while performing a Miles procedure. This patient died during the dissection of the perineum, secondary to significant intraoperative haemorrhage. The second case was complicated with sepsis and also diseased on day eight (described as "peritonitis"). The third patient died two weeks following surgery from pyelonephritis. The fourth patient's operation was complicated with a urinary fistula at the perineum. The tumour eventually invaded the spine paralysing the patient before he died. The fifth patient was operated for recurrence and was alive a year following the procedure deeming the procedure successful.

With the development and evolvement of the radiological modalities resulting in an improvement of the preoperative staging with more studies reporting their outcomes following total pelvic exenteration and demonstrating the potential benefits of the

procedure. Once more, there was wide variability on the reported outcomes. The perioperative mortality reported from the studies ranged between 0.3 and 8%, demonstrating at the same time significant perioperative morbidity ranging as low as 22% to as high as 71%. There were also significant variations in the reported clearance rates that were achieving. With the further improvement of diagnostic modalities, the total pelvic exenteration for female patients has been modified involving the resection of cancer with the posterior vaginal wall (posterior exenteration), (166-168) sparing the bladder and reducing the need to perform an ileal conduit or other forms of urinary diversion.

1.9.3 Mortality and morbidity following surgery for locally advanced primary and recurrent rectal cancer

Exenterative pelvic surgery (including abdominosacral resection) for locally advanced primary and recurrent rectal cancer carry significant mortality and morbidity. The rate of mortality was high during the initial period that exenterative pelvic surgery was performed. With the development of risk assessment tools and the advancement of anaesthesia and peri-operative care, the patient selection has been improved and consequently, a reduction of the mortality rate has been noticed. However, the rate is still considered high with more recent studies reporting rates that range from as low as 0.3% to up to 9% (130, 132, 164, 169-173).

Exenterative pelvic surgery (including abdominosacral resection) for locally advanced primary and recurrent rectal cancer carries significant risk for complications, both systemic and local. Morbidity has been reported to be as high as 82% (137). However, most of the studies report perioperative complications between 30 and 50% (129, 133,

155, 157). Complication rates following abdominosacral resection have been shown to be higher with the lowest rates reported at the range of 40% (156, 163).

With this variation in mortality and morbidity, the need to define the learning curve required to safely perform exenterative pelvic surgery for colorectal cancer was identified.

1.9.4 Survival & local recurrence rates following locally advanced primary and recurrent rectal cancer surgery

The survival of patients within this group has been reported to range between 18% and 58% at five years following surgery (137, 174). Patients with complete tumour resection (R0) were shown to have significantly better survival with the majority of the published studies reporting more than 35% five years survival following surgery (133, 174-178). Local recurrence rates have also been reported to vary significantly, with studies reporting rates between 24% (160) and 62%. (158)

A consisting finding among the published studies was that local recurrence rates were significantly influenced by the ability to obtain a complete tumour resection without any evidence of microscopic residual disease at the surgical margins (R0 resection). A number of studies have clearly demonstrated a statistically significant advantage of the patients that the tumour was completely removed (R0) compared to the patients that there was microscopically (R1) or macroscopically (R2) residual disease at the resection margins in terms of overall and disease-free survival (179).

Therefore, surgery is only considered curative when a complete tumour excision is achieved. There have been significant variations in the clearance rates that has been reported in literature, ranging as low as 20% (180) up to as high as 82% (155). The majority of the published studies however report rates approximately ranging between 30% to 60% of the operated cases (110, 133, 158, 160, 173, 175).

1.10 Conclusion

Despite these studies demonstrating the accuracy of MRI in diagnosing invasion or absence of invasion into individual organs or structures, there is little evidence regarding its efficacy in surgical planning for exenterative surgery. It is essential for the surgeon to plan the resection accurately according to the extent of the disease based on the anatomical pelvic fascial boundaries. In the absence of any existing classification this needs to be developed.

The significant variations in terms of mortality, morbidity, overall and disease-free survival reported in literature as well as clearance rates directed to the hypothesis that this may be due to the different selection criteria that are in place within the individual centres that might include high-risk patients for incomplete resection on a regular basis; due to the inconsistency of the preoperative staging; and partly due to the operating skills among the surgeons in the individual centres. This had subsequently led to the development of this thesis that aimed to investigate the value of different radiological modalities in the pre-operative staging of these patients and how can these be used to select patients for surgery and medical therapy, providing a unified radiological method to report and stage this group of patients that can identify the

high-risk patients. This may potentially improve the patient selection for surgery and consequently the operative and oncological outcomes. The clinical aims of the thesis were to investigate the oncological value of lateral pelvic sidewall lymphadenectomy and the learning curve of a surgeon required to achieve the necessary competencies to operate in this group of patients.

CHAPTER 2. Aims

1.1 Overall Hypothesis

Can the overall management of patients with advanced and recurrent and rectal cancer be improved using imaging and surgical strategies?

1.1.1 Aims:

1. To assess the value of lateral pelvic sidewall lymphadenectomy (EL) for primary rectal cancer regarding peri-operative, functional and oncological outcomes by reviewing the literature and meta-analyse published data.
2. To evaluate potential advantages for performing lateral pelvic sidewall lymphadenectomy (EL) in patients undergoing exenterative pelvic surgery (including abdominosacral resection) for locally advanced primary and recurrent rectal cancer.
3. Can the MRI assessment of patients with locally advanced and recurrent colorectal pelvic cancer be improved using a new classification, and validated against histopathology and oncological outcomes?
4. To assess the diagnostic accuracy of MRI and DW-MRI in predicting the extent of tumour invasion within the pelvis.
5. To review the literature and compare the diagnostic accuracy of PET versus conventional Diagnostic Investigation in the detection of recurrences following surgery for primary rectal cancer, using meta-analytical techniques.
6. To examine the feasibility of fusing the Positron Emission Tomography images with MRI and assess its clinical value in this group of patients.
7. To calculate the learning curve required to safely perform exenterative pelvic surgery in patients with locally advanced primary and recurrent rectal cancer.

CHAPTER 3: General Methods

1.1 Databases used in the thesis

A prospective database (held by Professor Tekkis and myself since March 2006) of consecutive patients that underwent exenterative pelvic surgery for locally advanced primary and recurrent rectal cancer was used for the purposes of this thesis. The patients' preoperative scans were collected and reviewed by the dedicated radiologists in retrospect.

1.2 Data collection

Data were collected prospectively throughout the entire patient pathway from diagnosis of the primary cancer, previous surgery, medical therapy, intra-operative details, histopathology, peri-operative adverse events and long term follow up.

1.3 Definitions of outcomes

The following definitions were used:

Non-advanced primary rectal cancer: cancer that does not invade any adjacent structure and suitable for total mesorectal excision (TME) or abdominoperineal excision if extremely low.

Advanced colorectal cancer: a primary rectal or sigmoid cancer invading adjacent intrapelvic structures/organs within the pelvis, requiring extended (exenterative) surgery beyond the standard planes of dissection (extramesenteric resection). In patients with recurrent disease, the term is applied when extended (exenterative) surgery is required to excise the tumour.

Recurrent pelvic colorectal cancer: tumour in the pelvis following a previous operation for colorectal cancer.

Peri-operative mortality included deaths up to 30 days following surgery.

Major complications were the surgical complications that required further surgical intervention. Minor complications included all complications (medical and surgical) that were managed conservatively.

R0 was defined as the complete tumour resection without any residual microscopic or macroscopic disease; **R1** was defined as the presence of microscopic residual disease at the resection margins; and **R2** was defined as the presence of macroscopic residual disease at the resection margins or irresectable / inoperable disease.

The diagnostic accuracy of statistical definitions for the present study are demonstrated in Table 3 in association with the reference standard. True positive (TP) was defined as the agreement between the assessed radiological modality (MRI, DW-MRI, PET/MRI) and the reference standard in diagnosing the presence of tumour invasion within the individual compartments. True Negative (TN) was defined as the as the agreement between the assessed radiological modality and the reference standard in diagnosing the absence of tumour invasion within the individual compartments. False positive (FP) was defined as the incorrect diagnosis of tumour presence within a compartment by the assessed radiological modality. False positive

(FP) was defined as the incorrect diagnosis of tumour absence from a compartment, by the assessed radiological modality.

Table 3. Diagnostic accuracy definitions used for each compartment

		Reference Standard
Diagnostic accuracy definitions	**MRI**	**HF**
True positive (TP)	+	+
True Negative (TN)	-	-
False Positive (FP)	+	-
False Negative (FN)	-	+

Abbreviations: MRI= magnetic resonance imaging, HF= histopathological findings.

1.4 Pelvic Compartments

For the purposes of this thesis the student and supervisors (Professor Paris P Tekkis and Professor Gina Brown) have proposed and utilised a new classification based on the fascial boundaries and planes of dissection between intra-pelvic organs (116). The recurrence is classified based on the MRI findings of tumour invasion within seven intrapelvic compartments (figure 2), which are the central, peritoneal reflection, anterior above and below the peritoneal reflection, posterior, lateral and inferior compartments (table 4).

The peritoneal reflection compartment includes the level of the rectovesical pouch or recto-uterine pouch of Douglas; the anterior compartment above the peritoneal reflection includes the ureters and iliac vessels above the peritoneal reflection, sigmoid colon, small bowel and lateral side wall fascia; the anterior compartment below the peritoneal reflection includes the genitourinary system (seminal vesicles, prostate, uterus, vaginal vault, bladder, urethra and pubic symphysis); the lateral compartment includes the ureters, external and internal iliac vessels, lateral pelvic lymph nodes, sciatic nerve, sciatic notch, S1 and S2 nerve roots and the piriformis or obturator internus muscle; the posterior compartment includes the coccyx, pre-sacral fascia, retro-sacral space and sacrum up to the upper level of S1; the central compartment includes the rectum or neo-rectum, intra-luminal recurrence, perirectal fat or mesorectum and extra-luminal recurrence; and the inferior compartment includes the levator ani muscles, external sphincter complex, perineal scar (if previously abdominoperineal excision of rectum - APER) and the ischio-anal fossa. It was demonstrated that when MRI diagnosed tumour invasion within the lateral, posterior or in more than two compartments the disease-free survival deteriorated.

Table 4. Pelvic Compartments

Compartment	Included organs and boundaries of compartment	Operations
Peritoneal Reflection	level of the rectovesical pouch or recto-uterine pouch of Douglas	Peritoniectomy
Anterior above PR	ureters and iliac vessels above the peritoneal reflection, sigmoid colon, small bowel and lateral side wall fascia	Small bowel loop resection, sigmoidcolectomy, ureterectomy, iliac vessels resection / reconstruction
Anterior below PR	genitourinary system (seminal vesicles, prostate, uterus, vaginal vault, bladder, urethra) and pubic symphysis	Prostatectomy, hysterectomy, vaginal wall resection and reconstruction, cystectomy, urethrectomy, sympysectomy
Central	includes the rectum or neo-rectum, intra-luminal, extra-luminal or/and perirectal fat or mesorectum recurrence	Local resection
Posterior	coccyx, pre-sacral fascia, retro-sacral space and sacrum up to the upper level of S1 vertebra	Coccycectomy, sacrectomy
Lateral	ureters, external and internal iliac vessels, lateral pelvic lymph nodes, sciatic nerve, sciatic notch, S1 and S2 nerve roots and the piriformis or obturator internus muscle	Ureterectomy, iliac vessels resection / reconstruction, pelvic sidewall lymphadenectomy
Inferior	levator ani muscles, external sphincter complex, perineal scar (if previously APER) and the ischio-anal fossa	Abdominoperineal resection of the rectum

Abbreviations: PR= peritoneal reflection, S1 and S2= sacral nerve root, APER= abdominoperineal resection of the rectum.

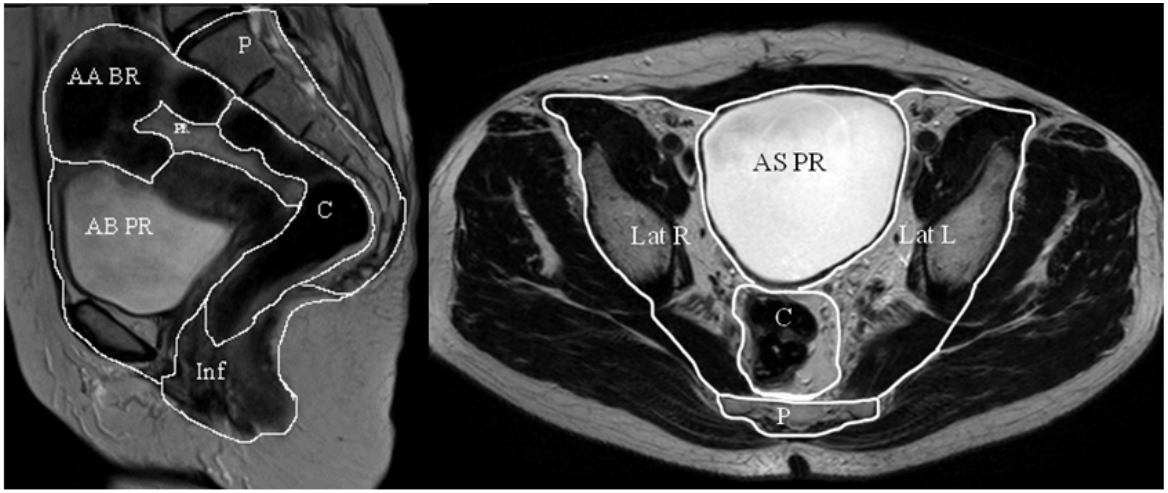
1.4.1 Central compartment

Recurrences within the rectum and neo-rectum that can be either intra-luminal or extra-luminal are considered as being within the central compartment. Central compartment recurrences are also considered those invading the perirectal fat or mesorectum. Sagittal views are initially used to identify the central recurrence. Its height from the anal verge and length need to be described. High resolution axial views are used to determine the extent of the disease within the central compartment. Limited to the central compartment recurrences might be amenable to local excision. This is rare though as central recurrences are usually the "tip of the iceberg" with the tumour invading other compartments as well. As previously described for primary rectal cancer, (181) perirectal fat appears as a high signal surrounding the low signal of muscularis propria, containing small vessels that do not show any signal (signal void vessels).

1.4.2 Peritoneal reflection

This compartment includes the level of the rectovesical pouch or recto-uterine pouch of Douglas. Tumour invasion within the compartment is identified through the sagittal and axial views. Invasion of this compartment can be due to peritoneal metastases or continuation of tumour from an adjacent compartment such as central, lateral, posterior and/or anterior above the peritoneal reflection. The peritoneal reflection appears as high signal on top of the bladder and / or uterus progressing inferiorly and posteriorly following their course, towards the higher part of the remaining rectum (if previously anterior resection).

Figure 2. Pelvic compartments



Sagittal and Axial MRI images showing the peritoneal reflection (PR), anterior above (AA) and anterior below (AB) the peritoneal reflection compartments; inferior (Inf), central (C) and posterior (P) compartments; lateral at right (Lat R) and lateral at left (Lat L)

1.4.3 Anterior compartment

The anterior compartment is divided to the anterior above and below the peritoneal reflection. The anterior above the peritoneal reflection consists of the ureters and iliac vessels at the level anteriorly of S1 vertebra, sigmoid colon, small bowel and lateral sidewall fascia. Tumour invasion within the compartment is identified by reviewing the sagittal and axial images. Tumour diagnosis within this compartment is important as informs the surgeon of the presence of intra-abdominal disease and the need to careful approach the tumour to remove it *en bloc* with the loops of small bowel that might be attached to it. The small bowel loops and sigmoid colon appear as low signal with their wall appearing as intermediate signal. The ureters appear as high signal (if there is urine within them) with their wall appearing as low signal. In the case that there is no urine within the ureters and are therefore collapsed, the ureters can be identified from the low signal appearance of their wall. The iliac vessels at the level anteriorly of S1 have a big diameter and appear as low signal.

The anterior below the peritoneal reflection compartment includes the genitourinary system and lies anteriorly to the mid and lower third of the remaining rectum. Depending of the level of the previous anterior resection the mesorectal fascia that previously separated the compartment from the rectum does not exist to its full length. If exist it can be identified as a fine low signal layer enveloping the perirectal fat and remaining rectum (181). In addition to the bladder, urethra and pubic symphysis, the vagina and uterus form the compartment in females whereas in males the prostate and seminal vesicles form the compartment. Sagittal and axial views are utilized to describe the extent of the disease within this compartment. Diagnosis of tumour

within this compartment is important as it indicates the need for prostatectomy and cystectomy (total or partial) in males; and the removal of the posterior vaginal wall and/or hysterectomy in female patients.

The vaginal walls appear as high signal whereas the uterus appears as low signal. In males, the prostate appears as low signal with its fibrous capsule appearing as higher signal. The bladder appears as high signal if full of urine with its wall appearing as low signal. In females, the bladder is usually protected from the tumour by the vagina and uterus eliminating the need for cystectomy in the majority of the cases. This is not the case for males where following mesorectal excision, tumour invasion anteriorly threads the bladder and therefore necessitate cystectomy. This can be either partial or total depending on the degree of invasion within the compartment and evidence of tumour breaching the bladder wall (total cystectomy is required). In early detection of recurrence in this compartment, the tumour may be limited within the seminal vesicles and or prostate. Therefore, excision of these structures *en bloc* with the tumour may provide the desired oncological result. These cases are rare though. In the event of tumour invasion in the pubic symphysis, careful evaluation of the clinical and radiological findings is required as the possibility the tumour to be resectable is very slim.

1.4.4 Posterior compartment

This compartment consists of the coccyx, pre-sacral fascia, retro-sacral space and sacrum up to the upper level of the first sacral vertebra. The sagittal views provide an estimation of the sacral level of tumour invasion. The high resolution axial views provide more detail helping to determine the depth of tumour invasion within the

sacrum. Invasion of the first sacral vertebra is considered as a contraindication for surgery by the multidisciplinary team involved in this research. Invasion of the second vertebra (S2) is considered a relative contraindication depending the depth and height of the invasion. A segmental S2 resection can be performed if the tumour is at the lower level of the second vertebra and invades less than half of the vertebra diameter. If the tumour is confined within the pre-sacral fascia anterior to S1 and S2, excision of the fascia can be performed. The radiologists need to be confident that the tumour hasn't breached the fascia though as this would result is an incomplete resection (R1). In the cases that the tumour has breached the pre-sacral fascia and is confined within the pre-sacral space anterior to S1 and S2, the lift of the periosteum can result in complete resection. This can be achieved by accessing the periosteum posteriorly following the sacrectomy of the lower sacrum.

In the MRI, the coccyx and sacrum appear as intermediate signal and the presacral fascial as a thin layer of high signal anteriorly to the sacrum. In between them lies the pre-sacral space that appears as low signal. When radiotherapy preceded the MRI, inflammation and oedema of the small vessels might occur within the pre-sacral space, which appears as high signal.

1.4.5 Lateral Compartment

The lateral compartment includes the ureters, external and internal iliac vessels, lateral pelvic lymph nodes, sciatic nerve, sciatic notch, sciatic (S1 and S2) nerve roots, lateral pelvic sidewall (fascia and bony), the piriformis and obturator internus muscles. Previous studies demonstrated that the MRI has low accuracy in determining whether the tumour invades this compartment (69). This might be partly secondary to

its complexity, which necessitate significant experience in the interpretation of MRI to confidently identify the individual structures involved. Invasion of the sciatic nerve and roots; and lateral pelvic bony sidewall are considered as contraindications for surgery. Invasion of the external iliac vessels is considered a relative contraindication for surgery since their reconstruction may be feasible. However, the morbidity is high along with the likelihood of distant metastases. Therefore, a thorough assessment using PET and CT scan is needed before the patient is planned for such an extensive operation.

The high-resolution axial and coronal views are used to diagnose tumour invasion within this compartment. The most challenging structure to describe in relation to the tumour is found to be the sciatic nerve and roots. The tumour relationship to the sciatic nerves and notch are better visualized using the coronal views. The height and the proximity to the nerves can be identified using this view. High resolution axial images are employed to assess this relationship in more detail. The tumour proximity to the nerves can determine its resectability. Therefore, the distance from its closest point should be always described. In these occasions the images should be reviewed and discussed in the presence of the operating surgeon.

The location and size of pelvic sidewall lymph nodes is recorded along with any suspicious features according to the morphologic criteria reported by Taylor *et al* (181). Evidence of persistent disease following radiotherapy will necessitate the performance of lateral pelvic lymphadenectomy.

1.4.6 Inferior Compartment

Inferior compartment recurrence is considered when the tumour invades the levator ani muscles, external sphincter complex, perineal scar (if previously APER) and the ischio-anal fossae. Invasion of this compartment can be in the form of the tumour fistulating at the perineum through the structures mentioned above. Assessment of the inferior compartment is performed using the sagittal, axial and coronal views.

The internal anal sphincter is a continuation of the lower segment of the circular muscle in the rectum. At the top of the anal sphincter, the puborectalis fibres join the outer muscle coat's fibres, forming the conjoint longitudinal smooth muscle coat that descends between the internal and external sphincters. The muscles appear as low signal whereas the ischiorectal fossae appear as a high signal between the external sphincters and ischium.

1.5 Magnetic Resonance Imaging Technique

Following informed consent including information about the procedure and the length of each sequence. It is important to ensure that the patient is comfortable and pain free as this will minimise any undesirable motion artefacts. In the institutes that this thesis took place, there is no role for purgative bowel preparation or enemas.

Intramuscular Buscopan/Glucagen is given as an antispasmodic, (Oral Mebeverine 135mg may be given 20 minutes prior to scan as an alternative). The patient is subsequently placed supine on the table, feet first and a five-element cardiac is placed firmly on the pelvis to ensure good compression and to minimise the possibility of

motion. An abdominal/pelvic phased array coil may be used. A full bladder is not required, as it would make the patient uncomfortable with the compression from the coil. In addition, an empty bladder minimises motion artefact secondary to resonance of urine.

It is fundamental that the referring surgeon indicates the tumour position (in terms of height above the anal verge; and fixation) and any history of past pelvic pathology and surgery.

The technique for the acquisition of the images is similar to the one described before by Brown et al. (55) The addition of coronal views and the increase of the axial plane up to the level of L5 vertebra complement that technique. The parameters are shown in table 5.

Table 5. Imaging sequences

Sequence	Sagittal TSE T2	Axial TSE T2	Axial TSE T2 High Res	Coronal TSE T2 High Res
TR	**3961**	**4018**	**5362**	**5362**
TE	**125**	**80**	**100**	**100**
TSE factor	**23**	**20**	**16**	**16**
FOV /RFOV	**250/100%**	**300/100%**	**160/90%**	**160/90%**
Slice thickness/gap	**3/0.4**	**5/1**	**3/0.3**	**3/0.3**
Number of slices	**24**	**32**	**24**	**24**
NSA	**4**	**2**	**6**	**6**
Matrix	**320/512r**	**256/512r**	**256/256**	**256/256**

Sat bands	**Ant/Sup**	**None**	**None**	**None**
Acquisition time	**6.00**	**3.28**	**7.35**	**7.35**

This table shows the sequences, which are used at the Royal Marsden Hospital to pre-operatively, stage patients with locally advanced primary and recurrent colorectal pelvic cancer.

A 1.5 Tesla MRI scanner is used with phased-array coils. These coils can maintain the high signal adequately and achieve superior coverage than the endorectal ones. It is important that the phased array coil is centred optimally to ensure adequate coverage of the rectum, mesorectum and anal sphincter complex. There should be adequate coverage from the level of the sacral promontory to below the symphysis pubis. The bottom of the coil should be 10cm below the symphysis pubis to cover the inferior compartment. The researchers' experience with the 3 Tesla MRI scanners was still limited for evaluating the local extend of recurrent rectal cancer at the time of writing this thesis. Further research is still needed to further assess its value.

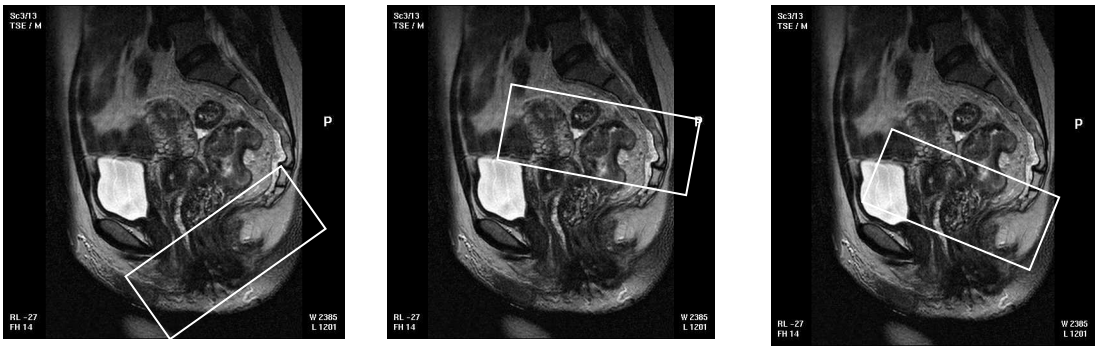
A 3-7mm section turbo spin-echo T2-weighted technique was employed using a surface pelvic phased array coil and a small field of view, (1.5T MRI) systems. The images obtained had an in plane resolution of 0.6 x 0.6mm to 0.9 x 0.9mm.

Coronal imaging was performed to include the lateral pelvic sidewall compartment. After a coronal localizer, sagittal scans (figure 3) were required from inner pelvic sidewall to sidewall using a 24cm field of view, 3-5 mm thickness contiguous/interleaved slices (no gap), TR>2500 and <5000, TR=85, field of view. These acquisitions were used to plan axial images.

The large field of axial TSE T2 acquisitions of the anatomic pelvis were taken by using a 24cm field of view, a 5mm contiguous section thickness, 512 x 256 matrix, an echo train length of eight, no fat saturation, a 32kHz bandwidth, and two signals acquisitions (2NEX).

The oblique axial TSE T2 high resolution images were obtained using a 16-24cm field of view, a 3 mm section thickness, no intersection gap, a 256 x 256 matrix, an echo train length of eight, no fat saturation, a 32kHz bandwidth and four acquisitions (4 NEX). It is critical that these images are performed perpendicular to the long-axis of the rectum (if present).

Figure 3. Oblique Axial high resolution TSE T2 through the tumour and adjacent perirectal tissues. It is important that these images are performed perpendicular to the long-axis of the rectum.



The coronal TSE T2 high resolution images (figure 4) were taken along the long axis of the anal canal (if present), using a 24 cm field of view, a 3 mm section thickness no intersection gap, a 256 x 256 matrix, no fat saturation, a 32kHz bandwidth and six acquisitions (6 NEX).

Figure 4. Coronals

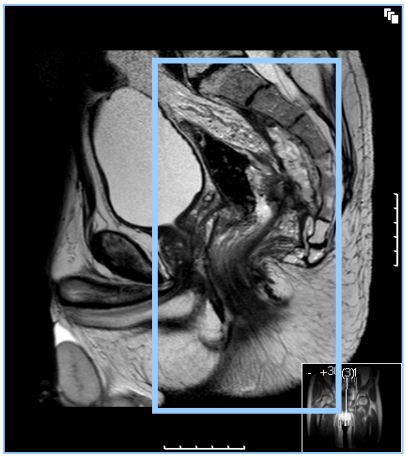


Figure demonstrates the angle that coronal sequences should be taken for recurrences. The field should be extended further back to include the sacrum so the sacral plexus can be visualised.

For the acquirement of the diffusion weighted images the following protocol was used. Axial DW-MR images were obtained by using free-breathing DW-MR echo-planar sequence (66.6/6000; field of view, 360 mm; matrix size, 128 x 128; section thickness, 3 mm; intersection gap, 1 mm; number of signals acquired, eight; receiver bandwidth 1750 kHz.). Three b-values of 0, 350, 750,sec/ mm^2 were used in directions x, y, and z to obtain the diffusion-weighted images and the apparent diffusion coefficient (ADC) maps. A whole pelvis coverage axial DW-MRI sequence was also performed using b-values of 0 and 900 sec/mm^2. The array spatial sensitivity encoding technique (factor of two) was used to reduce the distortion of echo-planar imaging. The imaging time of one DW-MR imaging sequence was 160 seconds. The whole process of the diffusion-weighted imaging was performed using the free breathing technique.

1.6 MRI and DW-MRI quantitative assessment of tumour invasion within the pelvis

Two radiologists (GB, UP), with 15 and 3 years of experience in pelvic and rectal cancer MR imaging, blinded to the clinical findings and the findings of other radiological modalities, assessed and scored the pre-operative images using a proforma specially designed for the study (Appendix 1). The authors used the following criteria to distinguish tumour from fibrosis on T2-weighted MR images. Intermediate signal intensity with pattern of nodular infiltration was defined as tumour. Uniform low signal intensity with linear or well-defined boundaries was defined as fibrosis. The distinction was clearer on higher resolution MR images (3mm slice thickness field view <18cm).

The same radiologists (GB, UP), blinded to the clinical findings and the findings of other radiological modalities, individually assessed and scored the pre-operative images using a proforma. For the Diffusion-weighted MRI study, this process was performed three times for each patient (MRI, DW-MRI, Both). The pelvic anatomy was depicted using the MR images. This was performed by overlaying the two modalities after marking the area suspected to be invaded by tumour by DW-MRI. Any discrepancy between them was resolved by discussion.

1.7 Images interpretation

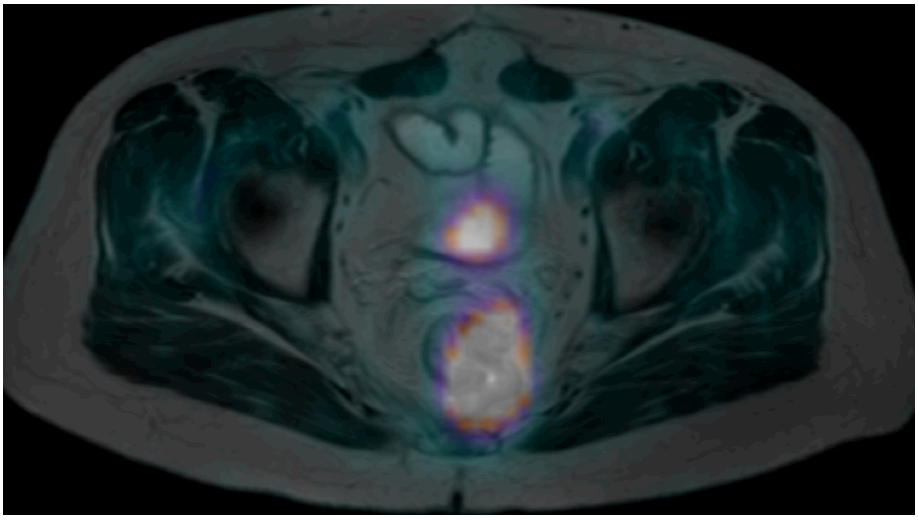
In order to interpret and report the images a form designed to report recurrent rectal cancers is used (Appendix 1). For reporting tumour invasion the primary investigators and student had divided the pelvis into seven compartments according to the fascial boundaries and planes of dissection between intra-pelvic organs as demonstrated

above. The radiologist always started the reporting by describing the main pelvic compartment that the tumour invades as it helps the surgeons to understand the extent of the disease better and plan the surgery. The tumour appears with a low signal in T2 MRI. Mucinous cancers are characterised by the high signal mucin pools within the tumour. The more mucin within the tumour the higher signal is visualised by the T2 sequence of the MRI.

1.8 PET and MRI fusion technique

The Hermes Workstation GOLD version 3 was used to fuse the MRI with the PET/CT images. The MRI images were initially co-registered with the CT component of the PET/CT. The appropriate orientation was achieved using bony anatomical landmarks such as the sacral vertebrae, the coccyx, the pelvic bones and the head of both femoral bones. The co-registration of the aligned to CT, MRI images with the PET component of PET/CT followed this process to provide the PET/MR images (figure 5). The student supervised the whole process ensuring that the co-registration was successful.

Figure 5: Successful PET/MRI showing tumour invasion within the posterior compartment



1.9 PET/MRI images interpretation

The PET/MRI images were reviewed and interpreted in retrospect following the fusion, by Dr Gina Brown, radiologist with special interest and expertise in pelvic MRI; and Dr Sue Chua, nuclear medicine physician with special interest in the value of PET and PET/CT in the management of advanced primary and recurrent colorectal cancer. Each reviewer scored the images independently using a dedicated proforma (Appendix 2), blinded to other clinical and radiological findings. Any disagreements were solved by discussion to provide one scoring for the purposes of the statistical analysis.

1.10 Reference standard

The intraoperative and histopathological findings were used as the reference standard. The intraoperative findings were reported by a specialist pelvic surgeon (Professor Paris P Tekkis), providing details of tumour invasion in each compartment. In the case of unresectable disease, biopsies were taken from the compartments where

possible for histological confirmation. All specimens were assessed by a gastrointestinal histopathologist with experience in recurrent pelvic cancer blinded to the MRI proforma scoring. After fixation, the operative specimen was cut up in the presence of one of the surgeons. A detailed histopathological report was reproduced with the completion of a dedicated proforma (Appendix 3) using the histopathology report. The reporting histopathologist was contacted when clarifications were necessary to complete the pro-forma. If any of the compartments was not resected due to the absence of radiological or intraoperative evidence of disease, radiological follow up was used in the long term to confirm the absence (true negative) or presence (false negative) of disease within the compartment within 12 months following surgery.

1.11 Technique of extended lymphadenectomy used for the operated patients included in the database used in this thesis

Following dissection and mobilization of the sigmoid and descending colon, the pelvis was exposed enabling the initiation of the lateral dissection. The retroperitoneum was dissected at the level of the bifurcation of the aorta, exposing the common iliac vessels. The lateral lymph node dissection was performed the same way as it was previously described in 1989 by Moriya. (33) The lateral pelvic lymphadenectomy was performed either *en bloc* with the internal iliac vessels or by preserving them, depending on the presence of tumour close to the internal iliac vessels or on the evidence of solitary lymph node metastases respectively. This decision was taken pre-operatively by the local multi-disciplinary team.

The dissection of the lateral pelvic sidewall lymph nodes commenced with the separation of the internal iliac vessels from the lateral ligament medially. All the branches of the internal iliac vessels were identified, ligated and divided as close to their root from the internal iliac vessels as possible. For the cases that the tumour was close to the iliac vessels, the lateral pelvic sidewall lymphadenectomy was performed en-bloc with the resected specimen including the unilateral internal iliac vessels with preservation of the superior vesical artery and the obturator nerve.

When the lateral pelvic sidewall lymphadenectomy was performed to remove suspicious for malignancy or isolated malignant lateral lymph nodes, the nerve-preserving approach was utilised ("conventional lateral dissection") (33). The specimen was resected *en bloc* with the tumour while the lateral pelvic sidewall spaces were opened between the lateral aspect of the internal iliac vessels and the pelvic wall, exposing the lateral lymphatic tissue and enabling the lymph nodes' harvesting. Using the nerve-preserving technique, the obturator nerve and internal iliac vessels with their branches were preserved without disturbing the sacral nerve plexuses.

With the completion of the lateral pelvic sidewall dissection and the abdominal mobilisation of the specimen and depending on the tumour's extend, a pelvic exenterative procedure was performed with or without the removal of the sacrum (abdominosacral resection).

1.12 Statistical methodology

1.12.1 Meta-analytical methods

Meta-analyses are studies that are employed to provide an answer to the same question that other studies attempted to answer but were unsuccessful due to sample size or other limitations. Meta-analyses use statistical methods to systematically review and analyse the outcomes of these studies. It involves statistical "pooling" of the results of individual studies producing a single estimate of the treatment's effect. Sources of bias are also investigated and attempts to eliminate these are made when possible. The meta-analysis included in this study followed the guidelines published by the Cochrane Collaboration and the conference of the Quality of Reporting of Meta-analyses (QUOROM; Appendix 4) (182, 183). Two meta-analyses were performed for this thesis, one of which was diagnostic. The details for the statistical methodology for each study are described in each chapter.

1.12.2 Diagnostic accuracy statistical methodology

The statistical definitions of diagnostic accuracy for the present study in association with the reference standard is demonstrated in Table 6.

Table 6: Diagnostic accuracy definitions

		Reference Standard	
Diagnostic accuracy definitions	**Index test**	**HF**	**R**
True positive (TP)	+	+	**NA**
	+	+	**NA**
True Negative (TN)	-	- *	-
	-	-	**NA**

False Positive (FP)	+	-	**NA**
	+	-	**NA**
False Negative (FN)	-	+	**NA**
	-	+ *	+

Abbreviations: Index test= radiological modality tested, HF= histopathological findings, R= radiological modalities, *= If the compartment was not resected due to no radiological or intraoperative evidence of disease, histopathological confirmation could not be obtained by definition. Therefore radiological modalities were used following surgery as a reference standard to confirm the absence of disease.

1.12.3 Sensitivity and specificity

Sensitivity is the ability of the radiological modality assessed (MRI, DW-MRI, PET/MRI) to correctly detect the presence of disease within an individual compartment. The calculation of the sensitivity is performed using the following equation (True Positive / [True positive + False Negative).

Specificity is the ability of the assessed radiological modality to correctly diagnose the absence of disease within the individual compartments. Specificity is calculated using the following equation: (True Negative / [True Negative + False Positive]).

1.12.4 Positive and negative predictive values

The positive predictive value (PPV) is the proportion of patients with tumour invasion within an individual compartment that are correctly diagnosed by the assessed

radiological modality. This is calculated by using the following equation: (True Positive / [True Positive + False Positive]).

The negative predictive value (NPV) represents the ability of the assessed modality to correctly diagnose the proportion of patients without tumour invasion into individual compartments (True Negative / [True Negative + False Negative]).

1.12.5 Receiver-operating characteristic (ROC) analysis

Receiver-operating characteristic (ROC) analysis was initially developed during World War II in order to assess the accuracy of the radar system in differentiating signal from noise. (184) In the recent years, it has found a widespread application on screening and diagnostic tests including radiological studies. It is a useful tool that can calculate and provide a value for the overall performance of a diagnostic test.

Therefore, its calculation it has gradually become the standard for diagnostic studies. ROC analysis was calculated on a compartment-by-compartment basis. The ROC analysis plots a curve using the values of sensitivity on the *y*-axis against the values of (1–specificity) on the *x*-axis for different thresholds. The line connecting (0,0) to (1,1) corresponds to a value of AUC= 0.5, which translates to 50% likelihood that the assessed modality is correct and therefore "random chance". (185) The ROC curve for the gold standard is the line connecting (0,0) to (0,1) and then to (1,1) and it is equal to a value of AUC= 1. (185) This point represents 100% Sensitivity and 100% Specificity and is called the perfect classification. The area under the ROC curve is an overall measurement of the accuracy of the diagnostic test and usually lies between

the two lines mentioned above (AUC= 0.5 - 1). Generally, an AUC of more than 0.9 is considered outstanding, between 0.8 and 0.9 very good and 0.7 and 0.8 acceptable.

The non-parametric method was used to calculate the sensitivity and specificity and consequently the ROC curve. This method has the advantage that no assumptions are made about the form of the plot and that the underlying distributions of the outcomes do not need to be specified. (186) Exact binomial 95% confidence intervals were obtained for sensitivity, specificity and predictive values. The STATA™ SE 10 for Macintosh (STATA Corp, Texas, USA) was used for the calculations of the diagnostic accuracy statistics and confidence intervals.

1.12.6 Cohen's Kappa (κ) coefficient

Cohen's kappa (k) coefficient (187) is used to evaluate the inter-observer or inter-rater agreement for qualitative assessments. This is an indirect measure of the reproducibility of the reported results. Cohen's kappa (k) coefficient was used to measure the degree of agreement between the two radiologists that reported the MRI and DW-MRI images and between the radiologist and nuclear medicine physician that reported the PET/MRI images. The kappa value was calculated using the SPSS software version 16, providing values of standard error and statistical significance. Confidence intervals were calculated using the standard error. The equation for the calculation of kappa value is the following:

Kappa = (Proportion of observed agreement - change agreement) divided by (1 - change agreement)

Based on the kappa value the inter-observer agreement would be characterised as follows:

1. Very good agreement = 0.80 to 1.00
2. Good agreement = 0.60 to 0.80
3. Moderate agreement = 0.40 to 0.60
4. Fair agreement = 0.20 to 0.40
5. Poor agreement = Less than 0.20

1.12.7 Kaplan-Meier methodology

The Kaplan Meier methodology was used to generate curves plotting the overall survival, disease and local recurrence-free survival following surgery. Kaplan Meier statistics is used in medical research to assess the percentage of patients alive at a certain time following treatment of diagnosis of disease. The advantage of this method is that it takes into consideration censored data which occur if the patient was alive and disease free within a shorter observed period than other patients or if the patient was lost on follow up or if the patient diseased for reasons other than a recurrence (for the disease and local recurrence-free curves). Censoring data aims to produce as accurate as possible survival curves by using all the available information at the time when the analysis is performed.

1.12.8 The Risk Adjusted Cumulative Sum (RA-CUSUM)

The cumulative sum (CUSUM) is a quality assessment tool that was developed to evaluate the efficiency of the ammunition production lines during World War II. It is a sequential analysis that is typically used to detect and monitor changes, (188)

allowing the observer to identify if the production line is “in control” or “out of control”. The risk-adjusted CUSUM was applied in this study to assess the difference between expected complications and those that actually occurred, to determine how far the surgeon’s complications were above or below the predicted cumulative complications, incorporating the risk associated with each type of surgery (189, 190). The analysis in the present study was performed following the same methodology as reported elsewhere (191). Each case in the series was plotted on a chart from left to right on the horizontal axis. The line ascends for every uncomplicated case and descends for every complicated case. The degree that the graph ascends or descends is determined by the risk of complication for the type of surgery based on the Weibull survival model.

For every uncomplicated case, the graph rises by an amount equal to the estimated probability of complication for the type of surgery and for every complication encountered postoperatively, the graph descends by an amount equal to the estimated probability of complication for the type of surgery. Therefore, if a complication occurs in a patient at higher risk for example after abdominosacral resection, the surgeon’s performance chart is not penalised excessively. The opposite is implied if a complication occurs in a patient at lower risk for example after pelvic exenteration.

In the present study, the RA-CUSUM graph evaluated the learning curve for pelvic exenterative surgery for recurrent and locally advanced primary colorectal pelvic cancer of one surgeon. Therefore, each case number represented the sum of the observed minus expected complication for the surgeon, for each case in a sequential

order. The expected complication rate was calculated based on the overall percentage of complications that occurred within the population.

1.12.9 Group Comparison

The chi-square test was used to compare the dichotomous outcomes between two groups. The Mann-Whitney test was used to compare continuous variables between two groups. The chi-square test using the gamma ordinal method was used to compare patients in the four groups quartiles for the learning curve chapter. Comparisons were considered statistically significant at a probability value of $p<0.05$.

CHAPTER 4: Extended Versus Non-Extended Lymphadenectomy for Rectal Cancer: A Meta-Analysis

1.1 Introduction

Lateral pelvic lymph nodes are part of the lateral compartment as described in this thesis. For decades, there has been a debate about the resection of the lateral pelvic lymph nodes (known as extended or lateral lymphadenectomy) when performing an anterior resection to remove rectal cancer.

1.2 Knowledge prior to this thesis

The findings of the published studies have been controversial without any definitive answers regarding the value of extended lymphadenectomy. Japanese surgeons have been the pioneers and bigger supporters of extended lymphadenectomy, with western surgeons challenging its value in the absence of evidence of tumour in the lateral lymph nodes.

Meta-analytical techniques have been found to be very useful in surgery when ethical issues and limited number of cases may prevent the randomisation of patients into groups and therefore the performance of higher quality studies.

1.3 Aims of the study

The current chapter aimed to investigate the value of extended lateral pelvic lymphadenectomy for patients with rectal cancer, by using meta-analytical

techniques. Published data from studies published by the 20th of June 2009 were used for this comparison.

1.4 Methods

1.4.1 Literature search and data extraction

A MEDLINE, Embase, Ovid, and Cochrane Library and Google Scholar database search was performed on all studies between 1965 and 2009, which compared extended lymphadenectomy with standard rectal resection in elective rectal cancer patients. The following MESH search headings were used: extended lymphadenectomy, lateral pelvic wall lymph node dissection, total mesorectal excision, rectal resection, extended resection, radical resection, rectal cancer, comparative study, randomized study and treatment outcome. The related articles function was used to broaden the search, and all abstracts, studies, and citations were reviewed irrespective of language. The latest date for this search was the 20th of June 2009.

All comparative studies examining extended versus non-extended lymphadenectomy in patients undergoing surgery for rectal cancer were included provided there was an accurate description of the surgical technique used. In the case of repeated studies by the same authors, the most recent or most informative was included. Two reviewers (the student and Dr Nikolaos Gouvas) independently extracted the following data from each study: first author, year of publication, study population characteristics, study design, inclusion and exclusion criteria, matching criteria, number of subjects enrolled in each type of rectal resection and the reported outcome.

1.4.2 Aims

The study aimed to compare to compare extended (lateral) pelvic lymphadenectomy to non-extended (lateral) pelvic lymphadenectomy for rectal cancer.

1.4.3 Outcomes of interest

The 5-year cancer specific and overall 5-year survival, 5-year disease-free survival, total, local and distant recurrence, peri-operative (30 day) mortality and morbidity, length of operation (minutes), intra-operative blood loss (mls), urinary dysfunction (urinary frequency, incontinence and inability to void), sexual dysfunction (erectile dysfunction, ejaculatory dysfunction, arousal) and defaecatory dysfunction (evacuatory difficulty) were recorded.

1.4.4 Statistical analysis

The meta-analysis was performed in line with recommendations from the Cochrane Collaboration and the Quality of Reporting of Meta-analyses (QUORUM) guidelines (182, 192). Hazard ratio was used as a summary statistic for censored outcomes (5 year survival and 5-year disease-free survival) as described by Parmar *et al* (193). A hazard ratio > 1 represented a survival benefit favouring the EL group. The odds ratio (OR) was used as the summary statistic to perform statistical analysis of dichotomous variables, and the weighted mean difference (WMD) was used to analyse continuous variables, such as the duration of the operation. Odds ratios represent the odds of an adverse event occurring in the extended lymphadenectomy group compared with the non-extended lymphadenectomy group and approximate to the relative risk. WMD

summarises the differences between the two groups with respect to continuous variables, accounting for sample size and event rate. For studies that presented continuous data as means and range values, the standard deviations (SD) were calculated using statistical algorithms (194). An odds ratio of less than one favoured the extended lymphadenectomy group. The point estimate of the OR or HR was considered to be statistically significant at the $P<0.05$ level if the 95 percent confidence interval (CI) did not include the value one. In the tabulation of the results, squares indicate the point estimates of the treatment effect (HR, OR, WMD) with 95% CI indicated by horizontal bars. The diamond represents the summary estimate from the pooled studies with 95% CI.

A fixed (weighted with inverse variance) or a random effects model was used for this meta-analysis (195). Heterogeneity between studies was assessed by the chi-square and I^2 statistic. Higher chi-square and I^2 statistic indicates greater heterogeneity between studies. The assumption of homogeneity between the groups was deemed invalid if the p-value was less that 0.1 and the random-effects model was reported after exploring the causes of heterogeneity (196). Otherwise, the fixed-effects model was reported. Begg's test and funnel plot analysis were used to determine the presence of publication bias. A two-tailed p value of less than 0·05 was considered statistically significant.

Analysis was conducted using the Review Manager Version 5.0.14 (The Cochrane Collaboration, Software Update, Oxford, UK) and STATA™ SE 9.1 for Macintosh (STATA Corp, Texas, USA).

1.4.5 Quality assessment

The quality of all observational studies was assessed with the use of the Newcastle-Ottawa Scale (NOS; Appendix 5) (197). This was evaluated by examining three factors: method of patient selection, comparability of the study groups and number of outcomes reported. A star rating of zero to nine was allocated to each study based on these parameters. The only RCT was considered to be of higher quality for the purposes of this study. Two reviewers (PG and NG) assessed the quality of the studies. Where discrepancies arose, papers were re-examined and consensus was reached by discussion. Studies achieving eight or more stars were also considered to be of higher quality. Sensitivity analysis was undertaken using (1) studies of high quality; (2) studies published after 2000; (3) studies that examined the value of EL in Dukes' B and C cancer, where groups were matched for neo-adjuvant or adjuvant radiotherapy. Only outcomes with more than three studies were included in the sensitivity analysis.

1.4.6 Graphical presentation of results

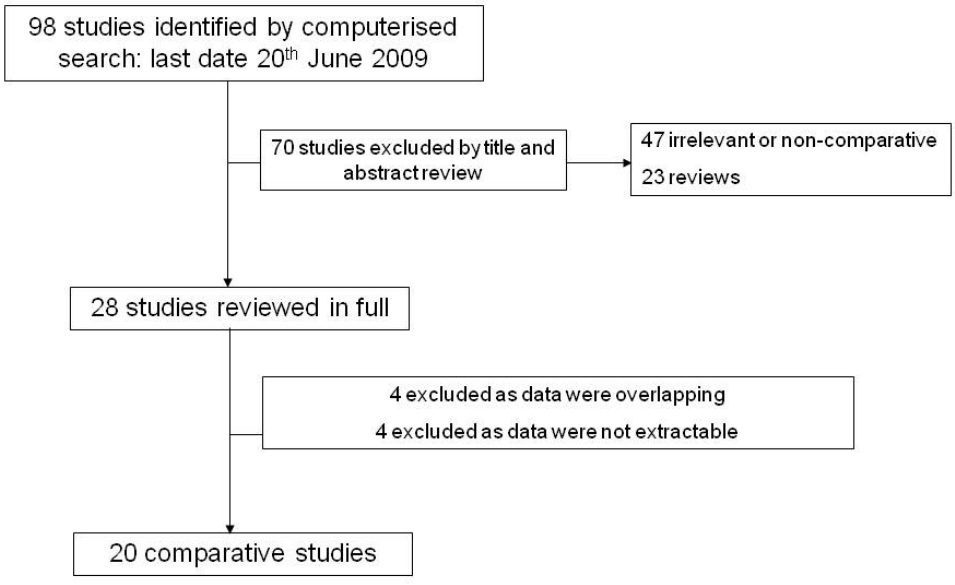
"Forest plot" is used to depict each outcome evaluated for each individual study with its confidence interval and the pooled summary statistic (were applicable). A black square (odds ratio) and a horizontal line (95% confidence intervals) represent each study. The 95% confidence intervals would contain the true underlying treatment difference in 95% of the occasions, if the study was repeated again and again. The vertical line signifies that there is no difference between the two groups and is equivalent to an odds ration of 1. If the confidence interval includes 1, then the difference in outcome between the two groups is not statistically significant for $p<0.05$. The area of the black square reflects the weight of each study in the meta-

analysis. The diamond represents the summary odds ratio from the pooled estimates with 95% confidence intervals.

1.5 Eligible studies

The literature search strategy is described in Chapter 3, General methods. Using the above search strategy, 98 publications were identified (figure 14). Seventy were excluded after title and abstract review. These included 23 reviews and 47 studies, which were either non-comparative or not relevant. The remaining 28 studies were fully reviewed. Of these, four were excluded because of overlap of authors, institutions and patient cohorts. Four more studies were excluded because the data were not extractable.

Figure 6. Flowchart of search strategy



There were thus twenty studies (table 7) published from 1984 to 2009, which fulfilled the selection criteria and were included in the meta-analysis. (34, 35, 198-215) Examination of the references given in these studies did not provide any further

studies for evaluation. Analysis was performed on a total of 5502 patients divided into the “extended lymphadenectomy” (EL) group with 2577 patients and the non-EL group with 2925 patients. Three studies had a possibly overlapping population (198, 199, 202) but were included since they investigated different outcomes. The study characteristics, patient demographic details, selection criteria, matching and quality scoring for each study are shown in Table 7. There was one randomised controlled trial (35) and three prospective non-randomised controlled studies. (203, 206, 215) The remaining studies were retrospective.

Table 7. Demographic characteristics of included studies

		Year	Type	Patients		Dukes' Stage	R status	Radiotherapy		Height of Tumour	Matching Criteria	Quality Score
				EL	Non-EL			EL	Non-EL			
1	Col * (199)	2006	R	13	78	A, B, C, D	NR	NR		a, b	i, vii	7
2	Col * † (198)	2005	R	24	160	NR	R0, R1	NR		a, b	i, vii	7
3	Enker (200)	1984	R	192	220	A, B, C	NR	2		a, b, c	ii, vi, vii, x, xi	6
4	Fujita (201)	2003	R	204	42	B, C	R0	0		a, b	ii, xi	6
5	Hasdemir † (202)	2005	R	24	160	A, B, C, D	R0, R1	NR		a, b, c	i, iii, vii	8
6	Hojo (34)	1989	R	192	245	A, B, C	R0	0		a, b	i, iii	8
7	Kim (203)	2007	P	176	309	B, C	R0	0	3	a, b, c	ii, iv, vii	8
8	Koyama (205)	1984	R	163	218	B, C	R0	0		a, b, c	NR	7
9	Kobayashi (204)	2009	R	784	488	A, B, C	R0	0		a, b	ii, vi, viii	8
10	Kusters (206)	2009	P	324	755	A, B, C		4	2	a, b	ii, iii, ix, x	8

11	Kyo (207)	2006	R	15	22	A, B, C	NR	0		a, b	NR	4
12	Matsuoka (208)	2005	R	15	42	A, B, C	R0, R1	5	0	a, b	i, ii	8
13	Michelassi (210)	1988	R	64	73	B, C	R0, R1	0		a, b, c	vii	8
14	Michelassi (209)	1992	R	17	10	A, B, C	NR	NR		a, b, c	i, ii, iii, vii, xi	6
15	Moreira (211)	1994	R	95	83	A, B, C	R0	NR		a, b	ii, x	7
16	Nagawa (35)	2001	RCT	23	22	B,C	R0, R1	1		a	i, ii, iii, vi, vii, viii, ix, x, xi	RCT
17	Shiozawa (212)	2007	R	143	26	A, B, C	R0	0		a	ii, ix, x	9
18	Suzuki (213)	1995	R	32	100	B, C	R0, R1	0		a, b	NR	7
19	Watanabe (214)	2002	R	75	40	B, C	R0, R1	2		a	i, ii, iii, vii, x, xi	9
20	Yano (215)	2007	P	39	70	A, B, C	R0	‡		a, b, c	v, viii	8

Abbreviations: R= retrospective study, RCT= randomised controlled trial, P= prospective study, EL= extended lymphadenectomy, non-EL= non-extended lymphadenectomy, NR= not reported, *= possible overlap of population but different outcomes investigated, †= same population

is used but a different outcome is evaluated in each paper, ‡= two patients received neo-adjuvant radiotherapy; *Stage:* A= Dukes' A, B= Dukes' B, C= Dukes' C, D= Dukes' D; *Clearance:* R0= R0 resection, R1= R1 resection; *Radiotherapy:* 0= no radiotherapy either neo-adjuvant or adjuvant, 1= neo-adjuvant radiotherapy - all patients, 2= neo-adjuvant radiotherapy - part of the group, 3= post-operative radiotherapy - all patients within the group, 4= post-operative radiotherapy - part of the group, 5= intraoperative radiotherapy – part of the group; *Height of tumour*: a= low rectum, b=mid-rectum, c=upper rectum; *Matching criteria:* i= age, ii= gender, iii= height of tumour, iv= patient co-morbidities, v= any neo-adjuvant therapy, vi= neo-adjuvant radiotherapy only, vii= procedure, viii= clearance of resected margin, ix= stage $N_{1,2}$, x= Dukes' stage, xi= tumour differentiation

1.6 Study outcomes

The outcomes of the study are summarised in table 8.

Table 8. Results of meta-analysis comparing extended lymphadenectomy (EL) versus non-extended lymphadenectomy (non-EL) for patients undergoing surgery for rectal cancer**.**

	No of Studies	Pts EL	Pts Non-EL	Pts Total	HR*/OR/ WMD†	95% CI	p-value	Study heterogeneity			
								Chi-square	df	I^2	p-value
Survival											
5 year survival	6	1261	999	2260	1.09 *	0.78 - 1.50	0.62	265.30	5	98%	<0.0001
5 year disease-free survival	4	394	250	644	1.23 *	0.75 - 2.03	0.41	13.51	3	78%	0.0037
Recurrence											
Total recurrences	7	677	746	1423	0.80	0.63 - 1.02	0.072	8.97	6	33%	0.18
Local recurrences	16	2524	2859	5383	0.83	0.61 - 1.13	0.23	34.57	15	57%	0.0028
Distant recurrences	8	774	898	1672	0.93	0.72 - 1.21	0.60	5.49	7	0%	0.60
Peri-operative outcomes											
Length of operation (mins)	4	443	469	912	76.7 †	18.8 - 134.7	0.0096	46.79	3	94%	<0.0001
Blood loss (mls)	3	419	309	728	536.5 †	353.7 - 719.2	<0.0001	3.62	2	45%	0.16
Peri-operative mortality	7	944	870	1814	0.81	0.34 - 1.93	0.63	1.67	3	0%	0.64
Peri-operative morbidity	4	302	238	540	1.45	0.89 - 2.35	0.13	1.11	3	0%	0.77

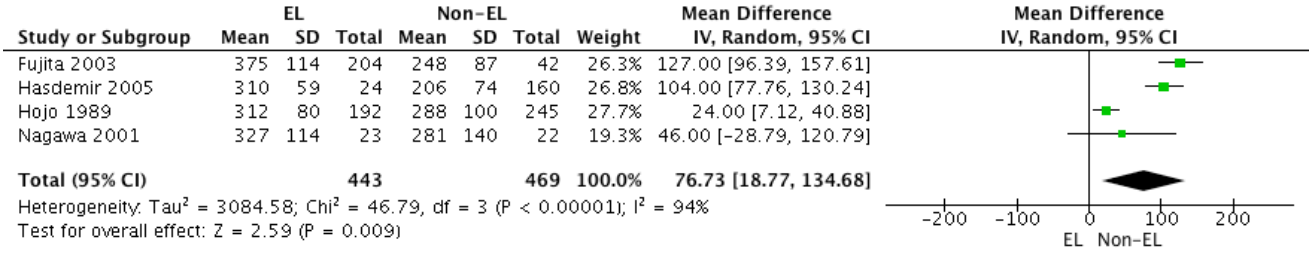
Functional outcomes											
Urinary dysfunction	3	53	86	139	3.70	1.66 - 8.23	0.0012	0.41	2	0%	0.81
Urinary incontinence	3	54	210	264	2.08	0.98 - 4.39	0.055	0.27	2	0%	0.87
Urinary retention	3	107	293	400	2.31	0.89 - 5.99	0.084	2.76	2	28%	0.25
Defaecatory dysfunction	2	27	57	84	2.36	0.54 - 10.35	0.25	2.01	1	50%	0.16

Abbreviations: Pts= patients, EL= extended lymphadenectomy, non-EL= non extended lymphadenectomy, HR= hazard ratio, OR= odds ratio, WMD= weighted mean difference, df= degrees of freedom, *= Hazard ratio, †= WMD

1.6.1 Length of operation (Figure 7)

Pooling the data of four studies (34, 35, 201, 202) demonstrated a statistically significant difference favouring non-extended lymphadenectomy (WMD 76.7 mins, 95% CI: 18.8 - 134.7 mins, p= 0.0096) with significant between-study heterogeneity, (Chi-square test= 46.79, degrees of freedom (df)= 3, p<0.0001; I^2= 94%). In addition Koyama *et al* (205) showed that EL increased the operation time by 60 minutes.

Figure 7. Length of operation



EL= extended lymphadenectomy, Non-EL= non-extended lymphadenectomy, SD= standard deviation, CI= confidence interval, p values significant if less than 0.05.

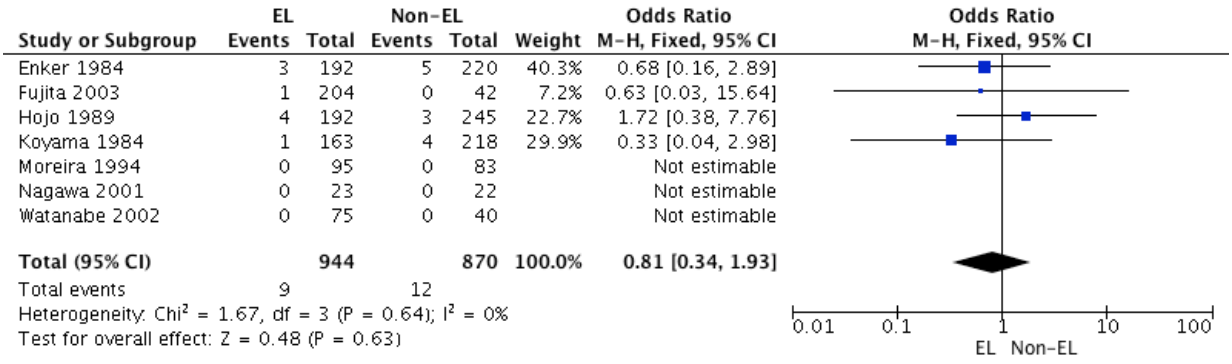
1.6.2 Intra-operative blood loss

Three studies (34, 35, 201) evaluating 728 patients, demonstrated a significant difference in intraoperative blood loss favouring the non-EL group (WMD= 536.5 mls, 95% CI: 353.7 - 719.2, p<0.0001) with moderate between-study heterogeneity (Chi-square test= 3.62, df= 2, p= 0.16; I^2= 45%). In addition, Koyama *et al* (205) reported that EL had higher intra-operative blood loss of 150 mls. Michelassi *et al* (209) reported 1616 and 1612 mls of intra-operative blood loss for EL and non-EL respectively and three patients had more than two litres blood loss in the EL group compared to one litre in the non-EL group.

1.6.3 Peri-operative mortality (Figure 8)

Peri-operative mortality data were available for 1814 patients across seven studies.(34, 35, 200, 201, 205, 211, 214) The mortality rate was higher for the EL group (OR= 0.81, 95% CI: 0.34 – 1.93, p= 0.63), with no significant between-study heterogeneity (Chi-square test: 1.67, df=3, p= 0.64; I^2= 0%).

Figure 8. Perioperative mortality

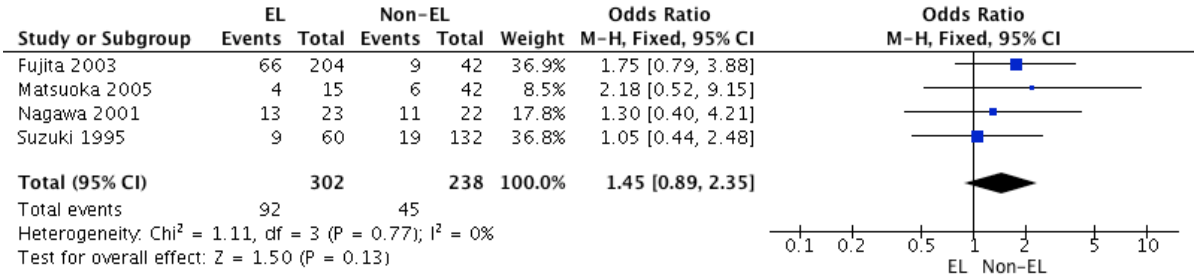


EL= extended lymphadenectomy, Non-EL= non extended lymphadenectomy, SD= standard deviation, CI= confidence interval, p values significant if less than 0.05.

1.6.4 Peri-operative morbidity (Figure 9)

Peri-operative morbidity was reported in four studies (35, 138, 201, 208) that investigated 540 patients. EL was associated with a higher overall post-operative morbidly compared with non-EL but this difference did not reach statistical significance (OR= 1.45, 95% CI: 0.89 - 2.35, p= 0.13). There was no significant heterogeneity (Chi-square test= 1.67, df=3, p= 0.77; I^2= 0%).

Figure 9. Peri-operative morbidity

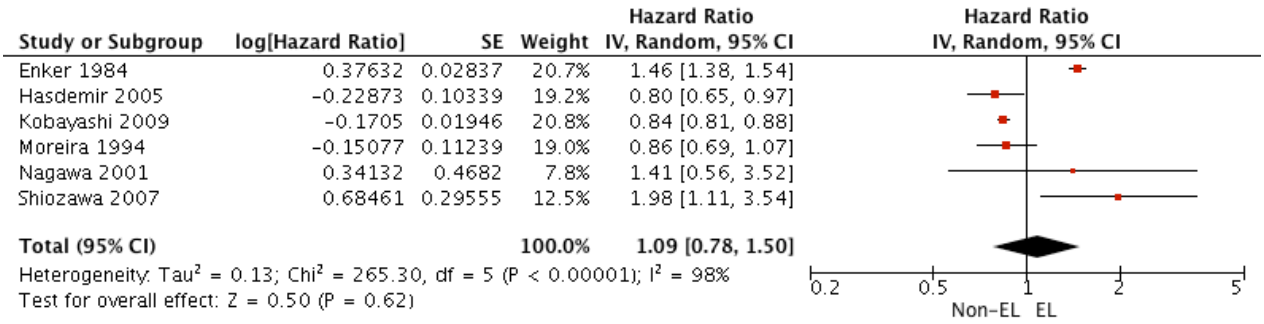


EL= extended lymphadenectomy, Non-EL= non extended lymphadenectomy, SD= standard deviation, CI= confidence interval, p values significant if less than 0.05.

1.6.5 5-year overall survival (Figure 10)

Data on 5-year survival were available in six studies (35, 200, 202, 204, 211, 212) evaluating 2260 patients. There was no significant difference between the two groups (HR= 1.09, 95% CI: 0.78 – 1.50, p= 0.62), with significant between-study heterogeneity (Chi-square test= 265.30, df= 5, p<0.0001; I^2= 98%). No publication bias was detected by Begg's test (p= 0.45).

Figure 10. 5-year overall survival

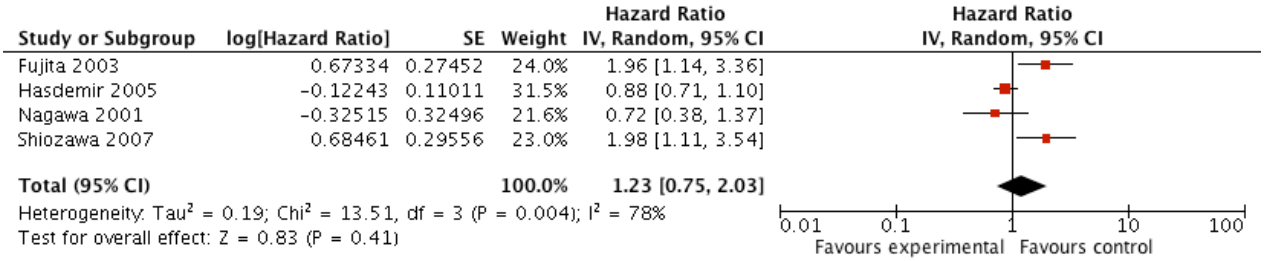


EL= extended lymphadenectomy, Non-EL= non extended lymphadenectomy, SE= standard error, CI= confidence interval, p values significant if less than 0.05.

1.6.6 5-year disease-free survival (Figure 11)

Four studies (35, 201, 202, 212) reported on 5-year disease-free survival. There was no significant difference between the two groups (HR= 1.23, 95% CI: 0.75 – 2.03, p= 0.41), with significant between-study heterogeneity (Chi-square= 13.51, df=3, p= 0.0037; I^2= 78%). No publication bias was detected by Begg's test (p= 1.00).

Figure 11. 5 year Disease free survival

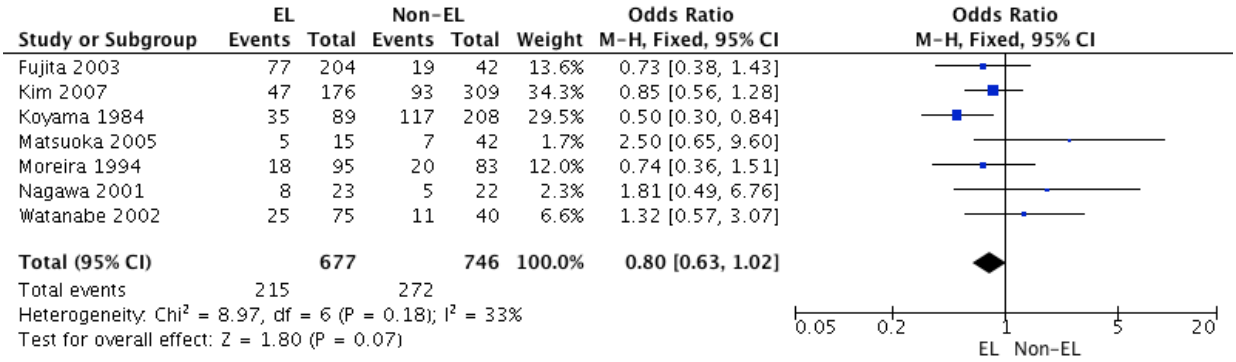


EL= extended lymphadenectomy, Non-EL= non-extended lymphadenectomy, SE= standard error, CI= confidence interval, p values significant if less than 0.05.

1.6.7 Total recurrences (Figure 12)

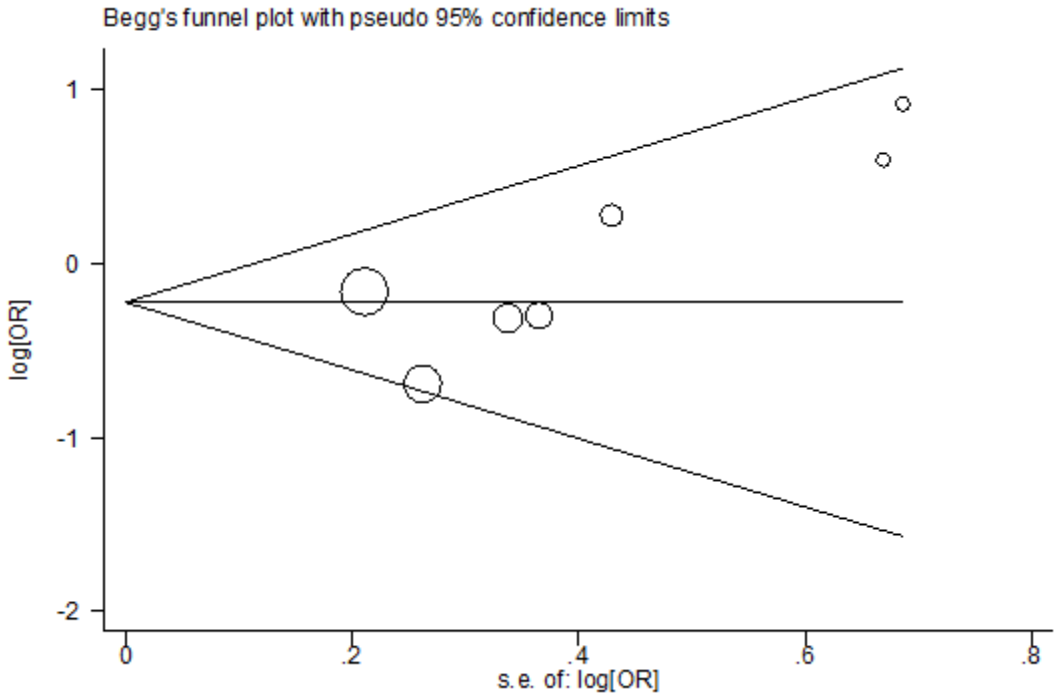
Data on total recurrences were extracted from seven studies (35, 201, 203, 205, 208, 211, 214) evaluating 1423 patients. There was no significant difference between the two groups in terms of diagnosing local or distant recurrence (OR= 0.80, 95% CI 0.63 – 1.02, p= 0.072), with moderate between-study heterogeneity (Chi-square test= 8.97, df=6, p= 0.18; I^2= 33%). There was evidence of publication bias by Begg's test (p= 0.04) with asymmetry in the funnel plot as shown in figure 13. Large studies (>100 subjects) were more likely to report a positive outcome (i.e. favouring the EL group).

Figure 12. Total Recurrences



EL= extended lymphadenectomy, Non-EL= non extended lymphadenectomy, SD= standard deviation, CI= confidence interval, p values significant if less than 0.05.

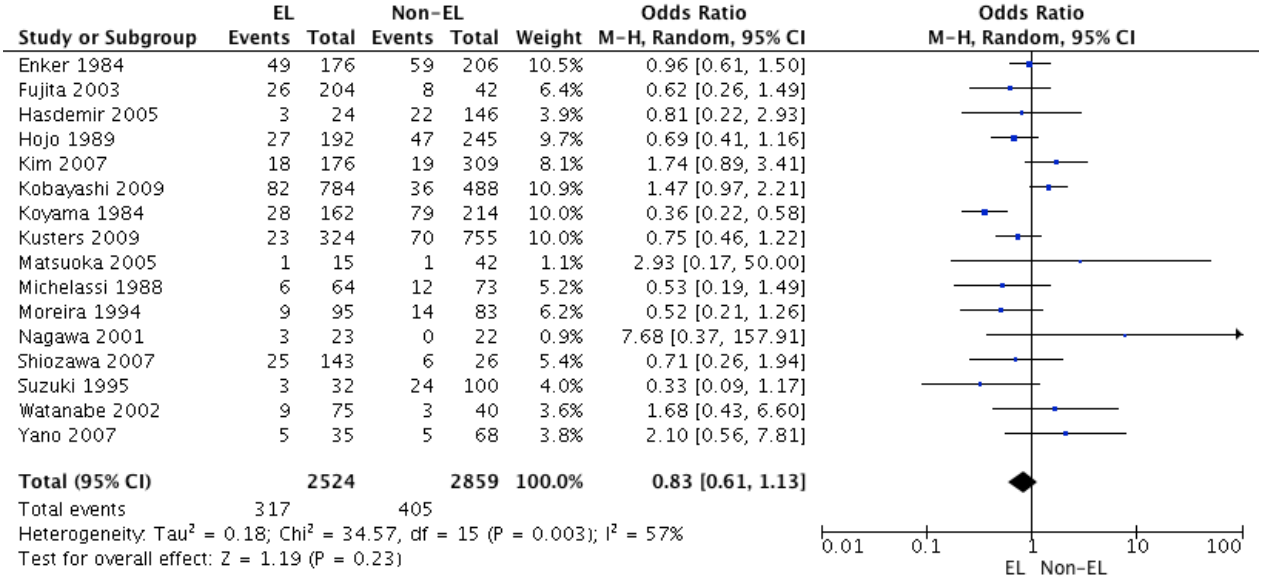
Figure 13. Funnel plot demonstrating asymmetry indicative of publication bias for total recurrences favouring EL in large sample size studies



1.6.8 Local recurrence (figure 14)

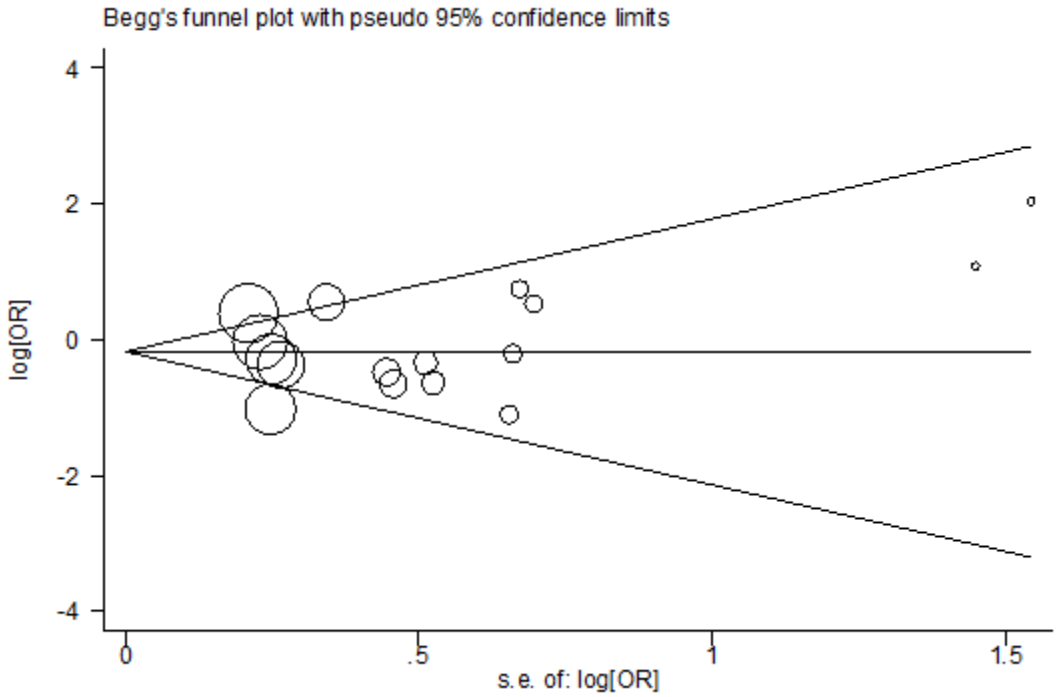
Sixteen studies (34, 35, 138, 200-206, 208, 210-212, 214, 215) evaluating 5383 patients reported on local recurrence. There was no significant difference for diagnosing local recurrence between the two groups (OR= 0.83 95% CI: 0.61 - 1.13, p= 0.23), with significant between-study heterogeneity (Chi-square test= 34.57, df=15, p= 0.0028; I^2= 57%). No publication bias was detected by Begg's test (p= 0.50) as shown graphically by the funnel plot in Figure 15.

Figure 14. Local Recurrences



EL= extended lymphadenectomy, Non-EL= non-extended lymphadenectomy, SD= standard deviation, CI= confidence interval, p values significant if less than 0.05.

Figure 15. Funnel plot for local recurrences

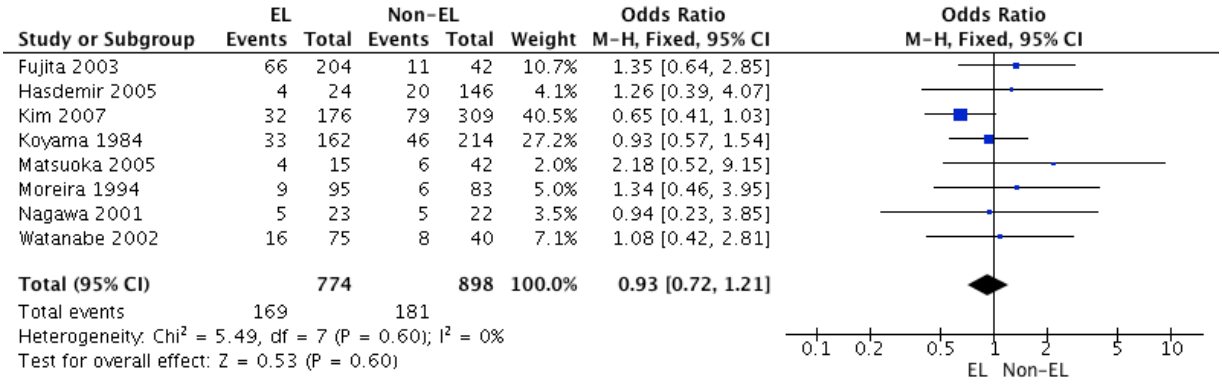


The Begg's test for local recurrences demonstrated symmetry around the reference line which is indicative of no evidence of publication bias.

1.6.9 Distant recurrence (figure 16)

Eight studies (35, 201-203, 205, 208, 211, 214) evaluating 1672 patients reported on distant recurrence. No significant difference was found for diagnosing distant recurrence between the two groups (OR= 0.93, 95% CI: 0.72 – 1.21, p= 0.60), with no significant heterogeneity (Chi-square test= 5.49, df=7, p= 0.60; I^2= 0%). No publication bias was detected by Begg's test (p= 0.17).

Figure 16. Distant recurrence



EL= extended lymphadenectomy, Non-EL= non extended lymphadenectomy, SD= standard deviation, CI= confidence interval, p values significant if less than 0.05.

1.6.10 Urinary dysfunction

Three (35, 207, 208) studies evaluating 139 patients reported on urinary dysfunction. The difference was statistically significant favouring non-EL (OR= 3.73, 95% CI: 1.69 – 8.25, p= 0.0012), with no significant between-study heterogeneity (Chi-square test= 0.41, df=2, p= 0.81; I^2= 0%). In addition Kyo *et al* (207) demonstrated that there was no significant difference in the number of patients who developed dysuria (p= 0.19), urinary tract infection (p= 0.13) or required intermittent self catheterization (p= 0.85) and that the patients who had EL had a significantly higher frequency of micturition (p= 0.042).

1.6.11 Urinary incontinence

Three studies (198, 207, 208) evaluating 264 patients reported on urinary incontinence. The difference was statistically significant favouring non-EL (OR= 2.08, 95% CI: 0.98 - 4.39, p= 0.055), with no significant between study heterogeneity (Chi-square test= 0.27, df= 2, p= 0.87; I^2= 0%).

1.6.12 Urinary retention

Three studies (34, 198, 215) evaluating 400 patients reported on urinary retention. The difference approached statistical significance favouring non-EL (OR= 2.31, 95% CI: 0.89 – 5.99, p= 0.084), with moderate between study heterogeneity (Chi-square test= 2.76, df= 2, p= 0.25; I^2= 28%).

1.6.13 Sexual dysfunction

Individual studies have reported the incidence of sexual dysfunction between the two groups favouring the non-EL group. This outcome was not suitable for meta-analysis. Nagawa *et al* (35) showed that 45.5% (5/11) and 92.3% (12/13) of patients who underwent non-EL and EL respectively had sexual dysfunction (p= 0.012). Kyo *et al* (207) reported that patients in the EL group had more erectile (p= 0.03) and ejaculatory (p<0.005) dysfunction compared with their pre-operative function, with no statistical difference shown for the non-EL group. Col *et al* (199) studied sexual function with the use of the International Index of Erectile Function and showed that in both groups the scores were significantly decreased following surgery, but no significant difference was demonstrated between the groups (p>0.05).

1.6.14 Defaecatory dysfunction

Two studies (35, 208) evaluating 84 male patients reported on defaecatory dysfunction. The difference was not significant between the two groups (OR= 2.36, 95% CI: 0.54 – 10.35, p= 0.25). Between-study heterogeneity was not significant

(Chi-square test= 2.01, df= 1, p= 0.16; I^2= 50%). Additionally Matsuoka *et al* (208) used anal manometry to investigate anal sphincter dysfunction and found no significant difference between the groups. Multivariable analysis demonstrated that the height of the anastomosis from the anal verge was an independent risk factor for defaecatory dysfunction (OR= 0.89 95% CI: 0.83-0.96, p= 0.0050).

1.6.15 Sensitivity analysis (Table 9)

When high quality (34, 202-204, 206, 208, 210, 212, 214, 215) and studies published after 2000 (35, 198, 199, 201-204, 206-208, 212, 214, 215) were assessed, no change in terms of the significance of each of the outcomes studied was demonstrated. Between-study heterogeneity was significantly reduced by the sensitivity analysis for local recurrence, but not for long-term survival outcomes where heterogeneity remained statistically significant.

Four studies (200, 205, 211, 212) evaluated 5-year survival for patients with Dukes' C cancer, matched for neo-adjuvant or adjuvant radiotherapy, favoured the EL group (HR= 1.49, 95% CI: 1.18 – 1.88, p= 0.0067) with evidence of between-study heterogeneity (Chi-square test= 45.35, df= 3, p<0.0001; I^2= 93%). In this analysis, only one study was of high quality and none were matched for patients' age. A similar advantage favouring the EL group was also present amongst five studies (34, 200, 201, 205, 211) evaluating local recurrence in Dukes' C patients (OR= 0.55, 95% CI: 0.40 – 0.77, p= 0.0048) with no evidence of between-study heterogeneity (Chi-square test= 1.58, df= 4, p= 0.81, I^2= 0%). No significant difference was found amongst five studies (34, 200, 201, 205, 211) in local recurrence (OR= 0.45, 95% CI: 0.15 – 1.38,

p= 0.16) for Dukes' B cancer with significant between-study heterogeneity (Chi-square test= 15.10, df= 4, p= 0.0045; I^2= 74%).

Table 9. Sensitivity analysis extended lymphadenectomy (EL) versus non-extended lymphadenectomy (non-EL) for patients undergoing surgery for rectal cancer**.**

	No of Studies	Pts EL	Pts Non-EL	Pts Total	HR*/ OR	95% CI	p-value	Study heterogeneity			
								Chi-square	df	I^2	p-value
High quality studies											
5-year survival	4	974	696	1670	0.95 *	0.75 - 1.21	0.67	9.87	3	70%	0.020
Total recurrences	4	289	413	702	1.11	0.72 - 1.71	0.63	3.58	3	16%	0.31
Local recurrence	11	1855	2214	4069	1.05	0.76 - 1.44	0.77	15.24	10	34%	0.12
Distant recurrence	5	313	559	872	0.82	0.57 - 1.17	0.37	3.69	4	0%	0.45
Studies published after 2000											
5-year survival	4	974	696	1670	0.95*	0.75 - 1.21	0.67	9.87	3	70%	0.020
5-year disease-free survival	4	394	250	644	1.23*	0.75 - 2,03	0.41	13.51	3	78%	0.0037
Total recurrences	5	493	455	948	0.98	0.70 - 1.37	0.91	4.36	4	8%	0.36
Local recurrence	10	1803	1938	3741	1.14	0.83 - 1.57	0.43	11.91	9	24%	0.22
Distant recurrence	6	517	601	1118	0.91	0.65- 1.26	0.57	5.03	5	1%	0.41
Dukes' B cancer only											
Local recurrence	5	294	260	554	0.45	0.15 – 1.38	0.16	15.10	4	74%	0.0045
Dukes' C cancer only											
5-year survival	4	593	547	1140	1.49 *	1.18 – 1.88	0.0067	45.35	3	93%	<0.0001
Local recurrence	5	442	351	793	0.55	0.40 – 0.77	0.0048	1.58	4	0%	0.81

Pts= patients, EL= extended lymphadenectomy, non-EL= non extended lymphadenectomy, HR= hazard ratio, OR= odds ratio, WMD= weighted mean difference, df= degrees of freedom, *= Hazard ratio

1.7 Discussion

This meta-analysis comparing extended and non-extended lymphadenectomy of the lateral pelvic wall nodes in patients with rectal cancer showed no overall difference in cancer specific outcome. On sensitivity analysis of high quality and studies published after 2000, no change in terms of the significance of each of the outcomes studied was demonstrated. A marginal benefit for EL in survival and local recurrence in patients with a Dukes' C but not Dukes' B carcinoma was suggested; however, these data were derived mostly from low-quality studies unmatched for age, and therefore these results should be interpreted with caution. Extended lymphadenectomy was associated with longer operating time, greater intra-operative blood loss and a higher incidence of urinary and possibly sexual dysfunction.

The present meta-analysis has the following limitations. Firstly, except for one, all the studies included were observational. They were carried out in clinical centres with varying protocols and probably different levels of surgical expertise. Secondly, the studies included in the analysis were mostly conducted at tertiary cancer centres and major institutions, and therefore the patients included might not reflect patient populations in the community. Thirdly, the heterogeneity of the survival and local recurrence rates has been shown to be significant. Sensitivity analysis eliminated the heterogeneity for local recurrence (studies after 2000, Dukes' C cancers) but did not for survival. The differences in sample size, patients' age, the height of tumour, the percentage of bilateral and unilateral lymphadenectomy, tumour stage and grade, neo-adjuvant and adjuvant medical therapy and other factors among the studies might be responsible for the high heterogeneity. Calculations using the random-effects model

for overall incidence estimation might minimise but do not abolish this. Fourthly, the Japanese patient eligibility criteria for extended lymphadenectomy differ from those in the west. The essence of Japanese surgery is that each patient with rectal cancer will have a lateral pelvic node dissection with or without nerve sparing. The eligibility criteria are therefore not stage-dependent but are based on the recommendations of the Japanese Research Society for Cancer of the Colon and Rectum. These selection criteria are acknowledged in the present meta-analysis but are potentially a source of significant bias. Fifthly, there was evidence of publication bias in one of the outcomes (total recurrences), and therefore the results should be interpreted with caution. Finally, this meta-analysis was performed at a study level and cannot, therefore, address or incorporate individual factors at patients' level.

The question, whether extended lymphadenectomy provides a survival benefit in rectal cancer patients cannot be safely answered by this meta-analysis. In an attempt to answer to this question, the Japanese Clinical Oncology Group (JCOG) has started a Phase III randomised controlled clinical trial comparing mesorectal excision with and without lateral lymph node dissection. (http://clinicaltrials.gov/ct2/show/NCT00190541). The selection criteria for this study include a single primary adenocarcinoma of the lower rectum of clinical Stage II or III with no evidence of extra-mesorectal lymph nodes metastases greater than 10mm in diameter. Patients undergoing neo-adjuvant chemotherapy or radiotherapy are excluded. Thus the value of neo-adjuvant chemoradiotherapy, which may be an alternative to extended lymphadenectomy, will not be assessed.

Pre-operative radiotherapy has been shown to reduce the yearly risk of local recurrence for rectal cancer by up to 46%. (216) A recent large multicentre randomised controlled trial (217) demonstrated that neo-adjuvant radiotherapy can reduce the risk of local recurrences by up to 61%, although without significant improvement in overall survival. One reason for this effect of radiotherapy may be that it sterilises involved pelvic sidewall lymph nodes. In the only randomised control trial of EL (n= 23) versus non-EL (n= 22) after pre-operative radiotherapy (50 Gy) in both groups, Nagawa *et al.* (35) reported no difference in disease-free survival or local recurrence. Given the small sample size and the fact that the study did not include patients with involvement of the lateral pelvic nodes, no safe conclusion can be made on the role of either radiotherapy or extended lymphadenectomy in this group of patients.

Similarly, Watanabe *et al* (214) in a retrospective non-randomized study of four patient groups comparing EL with non-EL using either 50 Gy pre-operative radiotherapy (n= 78) or no radiotherapy (n= 37) demonstrated a 5-year survival advantage in the radiotherapy group (74.6% vs 45.9%; p=0.006). The authors reported no significant survival difference between the patients who had neo-adjuvant radiotherapy with conventional surgery (n=25) compared with those who had conventional surgery plus extended lymphadenectomy without neo-adjuvant radiotherapy (n= 22). This result is consistent with the results of a more recent larger study. (206) The authors concluded that pre-operative radiotherapy can be an alternative to extended lymphadenectomy, but again the small sample size does not allow a safe conclusion. All the above studies (35, 206, 214), assessed the value of preoperative radiotherapy in the management of rectal cancer compared with

extended lymphadenectomy. However, at present the standard pre-operative neo-adjuvant regime combines chemotherapeutic agents including 5-FU, oxaliplatin, irinotecan or capecitabine with radiotherapy. Thus, studies, which do not include combined chemoradiotherapy as an alternative to EL, are no longer clinically valid. As a result, no conclusion regarding the impact of EL when compared with neo-adjuvant chemoradiotherapy can be drawn.

Peri-operative morbidity was 11.6% less in the non-EL group, a difference that failed to reach statistical significance possibly due to small sample size. A power calculation was undertaken to assess the likelihood of a type II error. To demonstrate a reduction of 11.6% in postoperative morbidity between the two groups at a probability of 5% with 90% power, a traditional randomised controlled trial would require 306 patients in each arm.

The differences in urinary and sexual function between EL and non-EL demonstrated in this meta-analysis were significant in favour of the latter. These results are to be expected, as the autonomic nerves are more vulnerable to injury during EL. Some of this dysfunction may, however, have been due to radiotherapy, although the dose and field in each of the included studies is not clearly stated. Radiotherapy has been shown to affect adversely bowel, urinary and sexual function (218) making difficult the interpretation of the functional results due to EL. A distinction should be made between the morbidity of radiotherapy and EL rather than using both.

In current practice where chemoradiotherapy is available, there would appear to be little indication for EL. Perhaps in the absence of these treatment modalities, EL

would seem reasonable to advise in addition to conventional surgery where there is preoperative evidence of lateral pelvic wall lymphadenopathy. This circumstance will be rare however, and there is no evidence from the present meta-analysis to support this speculation.

1.8 Chapter's Conclusion

Extended lymphadenectomy does not appear to confer any overall advantage for survival or local recurrence when compared with non-extended lymphadenectomy surgery for rectal cancer. It has the disadvantages of longer operating time, greater intra-operative bleeding, increased urinary and possibly sexual dysfunction.

1.9 Future Considerations

A randomised controlled trial, comparing EL with neoadjuvant chemoradiotherapy is likely to be able to provide a more definite answer to this long standing debate. No randomised study has been performed up to the writing of this thesis.

CHAPTER 5. Extended lymphadenectomy of locally advanced primary and recurrent rectal cancer

1.1 Introduction

The previous chapter demonstrated that the performance of extended lateral lymphadenectomy did not have a significant overall benefit for primary rectal cancer when performed to an unselected group of patients. It did show however that there may be a marginal benefit when performed for higher stage cancers (Duke's C; sensitivity analysis). This had led to the question whether there is a benefit performing this type of procedure in patients with locally advanced primary and recurrent rectal cancer that require surgery beyond the levels of TME to achieve cure. The performance of EL in patients with locally advanced primary and recurrent rectal cancer that require exenterative pelvic surgery for cure, was not previously investigated by the time of the conception of this thesis.

1.2 Aims of the study

This study aimed to compare the value of extended (lateral) lymphadenectomy to non-extended lymphadenectomy in patients diagnosed with locally advanced and recurrent rectal cancer requiring exenterative pelvic surgery to achieve complete clearance.

1.3 Results

1.3.1 Demographic data (table 10)

A total of 41 (28 males) patients with a median age of 64 (39-81) were included in the present study. Twelve (29.27%) patients with locally advanced primary and 29 (70.73%) patients with recurrent rectal cancer underwent exenterative pelvic surgery. Lateral pelvic sidewall lymphadenectomy was performed in 17 (41.4%) patients. The patients in the EL group were younger (median age 57 (40-71)) compared to the non-EL group (median 66 (39-81); p= 0.042). There was no statistically significant difference in the gender distribution between the two groups (p= 0.467). 31 (75.6%) patients were treated with neoadjuvant radiotherapy; 12 and 19 were in the EL and non-EL groups respectively. This difference did not reach statistical significance (p= 0.529). All patients had open surgery with 14 (34.15%) of them undergoing an abdominosacral resection with the remainder having other pelvic exenterative procedures. There was no statistically significant difference in the type of surgery that was performed in the two groups (p= 0.192). Four plastic reconstructions with flaps were performed in EL group and 13 in the non-EL group. This difference approached statistical significance (p=0.051).

Table 10: Demographic data

	Total (n=41)	EL (n=17)	Non-EL (n=24)	p
Age (mean; SD)	64 (39-81)	57 (40-71)	66 (39-81)	0.042
Sex (M/F)	28/13	11/6	17/7	0.678
Recurrent cancer	29	10	19	0.158
Primary cancer	12	7	5	

Radiotherapy	31	12	19	0.529
Surgery				0.228
• ASR	14	4	10	
• PE	27	13	14	
Flaps	17	4	13	0.051
Histopathology type				0.791
• Adenocarcinoma	37	15	22	
• Signet Cell	2	1	1	
Differentiation				0.636
• Well/moderate	20	7	13	
• Poor/Mucinous	19	9	10	
PNI	19	6	13	0.242
Vascular Invasion	20	7	13	0.433

Abbreviations: n= number, EL= extended lymphadenectomy, non-EL= non extended lymphadenectomy, p= probability of obtaining a test statistic at least as extreme as the one that was actually observed, M= male, RT= radiotherapy, F= female, PE= pelvic exenteration, APER= abdominoperineal excision of the rectum, SCC= squamous cell carcinoma, PNI= perineural invasion.

1.3.2 Perioperative outcomes *(table 11)*

The median intraoperative time (IOT) was 9 (3-13) and 8 (4-15) hours for the EL and non-EL groups respectively. The median intraoperative blood loss was 1.5 (0.3-7) and 1.6 (0.25-17) litres for the EL and non-EL groups. The median length of stay was 15 days for both groups. Neither of the above perioperative outcomes reached statistical significance ($p \geq 0.394$). A total of 4/17 (23.52) complications were observed in the EL group and 9/24 (37.5%) in the non-EL group. This difference was not

statistically significant between the two groups either (p=0.344). For the EL group, there were 2 patients with Clavien-Dindo (219) grade 4 complications and two with grade 3. For Non-EL group there were 1 grade 4, 5 grade 3, 2 grade e and 1 grade 1.There was no significance between the two groups (p=0.367) There was no perioperative mortality.

Table 11: Perioperative outcomes

	Total (n=41)	EL (n=17)	Non-EL (n=24)	p
IOT (median; range)	8(3-15)	9(3-13)	8(4-15)	0.903
Blood Loss (median; range)	1.6(0.25-17)	1.5(0.3-7)	1.6(0.25-17)	0.887
LOS (median; range)	15(10-86)	14(12-72)	14(10-86)	0.394
Morbidity	13	4	9	0.344

Abbreviations: n= number, EL= extended lymphadenectomy, non-EL= non extended lymphadenectomy, IOT= intraoperative time, LOS= length of stay, EL= extended lymphadenectomy, ASR= abdominosacral resection

1.3.3 Oncological Outcomes *(table 12)*

Curative resections were achieved in 30 (72.1%) patients: 12 (70.58%) in the EL group and 18 (75%) in the non-EL group. There were 8 (19.51%) patients with microscopic residual disease (R1) at the resection margins, 3 (17.64%) in the EL group and 5 (20.83%) in the non-EL group. In 3 (7.32%) patients, there was macroscopic residual disease at the resection margins (R2), 2 (11.76%) in the EL and 1 (4.17%) in the non-EL group. There was no statistically significant difference between the two groups in terms of tumour clearance (p= 0.649). There were 6 (35.29%) patients with malignant lateral pelvic sidewall lymph nodes. Other

histopathological data are shown in table 10. There was no significant difference between the two groups in terms of the histopathology either (p≥0.242). Two patients responded fully to neoadjuvant radiotherapy, one in each group.

Table 12: Oncological outcomes

	Total (n=41)	EL (n=17)	Non-EL (n=24)	p
Clearance				0.649
• R0	30 (73.17%)	12(70.58%)	18 (75%)	
• R1	8 (19.51%)	3 (17.64%)	5 (20.83%)	
• R2	3 (7.32%)	2 (11.76%)	1 (4.17%)	
Local Recurrence	12/38 (31.58%)	6/15 (40%)	6/23 (26.08%)	0.367
Distant Recurrence	8 (19.51%)	2 (11.76%)	6 (25%)	0.292

Abbreviations: n= number, EL= extended lymphadenectomy, non-EL= non extended lymphadenectomy, R0= complete tumour resection, R1= microscopic residual tumour at the margins, R2= macroscopic residual tumour at the margins or irresectable tumour, LR= local recurrence, DR= distant recurrence

Since three patients had R2 resections, 38 patients were included for recurrence and disease-free survival. There were 6 patients in each group that were diagnosed with local recurrence following potentially curative surgery (R0 and R1). There was no statistically significant difference between the two groups (p= 0.367). All local recurrences were diagnosed within three years from surgery. There were 2 local recurrences per year in the EL group (table 13). There were 4 local recurrences within the first year of surgery in the non-EL group, 1 in the second and 1 in the third. Distant metastases were diagnosed in 2 (13.33%) and 6 (26.08%) patients in the EL

and non-EL groups respectively (all patients). This difference did not reach statistical significance (p= 0.292).

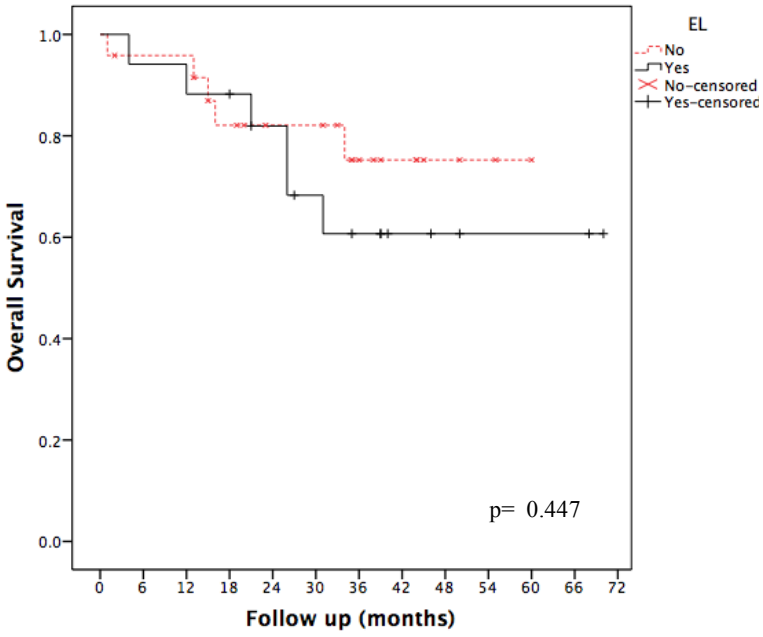
Table 13. Recurrences diagnosed per year

	1 years	2 years	3 years	5 years
Local Recurrence				
• EL	2	2	2	0
• Non-EL	4	1	1	0
Distant Recurrence				
• EL	1	1	0	0
• Non-EL	4	1	1	0

Abbreviations: EL= extended lymphadenectomy, non-EL= non-extended lymphadenectomy

Overall survival, disease-free survival and local recurrence-free survival curves were generated using the Kaplan-Meier method. The two groups were compared using the log-rank test. One (1/41; 2.44%) patient in the non-EL group was lost to follow up two months after curative surgery (R0). The longest follow up was 70 months with median follow up of 33 months. For overall survival, (figure 17) 88.2% (SE= 7.8%), 81.9% (SE= 9.5%) and 60.7% (SE= 12.7%) patients were alive at 12, 24 and 36 months respectively following surgery in the EL group; 95.8% (SE= 4.1%), 82.1% (SE= 8.2%) and 75.2% (SE=9.9%) patients were alive at 12, 24 and 36 months respectively in the non-EL group. There was no statistically significant difference between the two groups (p= 0.447).

Figure 17: Survival

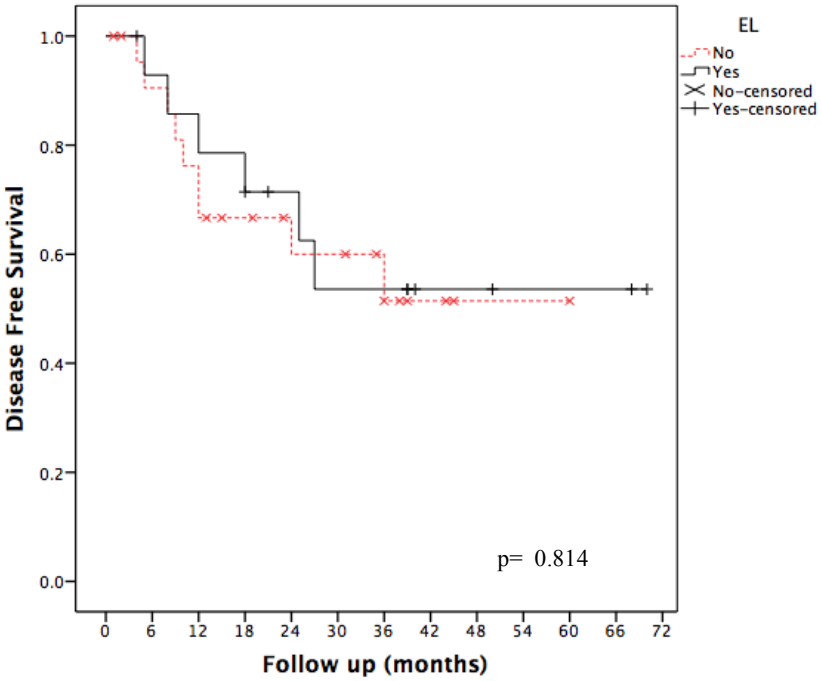


Months	0	6	12	18	24	30	36	42	48	54	60
No	24	22	22	17	14	14	8	6	3	2	0
Yes	17	16	15	14	12	9	7	4	3	2	2

Abbreviations: EL= extended lymphadenectomy

For the disease- and local recurrence-free survival curves, patients with either complete (R0) or residual microscopic disease at the margins (R1) were included. A total of 78.6% (SE=11%), 71.4%(SE=12.1%) and 53.6% (SE=14.2%) were disease free at 12, 24 and 36 months from surgery in the EL group respectively; 66.7% (SE=10.3%), 60% (SE=11.2%) and 51.4% (SE=12.5%) were disease free at 12, 24 and 36 months following surgery in the non-EL group respectively (Figure 18). This difference did not achieve statistical significance (p=0.814).

Figure 18: Disease free survival

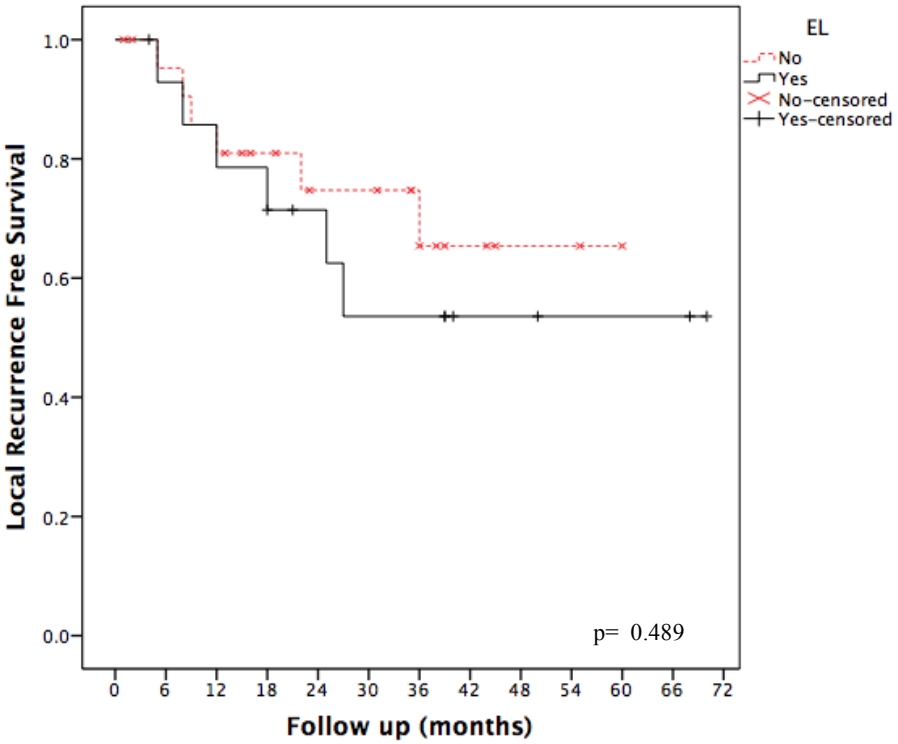


Months	0	6	12	18	24	30	36	42	48	54	60
No	23	19	14	12	9	9	5	3	1	1	0
Yes	15	13	11	9	8	6	6	3	3	2	2

Abbreviations: EL= extended lymphadenectomy

A total of 78.6% (SE=11%), 71.4% (SE=12.1%) and 53.6% (SE=14.2%) were local recurrence-free at 12, 24 and 36 months from surgery respectively in the EL group; 81% (SE= 8.6%), 74.7% (SE=9.9%) and 65.4% (SE= 12.3%) were local recurrence-free after 12, 24 and 36 months respectively following surgery in the non-EL group (figure 19). This difference did not reach statistical significance (p= 0.489).

Figure 19: Local Recurrence free Survival



Months	0	6	12	18	24	30	36	42	48	54	60
No	23	20	17	14	11	11	6	4	2	2	0
Yes	15	13	11	9	8	6	6	3	3	2	2

Abbreviations: EL= extended lymphadenectomy

1.4 Discussion

This was an observational study that investigated the value of lateral pelvic sidewall lymphadenectomy in a group of consecutive patients who underwent exenterative surgery for locally advanced primary and recurrent rectal cancer. The present study demonstrated no statistically significant differences between EL and non-EL in terms of peri-operative (intraoperative time and blood loss, morbidity and length of hospital stay) and oncological (clearance rates, recurrences, overall and disease-free survival) outcomes. However, the patients in the EL group were younger than the patients in the non-EL group.

Intraoperative time and blood loss always have concerned surgeons when planning extended lymphadenectomy in primary rectal cancer patients. Intraoperative time and blood loss have been previously shown to increase by 76 min and 500ml respectively when lateral pelvic sidewall lymphadenectomy was performed for primary rectal cancer (220). The present study investigated the value of EL in patients that underwent exenterative pelvic surgery for locally advanced primary and recurrent rectal cancer and demonstrated no substantial difference between the two groups. Exenterative pelvic surgery alone is known to last longer and to result in significant intraoperative blood loss (129, 221). This is reflected by the results of this study and may explain the absence of significant difference between the two groups.

Overall survival, local recurrence-free and disease-free survival rates were demonstrated to have no significant difference between the EL and non-EL group. However, the difference for the overall and local recurrence-free survival was large and cannot be overlooked on the basis of statistical significance, with the non-EL group having a more favourable outcome. This may be a reflection of a more advanced and challenging to treat disease, for the patients with tumour invading the lateral pelvic sidewall. These findings need to be interpreted with caution though due to the small size of this study. A prospective randomised study with a larger number of patients may provide the power to answer this question. All recurrences occurred within three years following surgery which is consistent with the results published by other studies that report the majority of the recurrences were diagnosed within three years from surgery (133, 159) although tumours may recur up to 10 years following surgery (159).

Neo-adjuvant (chemo)radiotherapy has been shown to reduce local failure significantly following surgery for recurrent rectal cancer (p= 0.036) but has not been demonstrated to influence overall survival and metastasis-free survival (222). For primary rectal cancer, published studies suggested that radiotherapy might have a similar result to EL in terms of overall and disease-free survival (35, 214). For recurrent and locally advanced rectal cancers, the evidence is not clear with regards to the value of radiotherapy. At the Institute of the authors, neoadjuvant chemoradiotherapy is always used for patients that undergo exenterative surgery for primary and recurrent rectal cancer when it is not contraindicated. It is also of high importance to emphasise that further research investigating the role of chemoradiotherapy is essential in this group of patients.

Lateral pelvic sidewall lymphadenectomy has an adverse impact in the quality of life of patients in terms of urinary (34, 198, 215) and sexual (35, 199, 207) function as previously demonstrated for primary rectal cancer, as the autonomic nerves in the region are at high risk or are sacrificed to achieve optimum oncological outcome. Therefore, a significant amount of time is required preoperatively to discuss the benefits and risks of extended lymphadenectomy with patients due to undergo surgery for primary cancer surgery. The quality of life of patients undergoing exenterative surgery has also been demonstrated to be adversely affected (223). This is due to the sacrifice of the nerves along with other intrapelvic organs due to their close relationship or close proximity to the tumour. Therefore, *en bloc* dissection of the lateral pelvic lymph nodes may be preferred to nerve preservation lymphadenectomy as it very rarely influences the postoperative quality of life in this group of patients. A

recent study (224) that aimed to measure the quality of life for long-term disease-free survivors after pelvic exenteration demonstrated comparable results to low anterior resection or abdominoperineal excision of the rectum for primary rectal cancer. They demonstrated a low score for the physical component but similar scores in the mental component of the scoring form.

In the present study, the patients that underwent lateral pelvic sidewall lymphadenectomy were younger than the patients who did not. However, age is not a factor in the decision process to perform this procedure. When a patient is deemed fit for exenterative surgery, it is extremely unlikely that extended lymphadenectomy will be rejected as an option, if required. Exenterative pelvic surgery carries significant risks with the morbidity ranging up to more than 50% of the operated patients (129, 133, 155, 157, 158). Therefore, patients are thoroughly examined and tested to ensure their fitness to endure the operation and minimise morbidity.

A decision for lateral pelvic sidewall lymphadenectomy was taken in this series of patients when there was either radiological or intraoperative evidence of malignant lateral pelvic sidewall lymph nodes, or the tumour invaded the lateral pelvic compartment and had to be removed *en bloc* with the lymph nodes. Tumours within the lateral pelvic compartment are considered to have a poorer prognosis (18, 19,(221). The fact that younger patients had to undergo lateral pelvic sidewall lymphadenectomy may indicate that their tumour was more aggressive, a factor that may need to be taken into account when considering young patients for exenterative pelvic surgery. However, further studies investigating the tumour histopathology of these patients are essential to conclude this.

Lateral compartment recurrences, including the lateral lymph nodes, can be up to 26.7% of the patterns of local recurrence and demonstrated to be a factor that adversely affects the survival following surgery (49, 225). This can be partially a result of the high risk of incomplete tumour resection when it extends within the lateral pelvic compartment. Moore et al (18) demonstrated that pelvic sidewall recurrence was a strong determinant of incomplete resection (p=0.004). Similarly, Sagar *et al.* (19), in a series of 40 patients that underwent abdominosacral resection for recurrent rectal cancer, demonstrated that 15/20 (75%) patients with non-curative resections had lateral compartment recurrence. This led them to consider extending their resection margins in future cases when preoperative MR imaging identifies tumour within the lateral compartment. Performing lateral pelvic sidewall lymphadenectomy might be a method of extending the lateral resection margins and may be considered in patients when aiming curative resection.

One of the strengths of the present study was that the patients were managed and operated by the same multidisciplinary team thus eliminating bias. One of the limitations of this study is the relatively small number of patients that were included requiring a careful interpretation of the results of this study. Exenterative surgery or this group of patients is performed on about 250 patients a year in the UK and several years will be required to gather adequate data to increase the power of the study significantly. A second limitation may be that a single colorectal surgeon, albeit with experience in pelvic cancer surgery, performed these procedures. Thus, the reported outcomes might not be representative since there is likely to be some variance between surgeons.

1.5 Chapter's Conclusion

The present study demonstrated that lateral pelvic sidewall lymphadenectomy does not offer a statistically significant advantage in terms of oncological and perioperative outcomes in patients that undergo exenterative surgery for locally advanced primary and recurrent rectal cancer and that it is safe to perform. However, the study size is small and these results should be interpreted with caution.

1.6 Future considerations

Randomised studies are required to look into the benefits of extended lymphadenectomy for this group of patients. No randomised study has been performed up to the writing of this thesis.

CHAPTER 6: Diagnostic accuracy and value of MRI

1.1 Introduction

As it is evident from the previous chapters, it is imperative for the surgeon to accurately know the pelvic compartments that the tumour invades, as this will determine the level of the resection required to achieve complete resection of the tumour successfully. Therefore, accurate pre-operative staging can help to better select patients for surgical and medical therapy and maximise the potential for cure. At the time of the conception of this thesis, no studies were performed to identify the surgical and oncological significance in determining the extent of cancer within the pelvis.

The following hypothesis was made for this group of patients. The pre-operative MRI is accurate in diagnosing tumour extent within the pelvis and can be used to plan exenterative pelvic surgery and to predict the oncological outcome.

1.2 Aims of the study

This study aimed to assess the value of MRI in detecting tumour invasion within the seven intrapelvic compartments for planning exenterative pelvic surgery for patients with locally advanced primary and recurrent colorectal pelvic cancer; and to assess its value in predicting the oncological outcome.

1.3 Study design and subjects

Consecutive patients treated for locally advanced rectal or recurrent colorectal pelvic cancer by a single surgical team between March 2006 and August 2010 were

included. MRI scanning was performed as part of the pre-operative staging. The decision for surgery was taken during the multidisciplinary meeting based on a combination of tumour marker measurement, colonoscopy, examination under anaesthesia, radiological staging and pre-operative biopsies. A dedicated gastrointestinal histopathologist examined all resected specimens. The interpretation of the MRI images using the proposed pro-forma was performed retrospectively and blinded to the initial reporting, operative and histopathological findings. The individual pro-forma scoring was compared with the intraoperative and histopathological findings (reference standard). The study followed the guidelines proposed by the Standards for the Reporting of Diagnostic accuracy studies (STARD criteria; Appendix 6) (226).

1.4 Inclusion and exclusion criteria

Entry to the study required evidence of a locally advanced primary rectal or recurrent colorectal intrapelvic cancer. Other inclusion criteria were age over 18 years, the capacity to consent to surgery, availability of pre-operative MRI, histologically confirmed cancer diagnosed by pre-operative biopsy or strong radiological evidence of recurrence by two modalities. Patients were excluded if a pre-operative MRI was not performed or if the MRI images were unsuitable for the evaluation of the individual compartments due to poor quality.

1.5 Surgical pelvic anatomical compartments

The same classification as described in methods was used to divide the pelvis into seven compartments according to the fascial boundaries and planes of dissection between the intrapelvic organs (table 4).

1.6 Qualitative MRI assessment of tumour invasion

This is described in the chapter of General Methods.

1.7 Reference Standard

The same reference standard as described in the chapter of methods was employed for this study.

1.8 Statistical analysis

Sensitivity, specificity, positive and negative predictive value and the area under the receiver operating characteristic curve (AUC) were calculated for the MRI sequences on a compartment-by-compartment basis. Exact binomial confidence intervals were obtained for sensitivity, specificity and predictive values.

Cohen's Kappa (κ) coefficient was used to assess the inter-observer agreement for the individual compartments with values of between 0.61-0.80 indicating good agreement and values above 0.81 indicating very good agreement. 95% confidence intervals were calculated for the diagnostic accuracy tests and Kappa value.

Multivariate and univariate Cox proportional hazards regression was used to evaluate the risk of death and disease recurrence following surgery (shown as hazard ratio (HR)) with an MRI diagnosis of tumour presence within each compartment.

Comparisons were considered statistically significant at a probability value of $p<0.05$. Data were entered in Statistical Package for the Social Sciences (SPSS® Inc., Chicago, IL) and Intercooled Stata™ version 9.0 for Mac (Stata Corporation, College Station, TX USA) statistical analysis software.

1.9 Results

1.9.1 Demographic characteristics (table 14)

One hundred and nineteen patients were diagnosed with recurrent pelvic or locally advanced rectal cancer during the study period. They were all discussed at the multidisciplinary meeting. Fifty-two were deemed irresectable/inoperable or unfit for surgery and three declined surgery and were therefore excluded from the study. No patient was excluded due to low quality MRI. This was because all the patients that underwent exenterative pelvic surgery also had a repeat pre-operative MRI. The remaining sixty-four patients (41 males; mean age 60.5 years) satisfied the criteria for inclusion in the study of which forty-nine received neoadjuvant chemoradiotherapy. Forty-one patients underwent surgery for recurrent and twenty-three for a locally advanced primary cancer. No patient received other forms of oncological therapy between the scan and surgery. The median interval from primary surgery to MRI for patients with recurrent cancer was 24 (4-121) months, and the interval from MRI to exenterative pelvic surgery was 5 (0-17) weeks.

There was only one patient with a 17 week interval between MRI and surgery. The operation was performed with palliative intent and it was deemed that a repeat MRI scan was not necessary. The patient was included as the intraoperative findings and biopsies enabled comparison with the MRI findings for the purposes of the present study. One patient underwent surgery for a locally advanced primary and for local recurrence that occurred within 12 months following the initial surgery. The pre-operative MRI images from both operations were included for the assessment of the diagnostic accuracy of MRI. The survival for this patient was calculated from the first operation resulting in a total number of evaluated patients for survival of 63. The performance of the MRI did not result in any adverse events.

Table 14: **Demographic data of included patients**

Age (years) Mean (SD)	60.6 (12.2)
Male/Female	41/23
Recurrence/Primary	41/23
Neo-adjuvant CRT	26 (40.6%)
Exenterative surgery: • ASR	18 (28.1%)
• Posterior exenteration	8 (12.5%)
• TPE	16 (25.0%)
• Other	16 (25.0 %)
• Palliative laparotomy	6 (9.4%)
Histology type	
• Adenocarcinoma	58 (90.6%)
• SCC	3 (4.7%)

• Full Response to Neo-adjuvant CRT	3 (4.7%)
Grade of differentiation: • Well/Moderate	29 (45.4%)
• Poor	22 (34.4%)
• Mucinous	7 (10.9%)
• Signet cell	3 (4.7%)
Clearance • R0	42 (65.6%)
• R1	10 (15.6%)
• R2	12 (18.8%)
Lymphovascular invasion	27 / 58 (46.55%)
Perineural invasion	26 / 58 (44.8%)
Lymph node positivity	16 / 58 (27.6%)

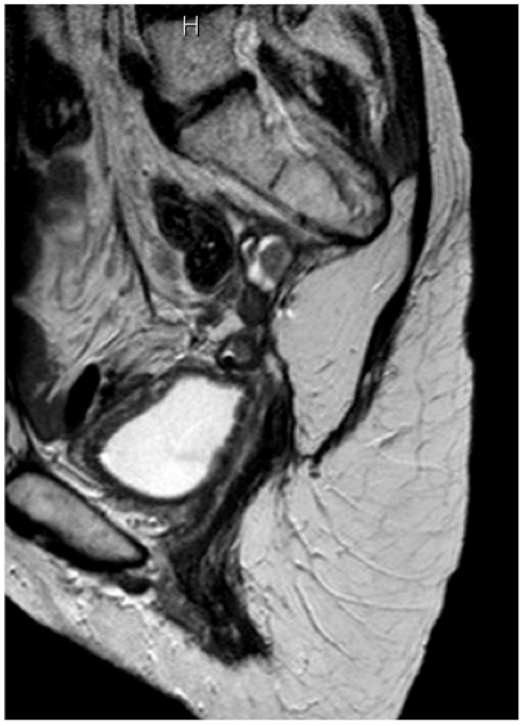
Abbreviations: SD= standard deviation, APER= abdomino-perineal excision of rectum, ASR= abdomino-sacral resection, TPE= total pelvic exenteration, SCC= squamous cell carcinoma, CRT= chemoradiotherapy, R0= complete tumour resection, R1= microscopic residual disease at the resections margins, R2 macroscopic residual disease at the resection margins; *= Hartmann's procedure (n= 1), right hemicolectomy (n= 2), local excision (n= 1)

1.9.2 Surgical Outcomes

The operations performed are shown in Table 14. Eighteen patients underwent abdominosacral resection (Figure 20) and sixteen total pelvic exenteration. Eight patients underwent posterior pelvic exenteration of which four had excision of the posterior wall of the vagina *en-bloc* with the tumour. Sixteen patients had other types of exenterative surgery including salvage abdominoperineal excision of the rectum

(APER= 7), partial prostatectomy (1), excision of the seminal vesicles (1), rectosigmoidectomy with retroperitoneal lymphadenectomy and peritoniectomy (1) and with partial cystectomy (4) and one with anterior exenteration including the left pelvic side wall and internal iliac vessels respectively. In six patients, a laparotomy was undertaken but the tumour was left *in-situ* because of unresectable extra-pelvic disease in two and unresectable pelvic disease in four. Forty-two (65.6%) patients had a curative (R0), ten (15.6%) an R1 and twelve (18.8%) an R2 resection. Other histopathological findings are shown in Table 14.

Figure 20: Sagittal T2 weighted MRI following abdominosacral resection



Sagittal T2 weighted MRI demonstrating the absence of the lower sacrum on a patient that previously had abdominosacral resection. There is an oblique musculocuteneous flap reconstruction.

1.9.3 Diagnostic accuracy of compartment invasion by MRI (table 15)

Cancer was most often found to invade the central compartment (79.7%) whereas the peritoneal reflection compartment was the least invaded (23.4%). The sensitivity of MRI for detecting tumour invasion exceeded 93.3% in all except the lateral

compartment (89.3%). The specificity was lower than 90% in the posterior (82.2%), lateral (86.1%), central (76.9%) and anterior compartment below the peritoneal reflection (86.4%). The positive predictive value was lowest in the posterior (70.4%) compartment. The negative predictive value was more than 91% in all compartments. The area under the receiver operating characteristic curve (ROC) was lower in the lateral (87.7%) and central compartment (88.5%). This was above 90% for the rest of the compartments.

Table 15. **Diagnostic accuracy of MRI in detecting intrapelvic tumour invasion in patients presenting with advanced pelvic cancer.**

Compartments	Prevalence (%)	TP	FP	FN	TN	Sens (%) (95% CI)	Spec (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	ROC area (95% CI)
PR	15 (23.4)	14	1	1	48	93.3 (68.1 - 99.8)	98 (89.1 - 99.9)	93.3 (68.1 - 99.8)	98 (89.1 - 99.9)	0.956 (0.888 - 1)
Anterior above PR	18 (28.1)	17	3	1	43	94.4(72.7 - 99.9)	93.5 (82.1 - 98.6)	85 (62.1 - 96.8)	97.7 (88 - 99.9)	0.94 (0.874 - 1)
Anterior below PR	42 (65.6)	40	3	2	19	95.2 (83.8 - 99.4)	86.4 (65.1 - 97.1)	93 (80.9 - 98.5)	90.5 (69.6 - 98.8)	0.908 (0.828 - 0.988)
Posterior	19 (29.7)	19	8	0	37	100 (82.4 - 100)	82.2 (67.9 - 92)	70.4 (49.8 - 86.2)	100 (90.5 - 100)	0.911 (0.855 - 0.968)
Lateral	28 (43.8)	25	5	3	31	89.3 (71.8 - 97.7)	86.1 (70.5 - 95.3)	83.3 (65.3 - 94.4)	91.2 (76.3 - 98.1)	0.877 (0.795 - 0.959)
Central	49 (79.7)	51	3	0	10	100 (93 - 100)	76.9 (46.2 - 95)	94.4 (84.6 - 98.8)	100 (69.2 - 100)	0.885 (0.765 - 1)
Inferior	28 (43.8)	27	0	1	36	96.4 (81.7 - 99.9)	100(90.3 - 100)	100 (87.2 - 100)	97.3 (85.8 - 99.9)	0.982 (0.947 - 1)

Abbreviations: CI= confidence intervals, PR= peritoneal reflection, CI= confidence interval, Sens= sensitivity, Spec= specificity, PPV= positive predictive value, NPV= negative predictive value, AUC= area under the curve, TP= true positive, FP= false positive, FN= false negative, TN= true negative, ROC= receiver operating curve

1.9.4 Interobserver agreement

The Cohen's Kappa coefficient (k) was used to assess the interobserver agreement for each compartment. For the peritoneal reflection compartment the agreement between the two observers was good (k= 0.79, 95%CI: 0.63 - 0.96). The agreement for the anterior compartment above and below the peritoneal reflection was also considered good at Kappa values of 0.73 (95% CI 0.54 - 0.91) and 0.77 (95% CI 0.60 - 0.93) respectively. The interobserver agreement for the lateral, central and inferior compartments was found to be good with Kappa values of 0.75 (95% CI 0.59 - 0.91), 0.76 (95% CI 0.54 - 0.98) and 0.78 (95% CI 0.62 - 0.93) respectively. For the posterior compartment the agreement was very good (k=0.90, 95% CI 0.79 - 1). These findings were found to be statistically significant for all the compartments ($p < 0.0001$).

1.9.5 Cox Regression Analysis per Compartment

Univariate Cox regression analysis was performed to investigate the risk of death, associated with the diagnosis of tumour by MRI (Table 16).

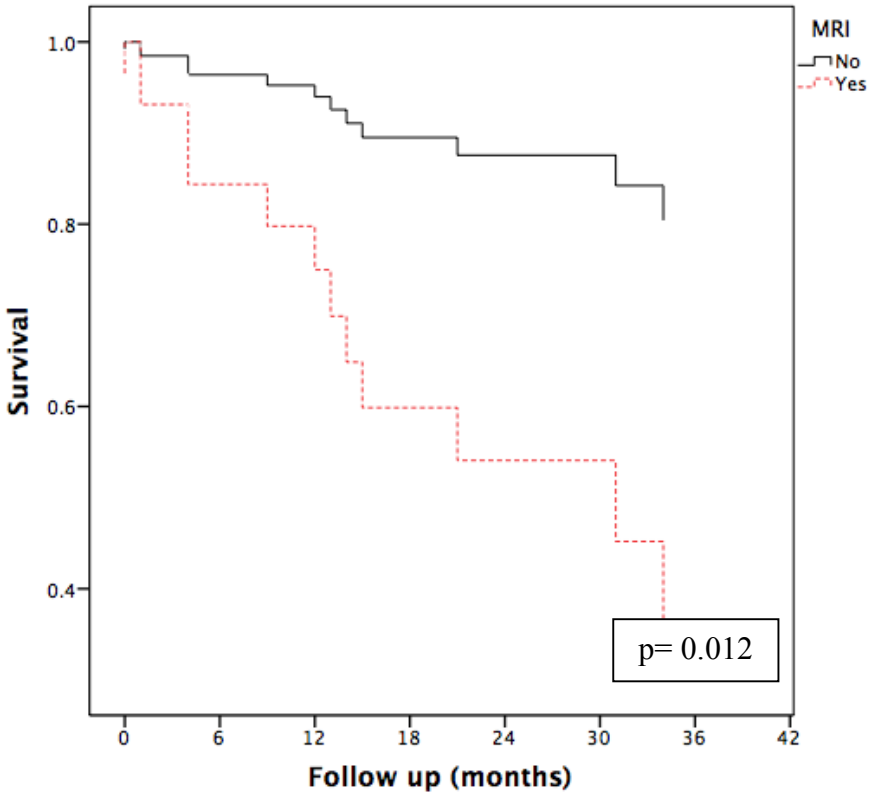
Table 16. Cox Regression analysis for the compartment involvement as diagnosed by the MRI.

MRI diagnosis	HR	95% CI	Coefficient	p
Peritoneal Reflection	3.066	0.972 - 9.675	1.120	0.056
Anterior Above the PR	4.621	1.391 - 15.352	1.531	0.012
Anterior Below the PR	1.182	0.320 - 4.370	0.167	0.802
Posterior	1.740	0.523 - 5.784	0.554	0.366
Lateral	4.356	0.954 - 19.891	1.472	0.058
Central	2.109	0.272 - 16.354	0.746	0.475
Inferior	1.438	0.456 - 4.533	0.363	0.535

Abbreviations: PR= peritoneal reflection, AA= anterior above, AB= anterior below, HR= hazards ratio, CI= confidence interval, p= probability of hazard ratio being significant

Presence of tumour by MRI criteria within the anterior compartment above the peritoneal reflection (figure 21; HR= 4.621, p= 0.012) was associated with significantly reduced overall survival.

Figure 21. Cox regression survival plots for MRI diagnosing tumour within the anterior compartment above the peritoneal reflection



Patients at risk

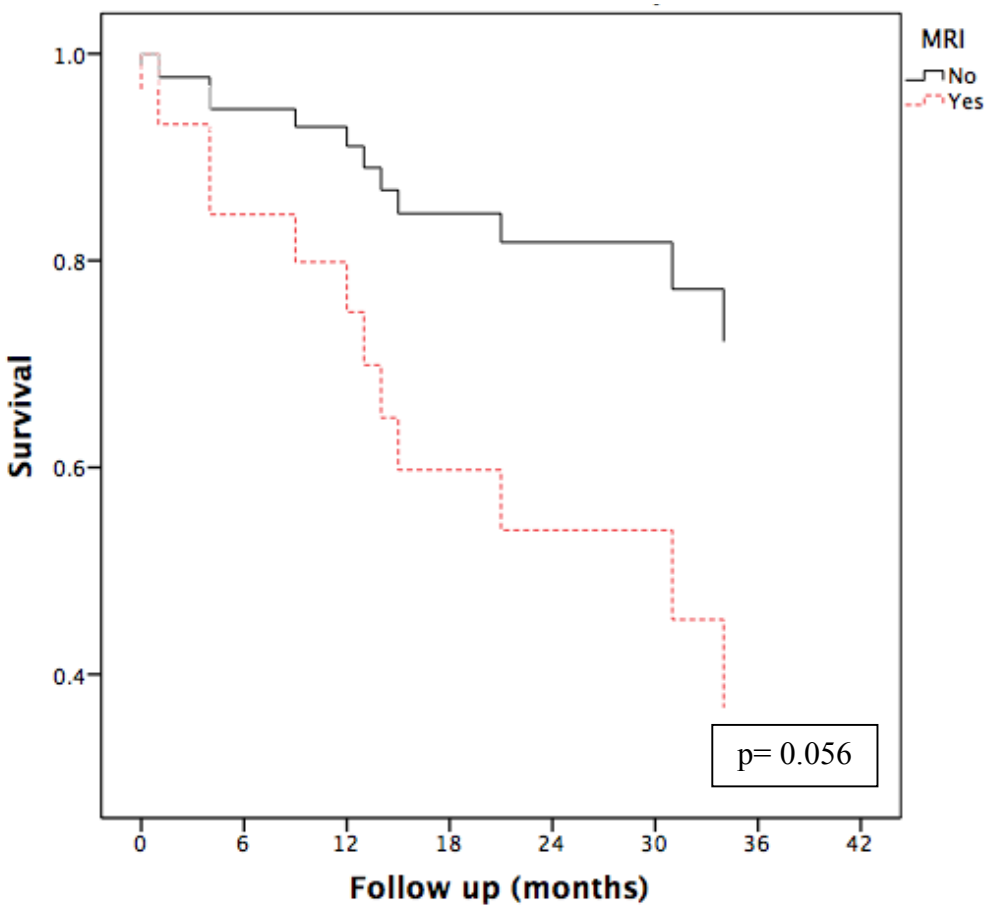
Months	0	6	12	18	24	30	36	42	48
AA +	20	12	12	8	6	3	2		
AA -	43	32	24	17	13	11	6	4	3

Abbreviations: MRI= magnetic resonance imaging, p= statistical probability of significance, AA + = patients that MRI diagnosed tumour invasion within the anterior

compartment above the peritoneal reflection, AA - = patients that MRI did diagnose tumour invasion within the anterior compartment above the peritoneal reflection.

Diagnosis of tumour invasion by MRI within the peritoneal reflection (figure 22; HR= 3.066, p= 0.056) and lateral compartment (figure 23; HR= 4.356, p= 0.058) approached statistical significance for poorer survival.

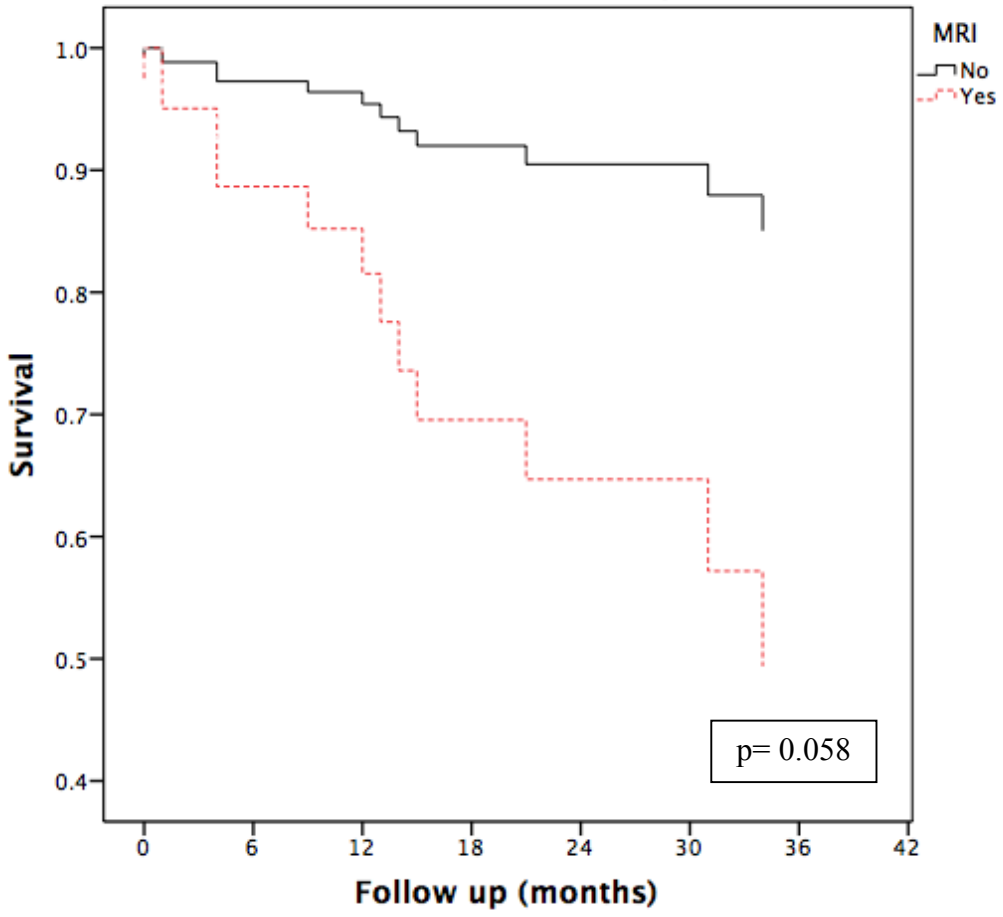
Figure 22. Cox regression survival plots for MRI diagnosing tumour within the peritoneal reflection



Months	0	6	12	18	24	30	36	42	48
PR +	15	8	6	4	4	3	2		
PR -	48	36	30	21	15	11	6	4	3

Abbreviations: MRI= magnetic resonance imaging, p= statistical probability of significance, PR + = patients that MRI diagnosed tumour invasion within the peritoneal reflection, PR - = patients that MRI did diagnose tumour invasion within the peritoneal reflection.

Figure 23. Cox regression survival plots for MRI diagnosing tumour within the lateral compartment



Patients at risk

Months	0	6	12	18	24	30	36	42	48
L +	30	22	18	13	10	8	6	3	3
L -	33	22	18	12	9	6	2	1	1

Abbreviations: MRI= magnetic resonance imaging, p= statistical probability of significance, L + = patients that MRI diagnosed tumour invasion within the lateral

compartment, L - = patients that MRI did diagnosed tumour invasion within the lateral compartment.

Invasion within the rest of the compartments did not reveal any statistically significant survival disadvantage. Multivariate Cox regression analysis was attempted, but the relatively small number of patients did not generate any statistically significant results (results not shown). Univariate and multivariate Cox regression analysis was also performed to identify the risk of local or distant metastases associated with MRI diagnosis of tumour invasion to each compartment without any significant risks identified.

1.10 Discussion

The present study demonstrated that MRI is highly accurate in diagnosing tumour invasion within the pelvic compartments (ROC>87.6%). The ability of MRI to exclude the presence of disease in a compartment was shown to be high in all compartments except the central (Specificity= 76.9%), which was likely a result of the relatively small number of patients without disease within this compartment. The negative predictive value was shown to be excellent in all compartments.

The secondary endpoint of this study was to assess MRI in predicting the oncological outcome. MRI diagnosis of tumour invasion within the anterior compartment above the peritoneal reflection was associated with poorer survival. Diagnosis of tumour invasion within the peritoneal reflection and lateral compartment showed a trend to poorer survival. No significant relationship between compartment involvement and

local and distant metastases was found either. However multivariate analysis was not possible due to the relatively small number of patients included in the study. A bigger multicentre study with a model designed to assess the MRI's value to predict the oncological outcome is necessary to confirm that these are independent predictive factors. The authors propose that it may be safer to manage these patients more aggressively when MRI diagnoses tumour invasion in these three compartments. This could be in the form of pre-operative boost radiotherapy; extended resections; intra-operative brachytherapy and radiotherapy; and/or post-operative radiotherapy or cyberknife along with chemotherapy when indicated. The evidence is still limited but this is a group of patients that can potentially benefit from these modalities and should be evaluated prospectively.

Variation in the interpretation of the images by the radiologists might have influenced the results of the study. The agreement between the two radiologists was, however, good, suggesting that the results should be applicable to wider clinical practice. The accurate communication of the radiological findings to the surgeon is critical for comprehension of the surgical anatomy of the tumour that will enable the appropriate procedure to be performed. The proforma designed for the present study provided an objective assessment as the reporting of the imaging is standardised. Good communication between radiologist and surgeon may improve the patient selection for surgery and subsequently the R0 rate.

Previous studies investigating MRI in a similar setting found it to be highly accurate in determining the presence (69, 70) or absence (71) of adjacent organ invasion. An R0 procedure depends, however, on the compartment rather than the individual

organ(s) invaded by tumour. The surgical approach to the tumour is mainly determined by the anatomical planes of dissection, which define the seven individual compartments and therefore enables safe en-bloc removal of the tumour within a given compartment. The compartments form the basis for the dissection planes. Therefore, R1 and R2 rates would be influenced by the presence or absence of tumour at the interfaces of the compartment. The staging system described by the present study has an inherent advantage over staging based on the reporting of the individual adjacent organs alone since these may not always be relevant to the planes of dissection. Therefore, the authors have found that this division into compartments allows a better understanding of the tumour invasion within the pelvis, facilitating optimal surgical planning to achieve a complete resection. This is also relevant to the accurate planning of radiotherapy, and the type of exenterative procedure that is needed to maximise the likelihood of curative resection. Although the distance of the peritoneal reflection from the anal verge is variable, in particular between genders, its identification by MRI is accurate and can be useful when planning the surgical approach. Involvement of the peritoneal reflection necessitates *en bloc* excision of all adherent surfaces and organs as well as wide margin peritoniectomy.

The present study has several strengths, including the utilisation of specialist pelvic surgeons, two radiologists with interest in advanced rectal cancer and gastrointestinal histopathologist. The radiologists were blinded to the clinical findings, and the histopathologists were blinded to the radiological scoring when the proformas were completed. Dedicated proformas were used to ensure consistency of MRI and histopathological reporting with prospective data collection to avoid the bias, which is inevitable in retrospective series.

Possible weaknesses of the study may have arisen from tumour progression within the time interval between the MRI scan and surgery, which varied between zero and 17 weeks. There were 16 patients with an interval of 7 or more weeks between MRI and surgery. A significant interval of more than six weeks between MRI and surgery may decrease the true negative rate and therefore the overall MRI specificity. In everyday clinical practice, however, pre-operative optimisation for surgery can be time-consuming and assessment by more than one specialist and repeated discussion in multidisciplinary meetings may be required before a final decision for surgery is made. Ideally, this should be undertaken within six weeks of the staging MRI to limit understaging and to possibly reduce surgical failure. A further limitation of the present study is that the MRI reporting was performed in retrospect. A future prospective study is vital to confirm the findings of the present study and determine whether the number of patients undergoing surgery can be increased without compromising R0 rates.

Most patients were referred from other centres with pre-existing MRI images resulting in some variation between MRI sequences. These were used only if felt to be of sufficient quality to take safe conclusions; otherwise, a repeat scan was performed. There were no significant differences in the diagnostic accuracy when compared to higher resolution images (results not shown). However, the radiologists involved in this study reported that they were quicker and more confident in interpreting the images when performed using 3mm slices.

This study examined the accuracy of MRI in staging advanced colorectal pelvic cancer in addition to its value in predicting the surgical and oncological outcome. It is shown to be highly accurate and should be used to stage patients that are considered for exenterative surgery in colorectal surgery. The division of the pelvis into seven compartments is of great value in treatment planning providing the surgeon with more precise information regarding the extent and position of disease. A better understanding of compartmental anatomy in the pelvis enables the radiologist to improve interpretation and to standardise reporting. These principles may in the future enable select patients for surgery and medical therapy in other specialties that deal with complex pelvic primary and recurrent malignancy, such as gynaecology, urology and sarcoma surgery as well as in colorectal surgery.

1.11 Conclusion of this study

This study demonstrated that MRI has a fundamental role in the pre-operative staging of patients diagnosed with locally advanced primary rectal and recurrent colorectal cancer within the pelvis. It has high sensitivity and specificity in predicting tumour invasion within the seven intrapelvic compartments as are described in this thesis, providing important oncological information that can be used to better select patients for surgery and medical therapy.

1.12 Future Considerations

Multicentre prospective studies are needed to validate the results and reproducibility of the findings of the present study.

CHAPTER 7. Diagnostic accuracy of Diffusion-weighted MRI

1.1 Introduction

As previously discussed, resection of the tumour with the adjacent structures involved is the only cure for this group of patients, provided that metastatic disease is excluded. In this effort to select patients, surgeons rely on diagnostic imaging with the current gold standard being the MRI. The use of Diffusion-weighted MRI is not widespread yet as the evidence regarding its clinical value in colorectal cancer surgery is limited. As the MRI is not 100% accurate in detecting the extent of the disease within all the pelvic compartments, DW-MRI may be an added option with no added cost. Therefore, the next chapter of the thesis was designed to evaluate the diagnostic accuracy of diffusion-weighted MRI and assess its added value to conventional MRI.

1.2 Aims of the study

The aim of the study was to assess the diagnostic accuracy and added value of DW-MRI compared to conventional MRI, in the local staging of locally advanced primary rectal and recurrent colorectal pelvic cancer.

1.3 Study design and subjects

This study was reviewed and approved by the institutional research committee and the regional cancer network. The image interpretation was performed retrospectively. This was a pilot study for future multicentre study and the decision to include 33 cases was taken. Consecutive patients that underwent exenterative pelvic surgery for locally advanced primary and recurrent colorectal cancer and were preoperatively

staged using MRI (including DW-MRI sequences), were included in the study. The decision for surgery was taken during the local multidisciplinary meeting based on a combination of tumour marker measurement, colonoscopy, examination under anaesthesia, radiological staging and pre-operative biopsies, where appropriate. The radiological findings were compared with the intraoperative and histopathological findings (reference standard). The study followed the guidelines proposed by the Standards for the Reporting of Diagnostic accuracy studies (STARD criteria) (226).

1.4 Inclusion and exclusion criteria

Patients that underwent pelvic exenterative surgery for locally advanced primary rectal or recurrent colorectal pelvic cancer with age of over 18 years were included in this study. Inclusion criteria also included the availability of pre-operative MRI with diffusion-weighted sequences, pre-operative biopsy positive for cancer or strong radiological evidence of recurrence by two modalities. Patients were excluded if a pre-operative MRI/DW-MRI was not performed or if the MRI images were unsuitable for the evaluation of the individual compartments due to poor quality or due to the absence of diffusion weighted images.

1.5 Surgical pelvic anatomical compartments

The same classification as described in methods was used to divide the pelvis into seven compartments according to the fascial boundaries and planes of dissection between the intrapelvic organs, as described in methods.

1.6 Qualitative DW-MRI assessment of tumour invasion

This is described in methods.

1.7 Reference Standard

The same reference standard as described in the chapter of methods was employed for this study.

1.8 Results

1.8.1 Demographic characteristics (table 17)

A total of 33 (18 males; mean age 60.64 (14.57) years patients had diffusion-weighted MR imaging performed before they underwent surgery for locally advanced primary rectal (n= 12) and recurrent (n= 21) colorectal pelvic cancer. Twenty five patients had neo-adjuvant chemoradiotherapy. The median time between the performance of the MRI and surgery was 5 (0 - 17) weeks. None of the patients received any oncological therapy between the time of the scan and surgery. No complications occurred as a result of the MRI.

Of the included patients, nine underwent abdominoperineal resection, six total pelvic exenteration, six posterior exenteration and seven other types of exenterative surgery including salvage abdominoperineal excision of the rectum (3) anterior resection with partial cystectomy (1) and seminal vesicles resection (1), lateral pelvic sidewall resection with lymphadenectomy (1) and local resection with peritoniectomy (1). Five patients underwent palliative procedures after the tumour was deemed irresectable or inoperable due to evidence of progressed local and distant disease respectively.

Table 17. Demographic characteristics

Age (years) Mean(SD)	60.64 (14.57)
Male/Female	18/15
Recurrence/Primary	21/12
Neo-adjuvant CRT	25 (75.76%)
Exenterative surgery: • Abdominosacral resection	9 (27.27%)
• Posterior exenteration	6 (18.18%)
• Total pelvic exenteration	6 (18.18%)
• Other	7 (21.21%)
• Palliative laparotomy	5 (15.15%)
Histology type • Adenocarcinoma	30 (90.90%)
• SCC	1 (3.03%)
• Full Response to Neo-adjuvant CRT	2 (6.06%)
Grade of differentiation: • Moderate	14
• Poor	11
• Mucinous	4
• Signet cell	2

Abbreviations: SD= standard deviation, APER= abdomino-perineal excision of rectum, ASR= abdomino-sacral resection, TPE= total pelvic exenteration, SCC= squamous cell carcinoma, CRT= chemoradiotherapy.

1.8.2 Diagnostic accuracy of DW-MRI (table 18)

The sensitivity of DW-MRI when used alone was found to be low in all compartments except the central (92%), ranging from 42.9% for the compartment of the peritoneal reflection to 59.1% for the anterior below the peritoneal reflection compartment. The specificity for the DW-MRI was high in all compartments ranging from 89.4%. The positive predictive value for the DW-MRI was lower in the inferior compartment (77.8%). It was 85.7 or more for the rest of the compartments. The negative predictive value was lower for the anterior compartment below the peritoneal reflection. For the remaining compartments, it ranged between 70.8% (inferior) and 86.7% (peritoneal reflection). The area under the receiver-operating curve was higher for the central compartment (96%) and ranged between 69.7% (inferior) and 79.5% (anterior compartment below the peritoneal reflection) for the rest of the compartments.

Table 18. DW-MRI

Compartments	Prevalence (%)	TP	FP	FN	TN	Sens (%) (95% CI)	Spec (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	ROC area (95% CI)
PR	7 (21.2)	3	0	4	26	42.9 (9.9 - 81.6)	100 (86.8 - 100)	100 (29.2 - 100)	86.7 (69.3 - 96.2)	0.714 (0.516 - 0.912)
Anterior above PR	8 (24.2)	4	0	4	25	50 (15.7 - 84.3)	100 (86.3 - 100)	100 (39.8 - 100)	86.2 (68.3 - 96.1)	0.75 (0.565 - 0.935)
Anterior below PR	22 (66.7)	13	0	9	11	59.1 (36.4 - 79.3)	100 (71.5 - 100)	100 (75.3 - 100)	55 (31.5 - 76.9)	0.795 (0.69 - 0.901)
Posterior	12 (36.4)	6	1	6	20	50 (21.1 - 78.9)	95.2 (76.2 - 99.9)	85.7 (42.1 - 99.6)	76.9 (56.4 - 91)	0.726 (0.571 - 0.881)
Lateral	12 (36.4)	7	1	5	20	58.3 (27.7 - 84.8)	95.2 (76.2 - 99.9)	87.5 (47.3 - 99.7)	80 (59.3 - 93.2)	0.768 (0.615 - 0.921)
Central	25 (75.8)	23	0	2	8	92 (74 - 99)	100 (63.1 - 100)	100 (85.2 - 100)	80 (44.4 - 97.5)	0.96 (0.906 - 1)
Inferior	14 (42.4)	7	2	7	17	50 (23 - 77)	89.5 (66.9 - 98.7)	77.8 (40 - 97.2)	70.8 (48.9 - 87.4)	0.697 (0.544 - 0.851)

Abbreviations: CI= confidence intervals, PR= peritoneal reflection, CI= confidence interval, Sens= sensitivity, Spec= specificity, PPV= positive predictive value, NPV= negative predictive value, AUC= area under the curve, TP= true positive, FP= false positive, FN= false negative, TN= true negative, ROC= receiver operating curve

1.8.3 Diagnostic accuracy of MRI (table 19)

The MRI alone was highly sensitive in detecting tumour within all the compartments. The lowest sensitivity was for the peritoneal reflection (85.7%). The specificity ranged above 95% in all compartments except the lateral (85.7%) and the anterior compartment below the peritoneal reflection (81.8%). The positive predictive value was lower for the lateral compartment (78.6%). The negative predictive value was 94.7% or higher in all compartments. Thus, the area under the receiver-operating curve was the lowest for the lateral (88.7%) and the anterior compartment below the peritoneal reflection (88.6%).

Table 19. Diagnostic accuracy of MRI

Compartments	Prevalence (%)	TP	FP	FN	TN	Sens (%) (95% CI)	Spec (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	ROC area (95% CI)
PR	7 (21.2)	6	0	1	26	85.7 (42.1 - 99.6)	100 (86.8 - 100)	100 (54.1 - 100)	96.3 (81 - 99.9)	0.929 (0.789 - 1)
Anterior above PR	8 (24.2)	7	1	1	24	87.5 (47.3 - 99.7)	96 (79.6 - 99.9)	87.5 (47.3 - 99.7)	96 (79.6 - 99.9)	0.918 (0.789 - 1)
Anterior below PR	22 (66.7)	21	2	1	9	95.5 (77.2 - 99.9)	81.8 (48.2 - 97.7)	91.3 (72 - 98.9)	90 (55.5 - 99.7)	0.886 (0.759 - 1)
Posterior	12 (36.4)	12	1	0	20	100 (73.5 - 100)	95.2 (76.2 - 99.9)	92.3 (64 - 99.8)	100 (83.2 - 100)	0.976 (0.93 - 1)
Lateral	8 (24.2)	11	3	1	18	91.7 (61.5 - 99.8)	85.7 (63.7 - 97)	78.6 (49.2 - 95.3)	94.7 (74 - 99.9)	0.887 (0.775 - 0.999)
Central	25 (75.8)	25	0	0	8	100 (86.3 - 100)	100 (63.1 - 100)	100 (86.3 - 100)	100 (63.1 - 100)	1 (1 - 1)
Inferior	14 (42.4)	14	0	0	19	100 (76.8 - 100)	100 (82.4 - 100)	100 (76.8 - 100)	100 (82.4 - 100)	1 (1 - 1)

Abbreviations: CI= confidence intervals, PR= peritoneal reflection, CI= confidence interval, Sens= sensitivity, Spec= specificity, PPV= positive predictive value, NPV= negative predictive value, AUC= area under the curve, TP= true positive, FP= false positive, FN= false negative, TN= true negative, ROC= receiver operating curve

1.8.4 Diagnostic accuracy of MRI and DW-MRI combined (table 20)

The addition of DW-MRI to MRI resulted in the increase of the sensitivity for the lateral compartment (100%) but in its reduction for the posterior (91.7%) and anterior compartment below the peritoneal reflection (85.7%). The specificity remained unchanged for all the compartments except the anterior compartment below the peritoneal reflection, which was significantly improved to 90.9% from 81.8%. The positive predictive value was increased for the lateral (80%) and anterior compartment below the peritoneal reflection (94.7%). The negative predictive value was decreased for the posterior and the anterior compartment below the peritoneal reflection to 95.2% and 76.9% respectively. It was improved for the lateral compartment (100%). The area under the receiver-operating curve (ROC) only increased for the lateral compartment by 4.2%. It was reduced by 4.2% and 3.6 % for the posterior (93.5%) and inferior (96.4%) compartment but remained at excellent levels. It remained relatively unchanged for the rest of the compartments. None of these differences reached statistical significance ($p \geq 0.317$). The overall incremental value (Accuracy (TP + TN / all) of MRI and DW-MRI together - Accuracy of MRI) of DW-MRI was improved for the lateral compartment by 3%. There was no change, for the peritoneal reflection, central and anterior compartment above the peritoneal reflection. The overall incremental value for the rest of the compartments was reduced.

Table 20. MRI + DW-MRI

Compartments	Prevalence (%)	TP	FP	FN	TN	Sens (%) (95% CI)	Spec (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	ROC area (95% CI)
PR	7 (21.2)	6	0	1	26	85.7 (42.1 - 99.6)	100 (86.8 - 100)	100 (54.1 - 100)	96.3 (81 - 99.9)	0.929 (0.789 - 1)
Anterior above PR	8 (24.2)	7	1	1	24	87.5 (47.3 - 99.7)	96 (79.6 - 99.9)	87.5 (47.3 - 99.7)	96 (79.6 - 99.9)	0.918 (0.789 - 1)
Anterior below PR	22 (66.7)	18	1	3	10	85.7 (63.7 - 97)	90.9 (58.7 - 99.8)	94.7 (74 - 99.9)	76.9 (46.2 - 95)	0.883 (0.766 - 1)
Posterior	12 (36.4)	11	1	1	20	91.7 (61.5 - 99.8)	95.2 (76.2 - 99.9)	91.7 (61.5 - 99.8)	95.2 (76.2 - 99.9)	0.935 (0.84 - 1)
Lateral	8 (24.2)	12	0	3	18	100 (73.5 - 100)	85.7 (63.7 - 97)	80 (51.9 - 95.7)	100 (81.5 - 100)	0.929 (0.852 - 1)
Central	25 (75.8)	25	0	0	8	100 (86.3 - 100)	100 (63.1 - 100)	100 (86.3 - 100)	100 (63.1 - 100)	1 (1 - 1)
Inferior	14 (42.4)	13	0	1	19	92.9 (66.1 - 99.8)	100 (82.4 - 100)	100 (75.3 - 100)	95 (75.1 - 99.9)	0.964 (0.894 - 1)

Abbreviations: CI= confidence intervals, PR= peritoneal reflection, CI= confidence interval, Sens= sensitivity, Spec= specificity, PPV= positive predictive value, NPV= negative predictive value, AUC= area under the curve, TP= true positive, FP= false positive, FN= false negative, TN= true negative, ROC= receiver operating curve

1.8.5 Interobserver agreement for DW-MRI

The interobserver agreement for the interpretation of the DW-MRI was good for the posterior (k= 0.672, 95% CI 0.38 - 0.97, p<0.0001), inferior (k= 0.744, 95% CI 0.48 - 1, p<0.0001) lateral (k= 0.742, 95% CI 0.4676 - 1, p<0.0001) and anterior compartment below the peritoneal reflection (k= 0.669, 95% CI 0.41 - 0.93, p<0.0001). It was very good for the rest of the compartments (k≥0.86, p<0.0001).

1.9 Discussion

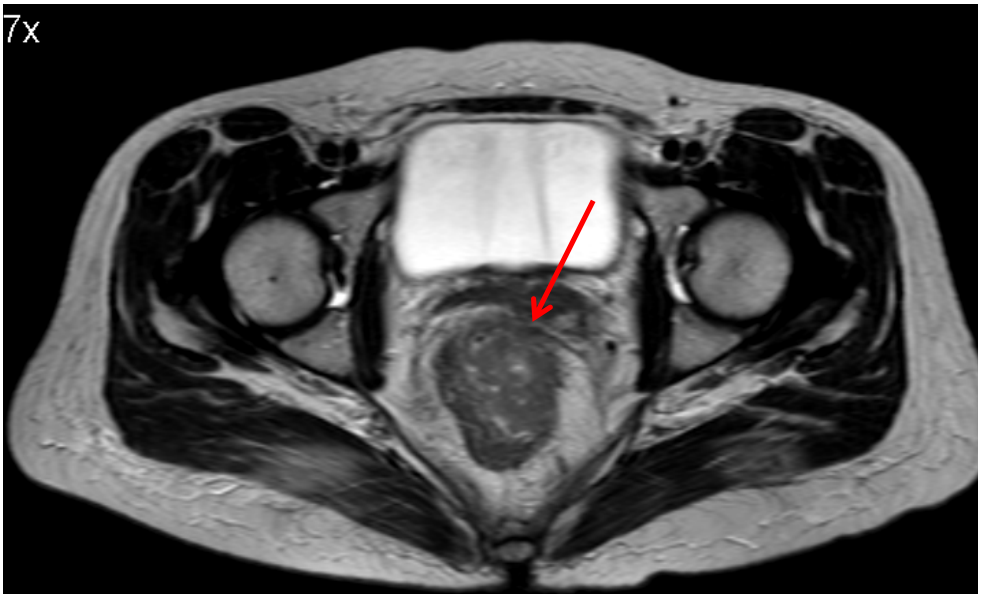
The present study investigated the diagnostic accuracy and added the value of diffusion-weighted MRI to conventional MRI, in the surgical planning of patients requiring exenterative surgery for locally advanced primary rectal and recurrent colorectal pelvic cancer. This study demonstrated that DW-MRI on its own has low sensitivity for all compartments except the central, but has excellent specificity in all compartments except the inferior one. The combined use of DW-MRI with conventional MRI increased the MRI sensitivity for the lateral compartment and the specificity for the anterior compartment below the peritoneal reflection. This has resulted in 4.2% increase of the area under the receiver-operating curve without though achieving statistical significance. The incremental value of DW-MRI for the lateral compartment was 3%.

Diffusion weighted MRI was found to be weak in detecting the presence of disease within a compartment. MRI alone was shown to have higher sensitivity with a

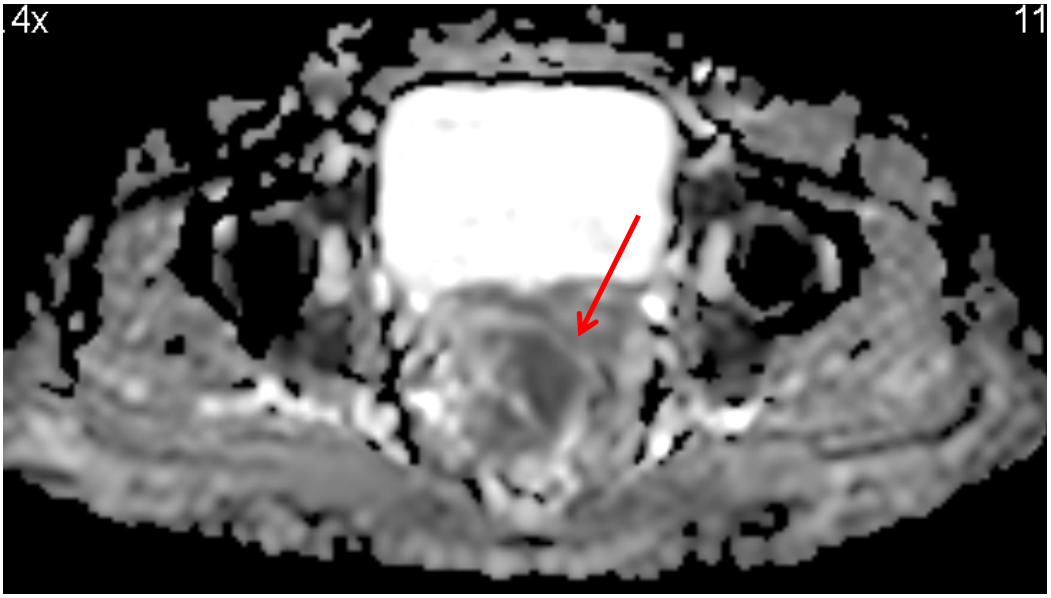
tendency however to overstage (figure 24) the lateral and anterior compartment below the peritoneal reflection.

Figure 24. Overstaging by MRI

a. T2 weighted MRI



b. DW-MRI



In figure a. T2-MRI demonstrating the tumour invading the anterior compartment below the peritoneal reflection. In figure b however, diffusion weighted MRI shows a

clear line separating the tumour from the vagina. Histopathology ruled out the presence of tumour from the anterior compartment below the peritoneal reflection. The arrows demonstrate the site of overstaging.

The excellent specificity of DW-MRI helped to improve the staging in four patients, one patient that was overstaged (false positive) by MRI for the anterior compartment below the peritoneal reflection and three that were overstaged for the lateral compartment. However, it led the radiologists to change their MRI reporting and understage two patients in the lateral compartment.

Lateral compartment is considered to be the most challenging to achieve complete resection when there is tumour present within it. Sagar et al. (133) identified this challenge in a series of 40 patients that underwent abdominosacral resection for recurrent rectal cancer, where thirteen out of the twenty (65%) incomplete resections were due to tumour invasion into the lateral pelvic sidewall. They suggested that a more radical resection should be considered when the tumour is pre-operatively identified within the compartment. The altered anatomy secondary to surgery and fibrosis from radiotherapy and post-surgery scarring makes the interpretation of morphological imaging such as MRI and CT more challenging. As a functional imaging modality DW-MRI provides added information that may aid to distinguish post-surgical/radiotherapy changes from recurrent/residual tumour something that was previously demonstrated for laryngeal cancers (227). A recent study (228) also demonstrated that DW-MRI could distinguish patients with complete or good response following chemoradiotherapy for rectal cancer reinforcing its role in the pre-operative staging and decision making prior to surgery. However, the present study

has not been able to demonstrate a statistically significant benefit in using DW-MRI during the preoperative staging of these patients. DW-MRI did help with the staging of 4 patients, but at the same time changed the staging for two others, something that may have prevented the patients to undergo potentially curative surgery. Therefore, its findings should be carefully examined and until more research is available should be not used to deem a patient inoperable when there is no such evidence from the high-resolution MRI.

A number of studies have investigated the value of DW-MRI in colorectal cancer, mainly focusing on its value to detect primary (229) rectal cancer, recurrence (230) and lymph node metastases (89, 231, 232). Other studies investigated its value in predicting the tumours' response to neo-adjuvant therapy either for local (88, 90, 231) or distant disease (233). Ichikawa *et al.* (87) demonstrated DW-MRI to be highly accurate in detecting colon and rectal cancer with high sensitivity (90%), specificity (100%) and interobserver agreement (k=0.83–0.89). Another study (229) investigated the value of DW-MRI in detecting primary rectal cancer and demonstrated 100% sensitivity and 93% specificity on visual evaluation of the images with very good agreement between the radiologists. Ono *et al*. (232) showed that DW-MRI was more sensitive to detect lymph node metastases but less sensitive to detect primary cancer compared to PET scan. Lambregts *et al.* (89) showed that DW-MRI can be used to characterise lymph nodes and to improve the positive predictive value of MRI, concluding however that its value is limited when used alone. Kim *et al.* (90) demonstrated that there is an added value of DW-MRI as it can improve the diagnostic accuracy of MRI in the evaluation of the tumours' response to neoadjuvant chemoradiotherapy.

All these studies investigated the DW-MRI value in detecting but not planning surgery. The planning of exenterative pelvic surgery for colorectal cancer relies on the principle of en-bloc resection of the tumour with adequate margins. This depends on the compartment(s) that is/are invaded by the tumour. An incomplete resection would be catastrophic, as it would result in the reduced survival as demonstrated in literature. An incomplete resection would be catastrophic, as it would result in the reduced survival as demonstrated in the literature (132, 133, 157). The present study analyses the imaging involvement within seven surgically relevant pelvic compartments, which were divided according to the fascial boundaries and planes of dissection between intra-pelvic organs. This helps the accurate planning of radiotherapy and of the type of exenterative procedure that would be required to increase the likelihood of achieving a curative resection. To the authors' best knowledge, this is the first study to investigate the value of DW-MRI in this setting.

The present study has the following strengths. The interpretation of the images was performed by radiologists with a special interest and experience in reporting colorectal cancer and advanced pelvic cancer. This may also be viewed as a limitation of the study, as it is not known to what degree this expert performance could be translated to the general setting. However, the interobserver agreement for all the compartments was good or very good, suggesting that the results of this study can be reproducible in a broader clinical setting. Another strength was that senior histopathologists, with special interest and vast experience with recurrent pelvic cancer, reported the findings from the specimens.

One of the limitations of the study might be the small sample size. This is a reflection however of the small number of patients that undergoes exenterative pelvic surgery for colorectal cancer each year in the UK (up to about 250). Diffusion-weighted MRI sequences became part of the standard MRI protocol at the authors' institute in mid-2007 following the findings of the first studies reporting a potential benefit in the diagnosis and management of primary and recurrent colorectal cancer.

Following the results of the present study, the role of the diffusion-weighted MR imaging in the management of the patients with locally advanced primary and recurrent colorectal pelvic cancer seems to be limited to the identification of the recurrence and the degree of response following neoadjuvant treatment. This study has shown that DW-MRI can improve the local staging for some of the patients with advanced local disease; while at the same time has an adverse effect in the staging for others. These patients undergo a demanding procedure that takes from five to fifteen hours to complete, carrying significant mortality and morbidity risk with high impact on the patients' quality of life as a result of bowel, urinary and sexual dysfunction. Even though every tool should be employed to maximise the possibility for a curative resection, DW-MRI has not been shown by this study to be a safe predictor of resectability, and its use as such a tool should be avoided in these cases. Further research is still essential to further verify the strengths and weaknesses of the diffusion imaging in the management of locally advanced primary and recurrent rectal cancer.

1.10 Conclusion

Based on the current study diffusion weighted MRI cannot be used as a predictor of curative resection for patients with locally advanced primary and recurrent rectal cancer.

1.11 Future Considerations

Bigger studies are essential to compare the DW-MR Images with histopathology at a cellular level, to better understand its value in the management of this group of patients.

CHAPTER 8: Diagnostic Precision of Positron Emission Tomography Compared with Conventional Diagnostic Imaging in Managing Recurrent Colorectal Cancer; a meta-analysis

1.1 Introduction

The previous chapters illustrated the value of MRI and DW-MRI in the assessment of the tumour extent within the pelvis. This chapter is using meta-analysis techniques to assess the value of different radiological modalities in detecting the presence or recurrent and metastatic disease.

Meta-analysis of published studies can be a useful tool that consolidates information from published studies and guide further research by analysing the data and identifying limitations from the included studies. The treatment of choice for patients diagnosed with recurrent colorectal cancer is the resection of the local recurrence and distant liver or lung metastases. This is feasible when there is no evidence of disseminated disease, and there are no contraindications for surgery. Early diagnosis of the recurrence maximises the likelihood of curative resection (RO) and prevents the dissemination of the disease. Clinical examination and diagnostic modalities such as ultrasound (USS), computerised tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) are routinely used in diagnosing disease recurrence, staging and planning of further treatment/management. Carcinoembryonic antigen (CEA) has also formed part of the repertoire for early detection of recurrence, especially when serial measurements are taken, or as an early trigger for further radiological testing.

1.2 Chapter's Outlines and Objectives

This chapter comprises of one study that aimed to compare the diagnostic accuracy of PET compared to conventional diagnostic investigation (CDI) using meta-analytical techniques. Sensitivity analysis was performed including studies of higher quality (QUADAS score of more than 8).

1.3 Methods

1.3.1 Literature search

A literature search of Ovid, Embase, the Cochrane database, Medline using Pubmed as the search engine and Google™ Scholar was used to identify studies reporting on comparative data between PET and other imaging modalities used to diagnose recurrent rectal cancer (most recent search: 27th October 2009), was performed. The following keywords were used for the search: "positron emission tomography", "PET", "colorectal cancer", "recurrent colorectal cancer" and "recurrence". Articles were also identified using the "related articles" function in PubMed. References of the articles identified were also evaluated using the electronic search engines stated above. No language restrictions were made. Authors were not contacted for their raw data.

1.3.2 Eligibility Criteria and Data Extraction

All studies comparing diagnosis of recurrent colon or rectal cancer with PET and conventional diagnostic investigation (CDI) were examined. Conventional diagnostic investigation included the use of computerised tomography, magnetic resonance

imaging, endo-anal / transabdominal ultrasonography, bone scintigraphy and tumour markers in various combinations to investigate the possibility of local or distant recurrence. Intra-operative findings, histopathology, tumour markers, clinical and / or radiological follow-up were used as reference standard. Studies, where patients did not have subsequent histological or radiological confirmation of rectal cancer recurrence, were excluded. Data were extracted on the authors, date of publication, institution, study design, patient demographics and technical aspects of the studies. Two reviewers extracted all data independently, and any discrepancies were resolved by consensus. Studies providing insufficient information for the calculations of sensitivity and specificity were excluded. Studies that included only patients with confirmed recurrence were excluded (no true negatives and therefore specificity would be equal to zero). The quality of the studies was assessed with the use of the QUADAS tool (234).

1.3.3 Endpoints and definitions

The primary endpoint was the sensitivity and specificity of PET and conventional diagnostic investigation compared to histological, radiological or clinical confirmation of recurrence of rectal cancer. This was either quoted directly in the studies or was extractable from analysis of the true positives (TP), true negatives (TN), false positive (FP) and false negatives (FN).

1.3.4 Statistical Analysis

True positive finding (TP) was the agreement between the index test (either PET or CDI) and reference standard (histology or radiological follow-up) in diagnosing tumour recurrence. True negative finding (TN) was the agreement between index test

and reference standard in diagnosing the absence of recurrence. False positive finding (FP) was when the index test diagnosed the presence of recurrence incorrectly (rejected by the reference standard). False negative finding (FN) was the failure of the index test to detect a recurrence that was subsequently confirmed by the reference standard. The individual study sensitivities and specificities were extracted or calculated using two by two contingency tables for each end-point of correct patient diagnosis.

Pooled sensitivity and specificity along with 95% confidence intervals were estimated with the use of random and fixed effects calculations to calculate the Q-value, a measure of heterogeneity across the studies. SROC analysis quantified PET or other imaging modality performance using area under the curve (AUC), diagnostic odds ratio (DOR) and Q-value as summary estimates (235, 236). Subgroup analysis assessed the effect of study quality a QUADAS (234) score of greater than or equal to 9) and year of publication (studies that were published after 1998 were compared with older studies). Inverse variance weighted meta-regression was used to compare PET to CDI, and appropriate adjustments were performed for the same variables that were evaluated in the subgroup analysis described above.

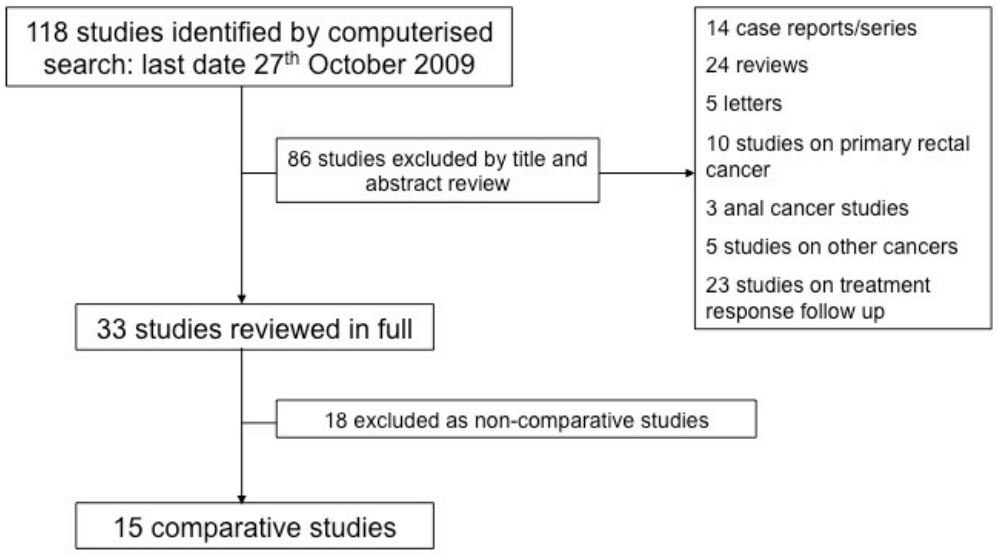
The analysis was conducted using Meta-DiSc© for Windows Version 1.1.1 (XI Cochrane Colloquium, Barcelona, 2003) software. The study followed the guidelines for meta-analyses evaluating diagnostic tests (237, 238).

1.4 Results

1.4.1 Eligible studies

A total of 118 studies were initially identified of which 86 were excluded by title and abstract review. 33 articles were fully reviewed, and further 18 were excluded for reasons outlined in Figure 25.

Figure 25: Flowchart of literature search



A total of 15 comparative studies comprising 916 patients were used for data analysis ranging from 18 to 134 patients in each study. The characteristics of the included studies are shown in Table 21. Twelve and three were prospective and retrospective designed studies respectively (120, 239, 240). All studies used histopathology as part of the reference standards. Two of the studies used radiological means in addition to

histopathology, to confirm the diagnosis (241, 242). Of these two, one used tumour markers as part of the reference standard (241).

Table 21. Characteristics of the included studies

Study	Year	Number of patients for type of imaging		Design	CDI	Method used to confirm Diagnosis	Comparisons	Inclusion/Exclusion Criteria	Quality Score (Max 14)
		PET	CDI						
Arulampalam (243)	2001	42	42	P	1	H	3	1 / -	8
Beets (244)	1994	35	35	P	1	H	1, 3	1, 2, 3 / -	8
Delbeke (241)	1997	52	44	P	1, 2	H, TM, R	2, 3	1, 2, 3 / -	8
Flamen (245)	1999	103	103	P	1, 3, 4, 5	H	1, 2	1, 2 / 1, 2, 3	11
Fong (246)	1999	40	40	P	1, 2, 3, 4	H	3	1, 2, 3 / -	9
Johnson(247)	2001	41	41	R	1	H, I	1, 2, 3	1, 2, 3/ -	7
Hung (248)	2001	33	33	P	1	H, C	1, 2, 3	1 / -	9
Keogan (249)	1997	18	17	P	1	H	1	1, 2, 3 / -	7
Lai (242)	1996	34	34	P	1, 2, 3	H, R	2	1, 2 / -	8
Lonneux (239)	2002	79	79	R	1, 2, 3, 5, 6	H	1, 2, 3	1, 2, 3 / -	8
Schiepers (250)	1995	76	76	P	1, 7	H	1, 2	1, 2 / -	9
Staib (251)	2000	100	100	P	1, 7, 8	H	1, 2, 3	1 / -	9

Valk (252)	1999	134	115	P	1	H	1, 2, 3	1, 2, 3 / -	11
Vitola (253)	1996	24	24	P	1, 2	H	2	1, 2 / -	8
Whiteford (240)	2000	105	101	R	1	H	1, 2, 3	1, 2 / -	10

CDI: 1= CT, 2= CT portography, 3= MRI, 4= Endorectal USS, 5= CXR, 6= Bone scintigraphy, 7= USS, 8= CEA

Comparisons: 1 = Detection of local recurrence; 2 = Detection of liver metastases; 3 = Detection of distant metastases

Method used to confirm diagnosis: H= histology; C= clinically; TM= tumour markers; R= radiologically, I= intra-operative findings

Inclusion criteria: 1= Previous Rx for CRC of any stage; 2= Suspicion of metastases from recurrent CRC; 3= Elevated CEA

Exclusion criteria: 1= Previous chemotherapy; 2= IBD; 3= More than 2 months between scans

Abbreviations: PET= Positron Emission Tomography, CDI= Conventional Diagnostic Imaging

Using the QUADAS criteria, eight studies were classed as high quality as shown in Table 21. There were two studies with a score of eleven (245, 252) and one that scored ten (240). There were five studies with a score of nine (246, 248, 250, 251, 254).

1.4.2 Verification bias

Verification bias occurs when the result of one test influences selection for the other test and occurs when subjects undergoing both tests are included for analysis (255). Every patient underwent both the test (either PET or CDI) and the reference standard (other radiological or clinical examination, surgery/histology). Therefore, the primary endpoint verification bias was zero.

1.4.3 Local recurrence (table 22)

Nine studies (239, 240, 244, 245, 247-250, 252) evaluated 624 and 600 patients for the PET and CDI group respectively, reported on the diagnosis of local recurrence and therefore included. The sensitivity for PET was 0.949 with no significant between-study heterogeneity ($Q= 4.21$, $p= 0.838$); and specificity was 0.956 with no significant between-study heterogeneity ($Q= 10.70$, $p= 0.219$). The sensitivity for CDI was 0.708 with no significant between-study heterogeneity ($Q= 9.7$, $p= 0.287$); and specificity was 0.844 with significant between-study heterogeneity ($Q= 36.52$, $p<0.001$). The summary AUC for PET and CDI was 0.982 and 0.825 respectively.

1.4.4 Liver Metastases

Ten studies (239-241, 245, 247, 253) evaluated 748 and 717 patients for PET and CDI group respectively, reporting on the detection of liver metastases and therefore were included in the analysis. The PET sensitivity for detecting liver metastases was 0.94 with no significant between-study heterogeneity (Q= 13.22, p= 0.153) with the specificity being 0.983 with moderate heterogeneity among the studies (Q= 22.52, p= 0.007). The sensitivity of CDI was 0.869 with moderate between-study heterogeneity (Q= 14.03, p= 0.081); and the specificity was 0.893 with significant between-study heterogeneity (Q= 53.82, p<0.001). The overall AUC for PET and CDI group was 0.984 and 0.935 respectively.

1.4.5 Distant recurrence

Nine studies (239-241, 243, 246-248, 251, 252) evaluated 593 and 562 patients for PET and CDI group respectively, reported on the diagnosis of distant metastases and included in this analysis. The sensitivity of PET for detecting distant recurrence is 0.934 with moderate between-study heterogeneity (Q=15.54, p=0.046); and the specificity was 0.839 with moderate between-study heterogeneity among the studies (Q=14.91, p=0.061). The sensitivity of CDI for detecting distant recurrence is 0.734 (95% CI: 0.690, 0.772) with significant heterogeneity among the studies (*Q=39.08, p<0.001*); and specificity of 0.679 with moderate heterogeneity among the studies (*Q=19.62, p=0.006*). The AUC for PET and CDI group was 0.946 and 0.728 respectively.

Table 22: Pooled Results for PET and CDI

	No. Patients	No. Studies	Sensitivity (95% CI)	HG (*p* value)	Specificity (95% CI)	HG (*p* value)	Likelihood ratio LR +	Likelihood ratio LR -	HG (*p* value) LR +	HG (*p* value) LR -	AUC (SE)
PET											
Local recurrence	624	9	0.949 (0.91, 0.974)	4.21 (0.838)	0.956 (0.929, 0.974)	10.70 (0.219)	15.484 (9.008, 26.616)	0.067 (0.039, 0.115)	16.62 (0.224)	2.77 (0.948)	0.982 (0.006)
Liver metastases	748	10	0.940 (0.913, 0.960)	13.22 (0.153)	0.983 (0.964, 0.993)	21.93 (0.009)	33.174 (9.047, 121.645)	0.081 (0.057, 0.116)	39.08 (**<0.001**)	9.13 (0.425)	0.984 (0.006)
Distant metastases	593	9	0.934 (0.910, 0.954)	15.54 (0.049)	0.839 (0.780, 0.888)	14.91 (0.061)	5.026 (9.191, 7.914)	0.090 (0.054, 0.152)	16.04 (**0.042**)	15.72 (**0.047**)	0.946 (0.026)
CDI											
Local recurrence	600	9	0.708 (0.641, 0.769)	9.70 (0.287)	0.844 (0.802, 0.880)	36.52 (<**0.001**)	3.760 (2.353, 6.008)	0.388 (0.313, 0.482)	28.45 (<**0.001**)	6.61 (0.579)	0.825 (0.032)
Liver metastases	717	10	0.869 (0.831, 0.901)	14.06 (0.12)	0.893 (0.859, 0.922)	66.44 (**<0.001**)	6.867 (2.592, 18.195)	0.173 (0.127, 0.236)	145.46 (**<0.001**)	10.61 (0.303)	0.935 (0.015)
Distant	562	9	0.734	39.28	0.679	19.96	1.860	0.479	14.21	27.03	0.728

metastases	(0.692, 0.773)	(**<0.001**)	(0.608, 0.744)	(**0.010**)	(1.398, 2.475)	(0.329, 0.699)	(**0.077**)	(**0.001**)	(0.046)

Abbreviations: PET= Positron Emission Tomography, CDI= Conventional Diagnostic Imaging, CI = Confidence interval; HG = Heterogeneity; AUC = Area under receiver operator characteristics curve; SE = Standard error

1.4.6 Sensitivity Analysis (table 23)

Sensitivity analysis was performed for studies of higher quality and studies published after 1998. Studies with QUADAS quality score of more than eight were considered of higher quality. Seven studies (240, 246, 248, 250-252) evaluating 591 patients had a QUADAS score of more than >8; nine studies were published after 1998 and were included in sensitivity analysis.

Sensitivity analysis for high quality studies did not significantly change the accuracy of PET for any of the results. It did though reduce the heterogeneity for liver metastases specificity without having a significant impact on the heterogeneity for the rest of the outcomes. The accuracy of CDI was improved for the specificity for diagnosing liver and distant metastases respectively, which was reflected by an increase of the AUC by 3.2 and 2.1% respectively. The heterogeneity was significantly reduced for the sensitivity and specificity for local recurrence and liver metastases. It did not significantly alter the heterogeneity for distant metastases.

Sensitivity analysis of the studies published after 1998 did not significantly change the results for the accuracy of PET or CDI except for the accuracy of CDI for local recurrence that showed a mild improvement of the AUC by 3.5%. This difference approached statistical significance (p=0.057). There was no significant change for the rest of the outcomes. Meta-regression was performed to compare the studies that were published after 1998 to the studies published before 1998. CDI were 322% more accurate in detecting local recurrences for the studies published after 1998. CDI were also about 214% and 78% more accurate in detecting liver and distant metastases respectively. This difference did not reach statistical significance. The heterogeneity

was reduced for the sensitivity and specificity of local recurrence and liver metastases but not for distant metastases.

Table 23: Sensitivity analysis

	No. Patients	No. Studies	Sensitivity (95% CI)	HG (*p* value)	Specificity (95% CI)	HG (*p* value)	Likelihood ratio		HG (*p* value)		AUC
							LR +	LR -	LR +	LR -	(SE)
Higher Quality Studies											
PET											
Local	451	5	0.947	2.40	0.957	5.32	17.558	0.065	6.39	1.74	0.983
recurrence			(0.898, 0.977)	(0.664)	(0.924, 0.978)	(0.257)	(8.348, 36.928)	(0.034, 0.124)	(0.172)	(0.783)	(0.009)
Liver	451	5	0.951	6.63	0.990	2.65	59.215	0.068	0.45	4.25	0.997
metastases			(0.912, 0.976)	(0.157)	(0.970, 0.998)	(0.618)	(24.60, 140.49)	(0.038, 0.122)	(0.978)	(0.373)	(0.002)
Distant	412	5	0.924	13.20	0.860	8.39	5.957	0.10	8.76	12.40	0.939
metastases			(0.886, 0.952)	(0.010)	(0.785, 0.916)	(0.078)	(3.039, 11.679)	(0.041, 0.239)	(0.067)	(0.015)	(0.043)
CDI											
Local	428	5	0.689	1.21	0.837	14.74	3.825	0.387	13.34	2.50	0.763
recurrence			(0.608, 0.762)	(0.876)	(0.785, 0.941)	0.005	(2.226, 6.573)	(0.304, 0.497)	0.010	0.645	(0.050)
Liver	428	5	0.864	2.76	0.946	2.08	14.868	0.151	1.77	2.15	0.967
metastases			(0.809, 0.909)	(0.60)	(0.913, 0.969)	0.720	(9.207, 24.008)	(0.106, 0.214)	0.779	0.708	(0.017)
Distant	389	5	0.720	29.61	0.726	12.67	2.033	0.503	5.64	19.14	0.747
Metastases			(0.659, 0.776)	**(<0.001)**	(0.638, 0.802)	(0.013)	(1.417, 2.916)	(0.293, 0.861)	(0.228)	(0.001)	(0.063)
Studies published after 1998											

PET											
Local recurrence	495	6	0.950 (0.90, 0.980)	3.91 (0.563)	0.953 (0.923, 0.974)	9.97 (0.076)	15.245 (7.623, 30.486)	0.067 (0.034, 0.131)	9.49 (0.091)	1.79 (0.877)	0.983 (0.007)
Liver metastases	562	6	0.961 (0.927, 0.982)	8.96 (0.111)	0.990 (0.972, 0.988)	2.95 (0.708)	55.687 (23.354, 132.789)	0.060 (0.033, 0.109)	0.64 (0.986)	5.26 (0.385)	0.997 (0.002)
Distant metastases	574	8	0.934 (0.905, 0.957)	15.54 (0.030)	0.836 (0.771, 0.889)	14.83 (0.038)	4.904 (2.962, 8.118)	0.090 (0.047, 0.171)	15.06 (0.035)	15.25 (0.033)	0.945 (0.031)
CDI											
Local recurrence	472	6	0.739 (0.656, 0.811)	4.62 (0.464)	0.862 (0.818, 0.899)	26.33 <0.001	4.765 (2.664, 8.521)	0.322 (0.242, 0.427)	19.23 (0.002)	1.86 (0..868)	0.860 (0.031)
Liver metastases	539	6	0.877 (0.826, 0.917)	4.37 (0.497)	0.924 (0.888, 0.950)	20.44 (0.001)	11.426 (4.009, 32.563)	0.149 (0.105, 0.212)	34.97 (<0.001)	4.71 (0.452)	0.941 (0.019)
Distant Metastases	551	8	0.704 (0.654, 0.751)	32.84 (<0.001)	0.690 (0.615, 0.757)	19.03 (0.008)	1.864 (1.333, 2.605)	0.509 (0.339, 0.763)	14.19 (0.048)	23.17 (0.002)	0.725 (0.0)54

Abbreviations: PET= Positron Emission Tomography, CDI= Conventional Diagnostic Imaging, CI = Confidence interval; HG = Heterogeneity;

AUC = Area under receiver operator characteristics curve; SE = Standard error

1.4.7 Weighted Meta-Regression Analysis: PET vs CDI (table 24)

The effect of other covariates was evaluated in a univariable metaregression analysis (inverse variance weighted) on DOR assessing local recurrence, distant recurrence and liver metastases. The relative DOR was calculated according to standard methods to analyse the change in diagnostic precision in the study per unit increase in the covariate.

PET was overall more accurate than CDI for local recurrence (rDOR= 28.94, p<0.001), liver (rDOR= 4.81, p= 0.010) and distant metastases (rDOR= 9.48, p<0.001). PET remained more accurate when the sensitivity analysis was performed. Meta-regression for higher quality studies increased the difference for local recurrence and liver metastases but reduced it for distant metastases. Meta-regression for studies published after 1998 reduced the gap for local recurrence and liver metastases but increased it for distant metastases.

Table 24: Weighted meta-regression analysis comparing PET vs CDI

a. Overall			
	Coefficient	*Relative DOR (95% CI)*	*p*
Local recurrence	3.365	28.94 (9.65, 86.82)	<0.001
Liver metastases	1.571	4.81 (4.81, 15.01)	0.010
Distant metastases	2.249	9.48 (1.54, 15.01)	<0.001
b. Higher Quality studies			
Local recurrence	3.806	44.95 (10.85, 186.27)	<0.001
Liver metastases	2.043	7.72 (1.72, 34.62)	0.014

Distant metastases	1.907	6.73 (1.46, 30.97)	0.020
c. Studies published after 1998			
Local recurrence	2.963	19.35 (5.0, 74.93)	0.001
Liver metastases	1.963	7.12 (1.43, 35.51)	0.021
Distant metastases	2.536	12.62 (3.06, 52.02)	0.002

Abbreviations: DOR= Diagnostic Odds Ratio, CI= Confidence Interval

1.5 Discussion

The present study evaluated the accuracy of PET scanning compared to the conventional diagnostic investigation in diagnosing local recurrence, liver and distant metastases. This established that PET provides a significant advantage in the diagnosis of recurrent rectal cancer. Such an advantage can improve and make diagnosis feasible at an earlier stage, enabling better management planning with higher chances for curative resection and better outcome. This study demonstrated that PET scanning possesses significantly higher sensitivity and specificity in diagnosing liver metastases, as well as local and distant recurrent disease compared with CDI. One in every fifteen patients with distant recurrence will still be missed (sensitivity= 0.937) however these patients will undergo laparotomy and closure with no resection performed and will receive all the potential risks of anaesthesia. PET's specificity for distant metastases was shown to be 82.3%. In clinical practice, this means that 17.7% of the patients will be over-staged by PET and undergo further unnecessary investigation if no other foci are identified and may be refused to have a potentially curative operation if there is a local recurrence which is resectable, due to the false impression of inoperable disease. Therefore when PET shows distant

metastases, this should be examined carefully and correlated with other diagnostic modalities and clinical picture/examination.

There are several reasons for this overstaging. Acute inflammatory lesions and abscesses can be misinterpreted as recurrent disease. The accumulation of FDG can also be enhanced following radiotherapy up to several months in patients with colorectal carcinoma (256, 257). These changes can imitate inflammation (258). Studies assessing the FDG accumulation following chemotherapy (HPC) for breast cancer showed that there is an increase in FDG uptake immediately after HPC treatment (259). Minn *et al.* (260) demonstrated that there is increase FDG uptake following treatment with doxorubicin on Lewis Lung carcinoma. Colorectal cancer chemotherapy might result in similar pathophysiology and affect the FDG uptake in the same way.

Diagnostic accuracy was higher when studies with a higher quality score (QUADAS 9 and above) only were analysed, mainly for detecting liver metastases (AUC improved from 0.987 to 0.997). There was, however, significant heterogeneity in some groups. When meta-regression was performed comparing PET vs CDI, there was a statistically significant 39-fold increase in the diagnostic odds ratio for the detection of local recurrence ($p<0.001$), 5-fold increase for detecting liver metastases ($p= 0.015$) and a 12-fold increase for detecting distant metastases ($p<0.001$). These results confirmed that PET scanning is a more effective diagnostic tool in detecting rectal cancer recurrence and liver metastases than current conventional means.

PET scanning has the advantage that it is highly sensitive with high specificity in detecting recurrent rectal cancer disease. It is also highly sensitive with high diagnostic accuracy in identifying peritoneal deposits, something which MRI and CT are less accurate in doing. The main disadvantage to PET is that it is more expensive at present than other modalities and at the same time in some countries is not widely available due to its high installation cost and lack of trained professionals to run and interpret it. In the UK, according to www.cancerhelp.org.uk (Aug 2008), each scanner costs about £4.2 m to be installed, and there are only five scanners in the UK. Each scan costs between £750 and £1,000 for each patient.

PET scan provides functional images instead of structural images that can be obtained by CT or MRI but offers poor anatomical detail. To correctly interpret the PET images, it is essential that they be correlated with the anatomical images from CT. This was initially done with complicated fusion techniques and software, but numerous limitation factors were reducing the accuracy of the results that is not for further discussion in this study. This issue has been addressed in the recent years with the addition of CT scan to PET. As a result, synchronous functional and structural images can be obtained by combining the advantages of both modalities and at the same time eliminating their weaknesses.

Early detection of colorectal cancer recurrence is crucial. It increases the possibility of a successful curative salvage surgery (40, 261) and can prevent dissemination. Consequently, it can increase the patients' survival time and also reduce the mortality and morbidity rate. Protocols for the multiple elements of CDI need to be implemented uniformly in everyday clinical practice. The threshold for diagnostic

investigations such as CT and MRI needs to be carefully monitored so that more patients get scanned. Simpler diagnostic imaging modalities such as trans-abdominal USS, Endorectal USS, rigid and flexible sigmoidoscopy can be part of regular examination when following up the patients. They are cheap to use but need appropriately trained specialists to use and interpret the results correctly. All these modalities are much cheaper to install and run than PET and they are readily and easily accessible in most the developed countries' hospitals. The more frequent use of these techniques will increase the number of the patients that will be examined and scanned and conclusively the number of the earlier diagnosed recurrent disease or metastases.

Endorectal USS is a relatively new diagnostic technique that can be used when patients are followed up; it can be useful in early detection or raising suspicions for local recurrence that will initiate further more specific investigations. There is no clear evidence though supporting its value for following up patients post-op. Ramirez *et al.* (262) showed that it could be useful in presenting evidence of recurrent disease. However its interpretation is more complicated following surgery due to the challenges to distinguish recurrence from inflammation or fibrosis (263). Löhnert *et al.* (264) showed that Endorectal USS correctly identified 92 out of 116 recurrences. The results were improved when tissue biopsy was added on the examination (116/116). Endorectal USS is not the gold standard and does not provide such comprehensive examination as other CDI (CT, MRI), but it is easy and cheaper to use. As with all ultrasound based investigations, interpretation varies widely with experience and skills of the user and has a significant learning curve (265-268).

Carcinoembryonic Antigen (CEA) is known to have high specificity but low sensitivity. A meta-analysis (269) evaluated its value in the raising suspicions of local or distant recurrent colon and rectal cancer disease. The suggestion that a cut-off of 2.2 ng/ml may be useful in guiding follow-up investigations in recurrent colorectal cancer is intriguing, thereby providing greater balance in both specificity and sensitivity, and providing an early trigger for beginning more extensive investigations. CEA can continue to form an essential part of the patients' follow up. Most hospitals can process the test in 24 hours and therefore can be a valuable tool at the clinicians' hands in the everyday practice. Therefore interpretation should always be made after a series of CEA measurements and always in association with the clinical picture and radiological findings.

Multi-Disciplinary Teams are crucial in guiding the patients' journey. It is important these MDT meetings take place as soon as the diagnosis of a recurrence is made to facilitate the prompt management of the patients. By centralising complex major cancer surgery, clinicians and patients will be able to benefit from the organisational structure and clinical governance of the tertiary referral setting. Burton et al. (270) evaluated the effects of discussing patients' MRI between surgeons, oncologists and radiologists, at organised MDT meetings. That study showed that there might significantly increase the number of curative resections (R0). It is also more likely that PET scanners will be available, together with the full range of other radiological systems in such an environment.

There is a number of limitations in this study. Heterogeneity was significant in some groups as analysed above. Not all the studies were prospective; three of them were

retrospective (120, 239, 240). Three other studies compared PET's results with tumour markers, clinical examination and other radiology modalities in addition to Histopathology, which is the gold standard (241, 242, 248). Study population differences among the studies significant but were well controlled during subgroup analysis since all the studies that were included, with the exception of Hung et al. (33 patients), had more than 100 patients.

1.6 Chapter's Conclusion

The present study demonstrated that PET scan is highly accurate in diagnosing liver metastases, local and distant rectal cancer recurrence. Its specificity for distant metastases is higher than other conventional diagnostic investigation. In clinical practice, this could enable better selection of patients for surgery and aid neo-adjuvant treatment and surgical planning. However, it is important to note that CDI improved with time and that the latest study included in this paper was published more than 10 years ago.

Future considerations

Updated meta-analysis comparing PET/CT scan with more modern CDI.

CHAPTER 9. Feasibility and value of PET/MRI

1.1 Introduction

The surgical planning of exenterative surgery for locally advanced primary and recurrent rectal cancer is challenging and requires accurate pre-operative staging to enable the selection of patients that would be benefited the most from surgery and medical therapy. As it has been previously demonstrated, surgery is the only potential cure for this group of patients, and its success is highly depended on the complete resection of the tumour (R0) as this has been shown to increase survival (132, 133, 157).

A number of radiological modalities have been evaluated over the years in the effort to improve the patient selection for surgery and improve the oncological outcomes. CT has been demonstrated to be highly accurate in predicting the tumour extension into surrounding tissues, providing detailed anatomical information of the affected organ and therefore aiding the planning of surgery (64). However, CT may often have difficulties determining if a suspected pelvic mass represents disease recurrence or tissue fibrosis. This becomes even more challenging if radiotherapy had previously been applied or there was previous pelvic sepsis from anastomotic dehiscence. (65) MRI also showed high diagnostic accuracy in diagnosing and staging pelvic malignancies with the advantage of providing an accurate depiction of the pelvic anatomy in relation to the tumour (67-70) and predict the absence of disease from non-resected organs/structures (71).

Positron Emission Tomography (PET) is a functional radiological modality that may have advantages over CT and MRI in differentiating scar tissue from cancer. It has been shown to have high sensitivity and specificity in detecting local and distant colorectal cancer recurrences/metastases (92) with influence on the patients' management in up to 34% of the cases. (91) However, PET scan may have limited value in identifying small volume disease (94) and mucinous adenocarcinomas. (95) PET alone does not provide sufficient anatomical information regarding the tumour relation to vital anatomical structures that can influence the feasibility of surgery. Therefore it was natural to be fused with CT (PET/CT) scan incorporating both modalities' advantages. Recent studies showed PET/CT to have a sensitivity of up to 95% and specificity of up to 75% when calculated per lesion in detecting colorectal cancer recurrences. (271-273) To the authors' knowledge, no studies have been performed yet to assess its value in planning exenterative pelvic surgery.

At the authors' institute, MRI is used as the standard method of pre-operative assessment of tumour invasion within the pelvis facilitating the neoadjuvant therapy and surgical planning. With an aim to eliminate the limitations and enhance the strengths of each modality the authors performed this study based on the following hypothesis: Fusion of MRI and PET images is feasible and can improve the preoperative staging of patients undergoing exenterative pelvic surgery for locally advanced primary and recurrent colorectal pelvic cancer.

1.2 Aims of study

The aim of the present study was to assess the feasibility and value of fused images of PET/MRI in the management of patients with recurrent and locally advanced primary rectal cancer that are considered for surgery.

1.3 Inclusion and exclusion criteria

Inclusion to the study required evidence of a locally advanced primary or recurrent colorectal intrapelvic cancer, age over 18 years, availability of both the pre-operative MRI and PET/CT. Patients were excluded if a pre-operative MRI or PET/CT was not performed; or if the MRI images were unsuitable for the evaluation of the individual compartments due to poor quality; or there was a significant interval (more than 3 weeks) between the performance of MRI and PET images; or the fusion of images could not be performed due to software limitations.

1.4 Surgical pelvic anatomical compartments

The same classification as described in methods was used to divide the pelvis into seven compartments according to the fascial boundaries and planes of dissection between the intrapelvic organs, as described in methods.

1.5 Qualitative assessment of images

The images were reviewed and reported using a modified proforma by a radiologist (Dr Gina Brown) and a Nuclear Medicine Consultant (Dr Sue Chua). Further details are described in methods.

1.6 Reference Standards

Histopathology was used as the reference standard.

1.7 Results

1.7.1 Demographic characteristics of the population (table 25)

The fusion images of 31 (20 males) patients with mean age of 62.77 (12.75) fulfilled the inclusion criteria and included in the study. Twenty two patients underwent surgery for recurrent and nine patients for primary cancer. Twenty four patients received neoadjuvant chemoradiotherapy. Abdominosacral resection was performed in eleven patients, posterior exenteration in four, total pelvic exenteration in six patients. Six other patients underwent other procedures including salvage abdominoperineal resection and local excision of the recurrence.

Histopathology revealed an adenocarcinoma in twenty eight cases, a squamous cancer in one and full response to neo-adjuvant therapy in two patients. There were thirteen patients with well/moderately differentiated cancer, eleven with poorly differentiated cancer, four with mucinous and one with signet cell cancer. Lymphovascular and perineural invasion was identified in 13 and 9 patients respectively.

Table 25. Demographic data of the included population for the PET/MRI study.

Age (years) Mean(SD)	62.77 (12.75)
Males	20 (64.52%)
Recurrence	22 (70.96%)
Neo-adjuvant CRT	24 (77.42%)

Exenterative surgery: • ASR	11 (35.48%)
• Posterior exenteration	4 (12.9%)
• TPE	6 (19.35%)
• Other	6 (19.35%)
• Palliative laparotomy	4 (12.9%)
Histology type	
• Adenocarcinoma	28 (90.32%)
• SCC	1 (3.23%)
• Full Response to Neo-adjuvant CRT	2 (6.45%)
Grade of differentiation: • Well/Moderate	13 (41.94%)
• Poor	11 (35.48%)
• Mucinous	4 (12.9%)
• Signet cell	1 (3.23%)
Clearance • R0	17 (54.84%)
• R1	8 (25.81%)
• R2	6 (19.35%)
Lymphovascular invasion	13 (41.94%)
Perineural invasion	9 (29.03%)

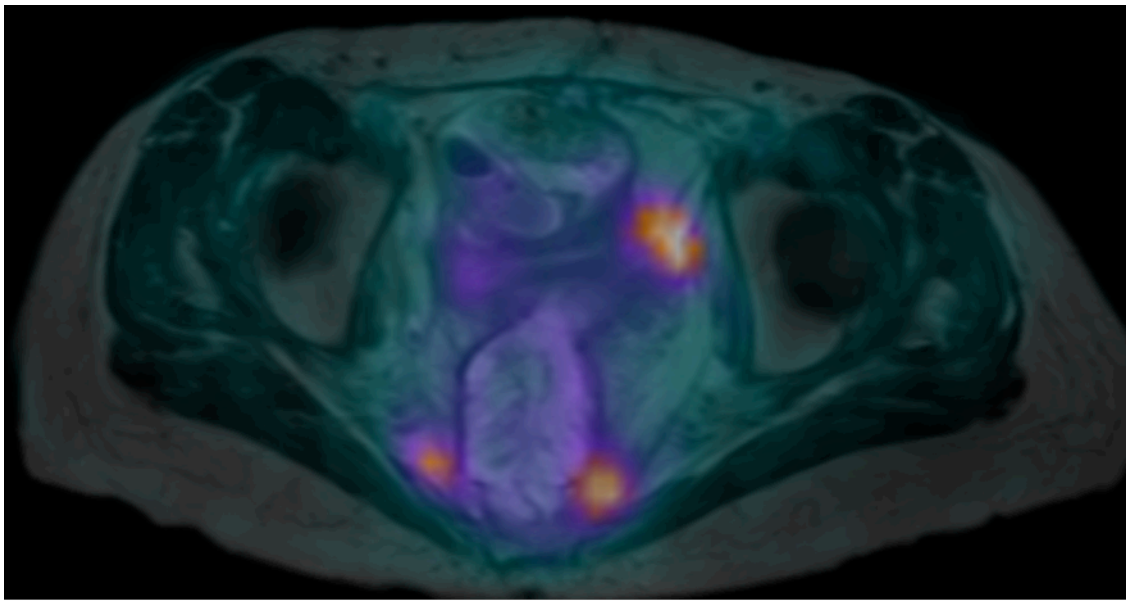
Abbreviations: SD= standard deviation, APER= abdomino-perineal excision of rectum, ASR= abdomino-sacral resection, TPE= total pelvic exenteration, SCC= squamous cell carcinoma, CRT= chemoradiotherapy.

1.7.2 Patterns of tumour invasion within the pelvis.

The tumour was more often diagnosed to invade the central (23 patients; 74.19%) and the anterior compartment below the peritoneal reflection (21 patients; 67%). The

compartment that was least involved was the peritoneal reflection (6 patients; 19.35%). The inferior and posterior compartments (figure 26) were involved in 15 patients (48.39%) and 14 patients (45.16%) respectively.

Figure 26: Fused image showing a mucinous cancer with areas of adenocarcinoma (hot areas)



Tumour was found within the lateral compartment in 12 patients (38.71%). The anterior compartment above the peritoneal reflection was invaded by tumour in 9 cases (29.03%).

1.7.3 Per compartment diagnostic accuracy of PET/MRI (table 26)

The PET/MRI sensitivity was very good for all the compartments (≥83.3%). For the inferior, central and anterior compartments above and below the peritoneal reflection the sensitivities were more than 90%. The lowest sensitivity was for the peritoneal reflection and lateral compartment (83.3%). The specificity of PET/MRI was equal or more than 90% for all the compartments except for the central compartment that it

was 75%. The lowest positive predictive value (PPV) was noted for the peritoneal reflection (71.4%) with the PPV for the rest of the compartments being over or equal to 90%. The negative predictive value was the lowest for the anterior compartment below the peritoneal reflection (81.8%). It was equal or above 90% for the rest of the compartments except the posterior compartment (88.9%). The area under the receiver-operating curve was higher or equal to 87.5% in all compartments. The largest area under the curve was for the inferior (0.967) and the anterior compartment above the peritoneal reflection (0.977).

1.7.4 Interobserver agreement.

Cohen's kappa coefficient was used to assess the interobserver agreement. The interobserver agreement was either good or very good for all the compartments. It ranged between 0.733 (SE= 0.120; $p<0.001$) for the anterior compartment below the peritoneal reflection, to 0.843 (SE= 0.107; $p<0.001$) for the anterior compartment above the peritoneal reflection.

Table 26. Per compartment diagnostic accuracy results of the fused PET/MRI.

Compartments	Prevalence (%)	TP	FP	FN	TN	Sens (%) (95% CI)	Spec (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	ROC area (95% CI)
PR	6 (19.35)	5	2	1	23	83.3 (35.9 - 99.6)	92 (74 - 99)	71.4 (29 - 96.3)	95.8 (78.9 - 99.9)	0.877 (0.705 - 1)
Anterior above PR	9 (29.03)	9	1	0	21	100 (66.4 - 100)	95.5 (77.2 - 99.9)	90 (55.5 - 99.7)	100 (83.9 - 100)	0.977 (0.933 - 1)
Anterior below PR	21 (67.74)	19	1	2	9	90.5 (69.6 - 98.8)	90 (55.5 - 99.7)	95 (75.1 - 99.9)	81.8 (48.2 - 97.7)	0.902 (0.785 - 1)
Posterior	14 (45.16)	12	1	2	16	85.7 (57.2 - 98.2)	94.1 (71.3 - 99.9)	92.3 (64 - 99.8)	88.9 (65.3 - 98.6)	0.899 (0.788 - 1)
Lateral	12 (38.71)	10	1	2	18	83.3 (51.6 - 97.9)	94.7 (74 - 99.9)	90.9 (58.7 - 99.8)	90 (68.3 - 98.8)	0.89 (0.769 -1)
Central	23 (74.19)	23	2	0	6	100 (85.2 - 100)	75 (34.9 - 96.8)	92 (74 - 99)	100 (54.1 - 100)	0.875 (0.715 - 1)
Inferior	15 (48.39)	14	0	1	16	93.3 (68.1 - 99.8)	100 (79.4 - 100)	100 (76.8 - 100)	94.1 (71.3 - 99.9)	0.967 (0.901 - 1)

Abbreviations: CI= confidence intervals, PR= peritoneal reflection, CI= confidence interval, Sens= sensitivity, Spec= specificity, PPV= positive predictive value, NPV= negative predictive value, AUC= area under the curve, TP= true positive, FP= false positive, FN= false negative, TN= true negative, ROC= receiver operating curve

1.8 Discussion

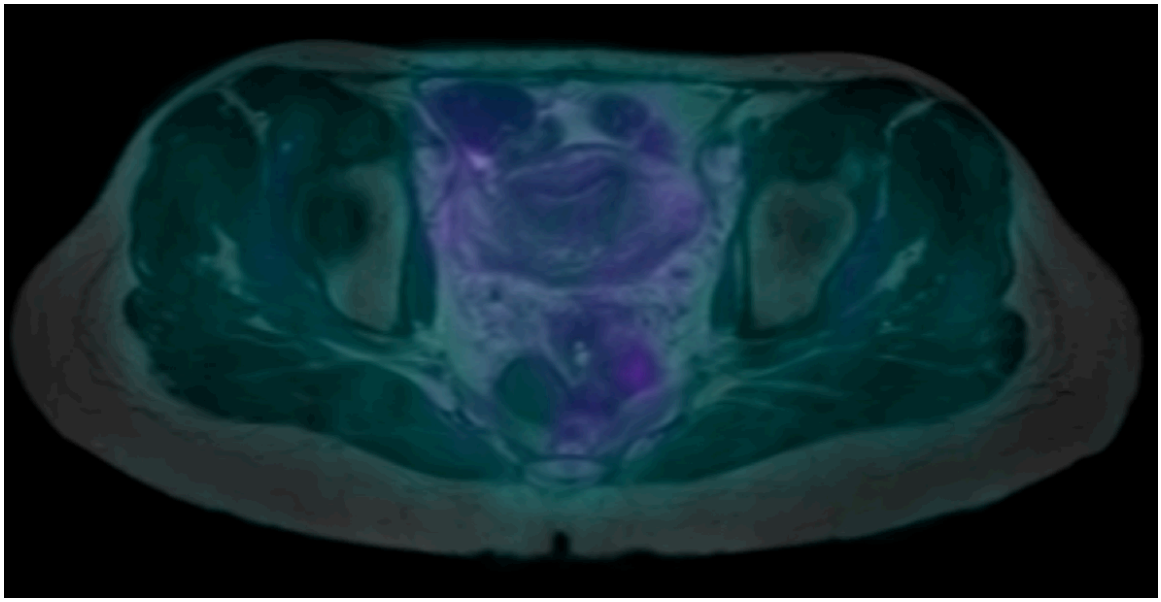
The success of PET/CT has directed industry and researchers to focus on the development of PET/MRI scanners, aiming to improve the diagnostic accuracy for various conditions. The main limitation of PET that led the researchers to develop the PET/CT was the lack of anatomical landmarks. Thus, the addition of CT was a natural step forward. However, both components have limitations that have brought into the new modality PET/CT. PET has low accuracy detecting lymph node disease and can provide False Positive readings in the presence of inflammation. At the same time, the addition of CT significantly increases the radiation that the patients receive, while it is reported to be inferior to MRI in depicting soft tissue. Furthermore, artefacts due to the time interval between PET and CT acquisition may impair its accuracy. MRI can depict better the soft tissues in some cancers; and can provide the anatomical landmarks for PET, which has raised the interest of researchers in fusing the images of PET with MRI.

The integration of PET to MRI carries significant cost though, and until the time this study was performed, small scanners have been used in rat models with promising results. Bigger scanners have been created and used in two pilot studies investigating its feasibility and value in the area of the head and neck (274, 275). Both confirmed that this is feasible without however investigating its cost/effectiveness. Current PET/MR scanners have their limitations. The attenuation correction and whole-body imaging are still challenging without substantial evidence to support its clinical value. The large “price tag” associated with current devices may prove prohibitive for many institutions, (276) especially with the absence of substantial evidence to support their clinical value.

To the authors' knowledge, this is the first study investigating the feasibility of fusing PET with MR images in colorectal pelvic cancer. The present study demonstrated that the fusion of PET and MR images is feasible and that it is highly accurate in determining tumour invasion within the pelvis. The sensitivity ranged from 83.3% in the peritoneal reflection and lateral compartment up to 100% in the central and anterior compartment above the peritoneal reflection. The specificity was the least for the central compartment, ranging above and equal to 92% for the remainder of the compartments. The positive predictive value was the lowest for the peritoneal reflection and was equal to above 90% for the rest of the compartments. The negative predictive value ranged from 81.8% in the anterior compartment below the peritoneal reflection to 100% for the central and anterior compartment above the peritoneal reflection. The overall area under the receiver-operating curve was equal or more than 0.875 (central compartment).

Taking into consideration the significant cost associated with PET/MR scanners, the fusion of PET with MR images seems promising in the pre-operative staging of patients that are due to undergo exenterative pelvic surgery for locally advanced primary rectal and recurrent colorectal pelvic cancer. Operating on this group of patients is very challenging and requires a thorough investigation of each patient before considering surgery. It is often a subject of debate in current multidisciplinary meetings with decision often postponed, to perform more studies to determine the resectability of cancer. Employing PET/MR fusion imaging (figure 27), only cost the time put to fuse the images and may provide critical information to this decision process, which will enable the better management of the patient.

Figure 27: Fused PET/MRI showing different uptake in different part of the tumour.



This study has several strengths. The reporting of images was performed by an expert to the field radiologist and a nuclear medicine consultant. At the same time, this may be one of the limitations of the study, as the findings may not represent the average hospital. Further studies are required to validate them. Furthermore, Hermes workstation was utilised, which is a widely used software for fusing brain PET with MRI images. Also, the trainee and supervisor supervised the co-registration of the images process to ensure the accuracy of the process without any errors.

This study has a number of limitations. This is a pilot study that included a small number of patients, preventing the extraction of safe conclusions regarding the clinical value of the fused images of PET/MRI. It does demonstrate thought that this feasible and can be used without adding significantly to the cost of pre-operative

staging for patients that both require PET and MRI scanning. The only added cost is the purchase of the software and the time to fuse the images. The cost-effectiveness of this technique compared to PET/MRI fusion scanner is yet to be investigated.

1.9 Chapter's Conclusion

In conclusion, this study has demonstrated that the fusion of PET with MR images is feasible without significantly increasing the cost of pre-operative staging. This study showed that PET/MRI has high diagnostic value in predicting tumour invasion within the pelvis and may potentially be used to better select patients for surgery and medical therapy. Further studies with a bigger number of patients are required to validate these results.

Further Considerations

To investigate the diagnostic value of fused PET/MR images in a prospective setting and the potential value of a PET/MRI scanner.

CHAPTER 10: Learning Curve for Exenterative Pelvic Surgery for Primary and Recurrent Rectal Cancer.

1.1 Introduction

Surgical performance of any procedure improves with time. The learning curve is the period corresponding to the acquisition of knowledge and skill that is necessary to perform the procedure with a stable and optimised morbidity (191, 277). In surgery it signifies the evolution of surgical technique, the improved decision making, the surgeon's familiarity with the procedure and its risks, and the development of the coordination of the team, leading to improved intraoperative performance and postoperative care (191, 277).

The significant variation in the patterns of tumour invasion within the pelvis dictates that surgery should be individualised for each patient. The involvement of each compartment needs to be studied using the available radiological images and discussed at the local multidisciplinary meeting. This often involves lengthy discussions among the radiologists, oncologists, surgeons, radiotherapists and pathologists before a final decision to the extent of the surgery required if the disease is amenable to surgery. Therefore, the operation is not standardised and prolonged time may be necessary to acquire the relevant skills and knowledge to become proficient in this type of surgery.

Despite advances in rectal cancer surgery in the last twenty years, local recurrence rates may still be high ranging from below 3% to over 30% (278, 279). Thus, pelvic

exenterative surgery is likely to continue to be required, and surgeons need to be trained to perform these procedures. The complexity of these procedures requires that they are performed in tertiary centres with the infrastructure already established.

1.2 Aims of the present study

The present study aimed to investigate and assess the learning of one colorectal pelvic surgeon (my supervisor Professor Tekkis), in performing pelvic exenterative surgery for locally advanced and recurrent rectal cancer.

1.3 Patients

Data were prospectively collected from patients who underwent exenterative surgery between March 2006 and December 2011 for advanced pelvic colorectal cancer by one surgeon (Professor P Tekkis) supported by a multispecialty team. The surgeon did not have any previous experience in pelvic exenterative surgery and his training took place under the supervision of an experienced pelvic colorectal surgeon (RJN). Patients were included if they were operated for locally advanced primary rectal or recurrent pelvic colorectal cancer. The operations were performed following the steps previously described by the authors. (280, 281) Patients deemed inoperable were excluded from the study. The study was approved by the local cancer network as part of an audit of services. The patients' demographic characteristics, use of neo-adjuvant radiotherapy, type and duration of resectional and reconstructive surgery, operative blood loss, perioperative complications, length of hospital stay, reoperation rate and tumour histopathology were all recorded.

1.4 Endpoints

The primary endpoints were the learning curve for 1) inadequate tumour clearance and 2) the incidence of reoperation for a major complication. Secondary endpoints included minor post-operative complications that were managed conservatively, the length of operation, operative blood loss and length of stay. The patients were divided into four quartiles, each comprising of 25 patients operated on sequentially.

1.5 Results

1.5.1 Demographic Data *(Table 27)*

Between March 2006 and October 2009, one hundred (100) patients (70 males and 30 females) underwent exenterative surgery for a locally advanced primary rectal cancer (n= 55) or a colorectal cancer pelvic recurrence (n= 45). The median age was 61 (25 - 85) years. The median age in the quartiles were: Q1= 61 (43 - 80), Q2= 58 (25 - 81), Q3= 62 (36 - 85), Q4= 59 (31 - 84). There was no statistically significant difference among the four quartiles (p= 0.969). There were 20, 16, 14 and 20 male patients in Q1, Q2, Q3 and Q4 respectively (p= 0.162). The patients that underwent surgery for recurrent pelvic cancer were reduced from 16 in the Q1 and Q2 to 4 and9 in Q3 and Q4 respectively. This difference was statistically significant (p= 0.001). Eighty-three (83%) patients received neoadjuvant radiotherapy (Q1 21, Q2 19, Q3 21, Q4 22; p= 0.718).

Thirty (30%) patients underwent abdominosacral resection, 51 (51%) pelvic exenteration and 19 (19%) had other types of exenterative surgery. Abdominosacral resection was performed in 11 patients in Q1, 8 in Q2, 4 in Q3 and 7 in Q4. Pelvic and

perineal plastic reconstruction was performed in 53 (53%) patients increasing from 12 in Q1 to 15 in Q4. This increase did not reach statistical significance (p= 0.781).

Table 27. **Demographic characteristics of included patients**

	Q					
	1 (n= 25)	2 (n= 25)	3 (n= 25)	4 (n= 25)	Total (n= 100)	
Age (median; range)	61 (43 - 80)*	58 (25 - 81)*	62 (36 - 85)*	59 (31 - 84)*	61 (25 - 85)	p= 0.969
Male patients (%)	20 (80.0)	16 (64.0)	14 (56.0)	20 (80.0)	70 (70.0)	p= 0.162
Recurrent Cancers	16 (64.0)	16 (64.0)	4 (16.0)	9 (36.0)	45 (45)	p= 0.001
Neoadjuvant Radiotherapy	21 (84.0)	19 (76.0)	21 (84.0)	22 (88.0)	83 (83.0)	p= 0.718
Surgery						p= 0.010
• ASR	11 (44.0)	8 (32.0)	4 (16.0)	7 (28.0)	30 (30.0)	
• PE	5 (20.0)	13 (52.0)	19 (76.0)	14 (56.0)	51 (51.0)	
• Other	9 (36.0)	4 (16.0)	2 (8.0)	4 (16.0)	19 (19.0)	
Plastic Reconstruction	12 (48.0)	12 (48.0)	14 (56.0)	15 (60.0)	53 (53.0)	p= 0.781

Abbreviations: Q= quartiles, n= number of patients, ASR= abdominosacral resection, PE= pelvic exenteration, EL= extended lateral pelvic lymphadenectomy; Numbers in brackets represent percentages. *= range

1.5.2 Perioperative outcomes and blood loss *(table 28)*

The median intraoperative time for all patients was 8 hours and ranged between 3 and 17 hours. The median intra-operating time (IOT) increased from 7.5 hours in Q1 to 10 hours in Q4. This difference did not reach statistical significance (p= 0.618).

The median intraoperative blood loss was 1.5 Litres and ranged between 100ml and 17 litres. The median blood loss ranged between 1.2 litres in Q2 and 1.5 litres in the rest of the quartiles. The intraoperative blood loss did not increase with time (p= 0.997).

The overall median length of stay (LOS) remained unchanged from Q1 to Q4 at 14 days (9 - 82). The LOS was 18 days though in Q3. The overall change in time did not significantly change with time (p= 0.265).

Table 28. **Perioperative outcomes**

	Q					
	1 (n= 25)	2 (n= 25)	3 (n= 25)	4 (n= 25)	Total (n= 100)	
Operative Outcomes						
• IOT (hours; median; range)	7.5 (5 - 13)*	8.5 (3 - 14)*	8 (5 - 17)*	10 (5 - 13)*	8 (3 - 17)*	p= 0.618
• Blood Loss (litres; median; range)	1.5 (0.5 - 7)*	1.3 (0.3 - 17)*	1.5 (0.5 - 3)*	1.5 (0.1 - 6)*	1.5 (0.1 - 17)*	p= 0.997
Clearance						p= 0.995
• R0	19 (76.0)	19 (76.0)	20 (80.0)	20 (80.0)	78 (78.0)	
• R1	4 (16.0)	4 (16.0)	3 (12.0)	4 (16.0)	15 (15.0)	
• R2	2 (8.0)	2 (8.0)	2 (8.0)	1 (4.0)	7 (7.0)	
Morbidity						
• Any complications	16 (64.0)	11 (44.0)	14 (56.0)	13 (52.0)	54 (54)	p= 0.553
• Minor complications	11 (44.0)	6 (24.0)	6 (24.0)	7 (28)	30 (30.0)	p= 0.356
• Major complications	6 (24.0)	3 (12.0)	6 (24.0)	5 (10.0)	20 (20.0)	p= 0.682
• Intraoperative complications	1 (9.1)	1 (9.1)	1 (9.1)	1 (9.1)	4 (36.4)	p= 1.000
Length of stay (days; median; range)	14 (10 - 72)*	14 (10-82)*	18 (9-60)*	14 (10-43)*	15 (9-82)*	p= 0.265

Abbreviations: Q= quartiles, n= number of patients, IOT= intraoperative time, R0= complete resection, R1= microscopic residual disease at the resection margins, R2= macroscopic residual disease; Numbers in brackets represent percentages. *= range

1.5.3 Complications (table 29)

Peri-operative complications occurred in fifty four (54%) patients. Twenty (20%) patients required reoperation for a major complication. Minor complications were observed in 30 (30%) patients. The incidence of any complication fell from 16 patients in Q1 to 13 in Q4 (p= 0553). Major complications declined from 6 in Q1 to 5 in Q4 (p= 0.682). Minor complications occurred in 11 patients in Q1 and 7 in Q4. This fall was not statistically significant (p= 0.356). A summary of all complications observed is demonstrated in table 29.

1.5.4 Multivariable Logistic regression analysis (table 30)

Multivariate regression analysis model was performed for major complications adjusted for gender, tumour type, type of surgery, resection margin status, operative experience and neoadjuvant therapy. Abdominosacral resection was shown to increase the risk for major complications (OR= 3.80, 95% CI 1.11 - 13.00, p= 0.034) as was age ≥65 years (OR= 4.08, 1.22-13.71, p= 0.023). Surgeon experience was not a significant predictor of major complications in this model (Q1: reference, Q2: OR= 0.36, 0.07 - 1.96, p= 0.235; Q3: OR= 2.48, 0.50 - 12.35, p= 0.268; Q4: OR= 1.20, 0.26 - 5.48, p= 0.813).

Multivariate regression analysis model for any complication adjusted for the same factors showed that neoadjuvant therapy to be the only factor to increase the risk of complications (OR= 9.31, 95% CI 2.28 - 37.98, p= 0.002).

Adjusted for the same factors multivariate model demonstrated that recurrent rectal cancer was a significant predictor (OR= 11.48, 95% CI 2.86 - 46.01, p= 0.001) for incomplete resection.

Surgical experience (Q1 vs Q2, Q3, Q4) was not shown to be a significant predictor of either complications or clearance in any of the adjusted models. There were no significant predictors for minor complications either (results not shown).

Table 29. **Complications**

	Q1&Q2 n= 50	Q3&Q4 n= 50	Total n= 100
Local Complications			
Abdominal wound sepsis	9	6	15
• Superficial	5	4	9
• Deep	4	2	6
Perineal/Pelvic wound sepsis	11	10	21
• Superficial	5	4	9
• Deep	6	6	12
Flap complications	5	5	10
• Flap necrosis (partial)	2	2	4
• Flap dehiscence	3	3	6
Sacral osteomyelitis	2	0	2
Ureteric necrosis	1	0	1
Ileal conduit leak	2	2	4
Urinary tract infection	3	4	7
Secondary haemorrhage	5	0	5
Sciatic nerve palsy	1	0	1
Enterocutaneous fistula	2	0	2
Chronic pelvic pain	4	1	5
Systemic Complications			
Prolonged ileus	6	10	16
Mechanical bowel obstruction	2	1	3

Systemic Sepsis (UTI, RTI)	7	1	8
Central line sepsis	4	2	6
Renal failure	5	1	6
Myocardial infarction	0	1	1
UGI bleed	1	0	1
DVT/PE	1	2	3
Calf muscle devascularization	1	0	1

Abbreviations: Q= quartiles, UGI= upper gastrointestinal, UTI= urinary tract infection, RTI= respiratory tract infection, DVT= Deep vein thrombosis, PE= pulmonary embolism

Table 30. **Multivariate Logistic Regression Analysis for Major Complications**

	Odds ratio	95% CI	P
Quartile 1	Ref		
Quartile 2	0.356	0.065 - 1.959	0.235
Quartile 3	2.478	0.497 - 12.345	0.268
Quartile 4	1.201	0.263 - 5.482	0.813
Age <65	Ref		
Age 65+	4.082	1.216 - 13.705	0.023
Primary tumour type	Ref		
Recurrent tumour type	1.688	0.426 - 6.69	0.456
Male	Ref		
Female	1.855	0.553 - 6.23	0.317
Straight to surgery	Ref		
Neoadjuvant therapy	6.268	0.725 - 54.185	0.095
No sacrectomy	Ref		
Sacrectomy	3.796	1.109 - 12.998	0.034
Negative resection margin	Ref		
Positive resection margin	0.887	0.237 - 3.326	0.859

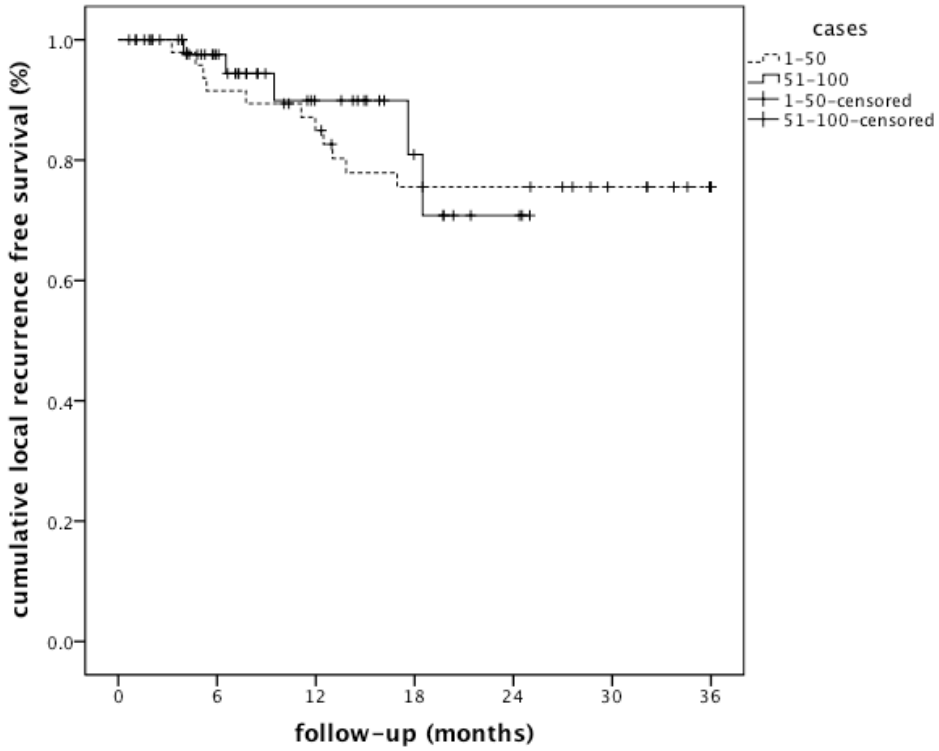
Abbreviations: CI= Confidence interval

1.5.5 Oncological Outcomes

Complete resection (R0) was achieved in 78 (78%) patients (table 27). There were 20 patients with R0 resection in Q1, 19 in Q2, 20 in Q3 and 20 in Q4. Microscopic residual disease at the resection margins (R1) was observed in 15 patients (4 in Q1, Q2 and Q4; and 3 in Q3). Macroscopic residual disease (R2) either at the resections margins or in the form of distant metastasis was observed in 7 patients (2 in Q1, Q2, Q3; and 1 in Q4). There was no statistically significant difference in terms of these outcomes with time (p= 0.995).

Among the first 50 patients, 78.9% and 67.5% were local recurrence-free at 12 and 24 months. There was no significant difference for three-year local recurrence free survival between cases 1-50 (75.6%) and 51-100 (70.8%, figure 28, p=0.717).

Figure 28. Local recurrence free survival between cases 1-50 versus 51-100.

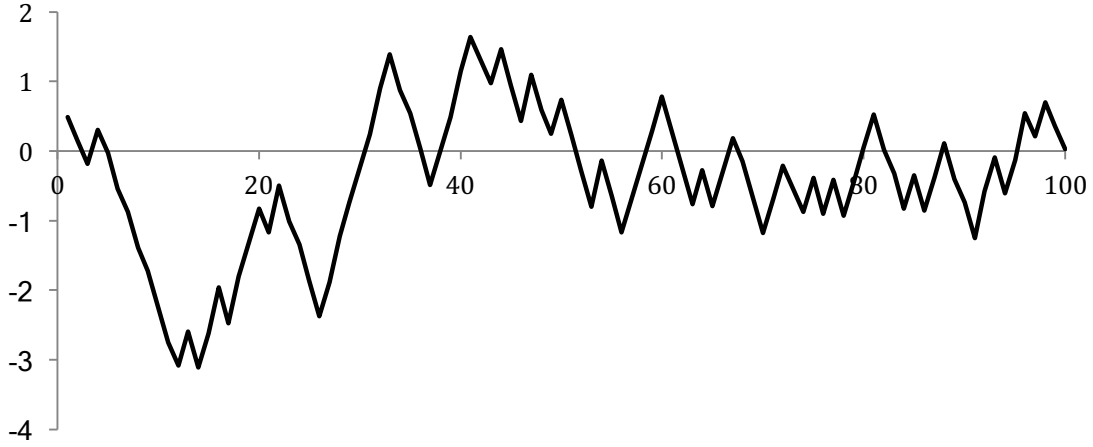


Months	0	6	12	18	24	30	36
1-50	50	43	38	32	31	26	22
51-100	50	32	17	8	3	0	0

1.5.6 Learning curve

The observed and therefore expected rate for any complications (figure 29), for primary and recurrent rectal cancer, was 50% and 59.1% respectively. Therefore, the RA-CUSUM plot increased by 0.5 or decreased (in the case of complication) by 0.5 if the case was for a primary rectal cancer. It increased by 0.591 and decreased by 0.409 for recurrent rectal cancer. The 14th case is when the learning point occurs. There is a drop of the learning curve after case 41 that normalised at case 56.

Figure 29. **Any complications RA-CUSUM**



The observed and therefore expected major complications (figure 30) rate for primary and recurrent rectal cancer was 16.1% and 25% respectively. Therefore, the RA-CUSUM plot for major complications increased by 0.25 or decreased by 0.75 in the case of a recurrent rectal cancer. It increased by 0.161 or decreased by 0.839 for

primary cancer cases. Figure 30 demonstrates that the learning curve for major complications occurred at the 12th case. There was a drop in the learning curve at the case 41 with an observed normalisation after the case 68.

Figure 30. **Major Complications RA-CUSUM**

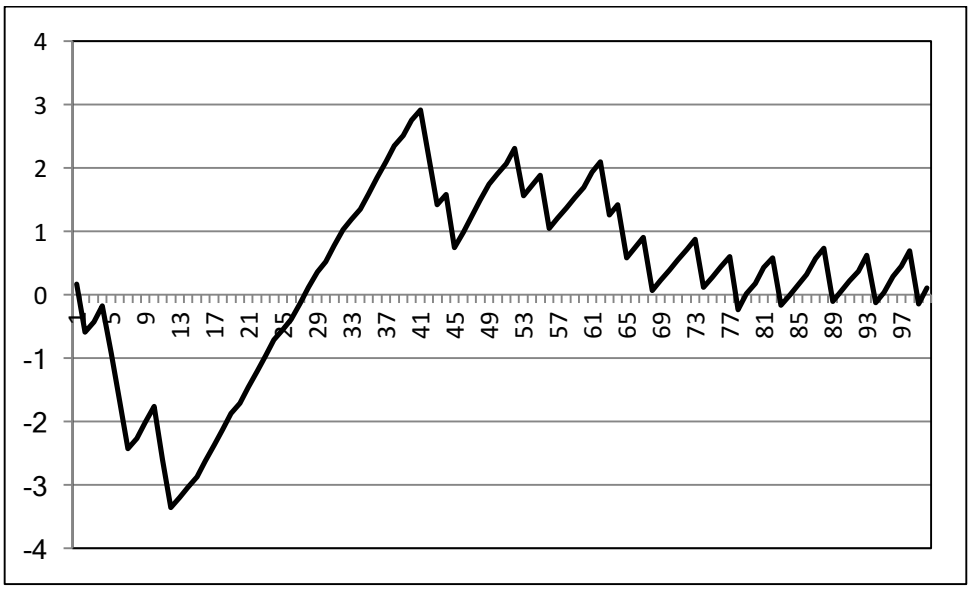
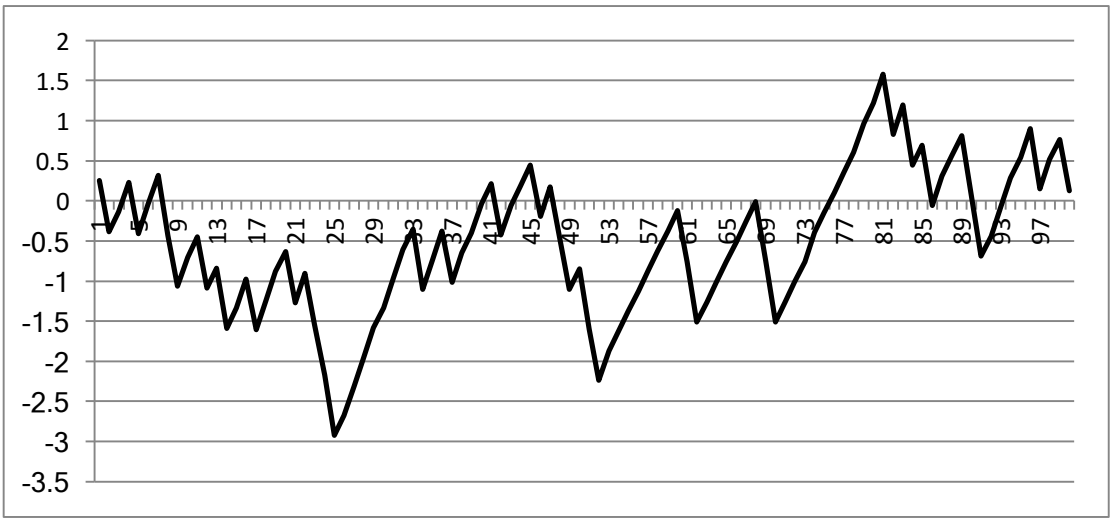


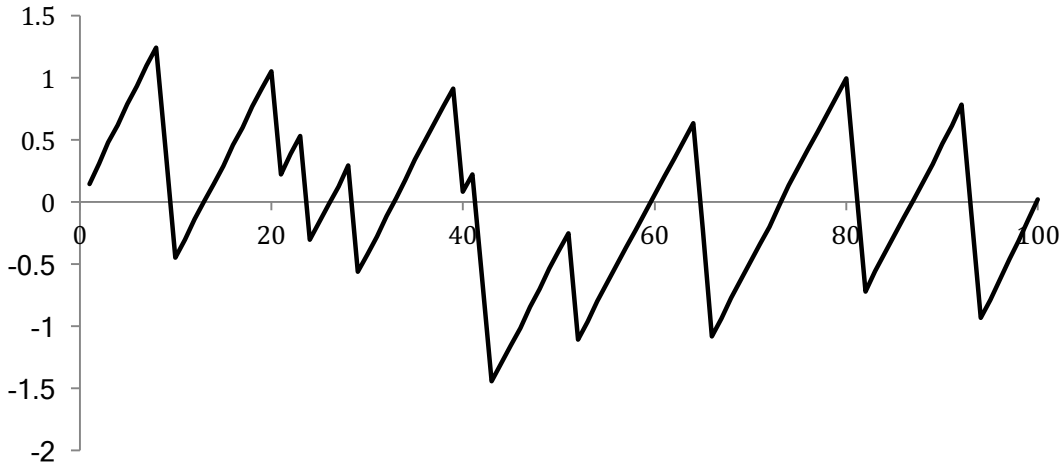
Figure 31 shows the learning curve for minor complications. The expected and overall rate for minor complications for primary and recurrent rectal cancer was 25% and 36.4% respectively. The CUSUM graph was raised by 0.364 or reduced by 0.636 in recurrent rectal cases. It increased by 0.25 or decreased by 0.75 in the primary cancer cases. The rate of minor complications started to improve after the 25th operated case, with a second learning curve observed after the 52nd case.

Figure 31. **Minor Complications RA-CUSUM**



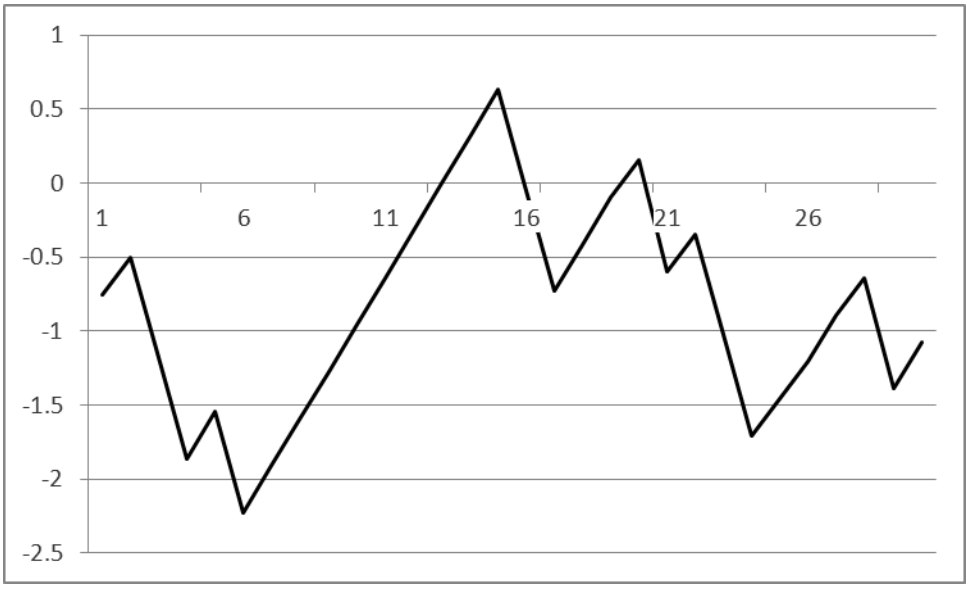
A risk-adjusted CUSUM analysis performed on R1 resections per case (figure 32) showed no learning curve and confirmed that the early cases were not disadvantaged oncologically.

Figure 32. **Microscopic residual disease (R1) RA-CUSUM**



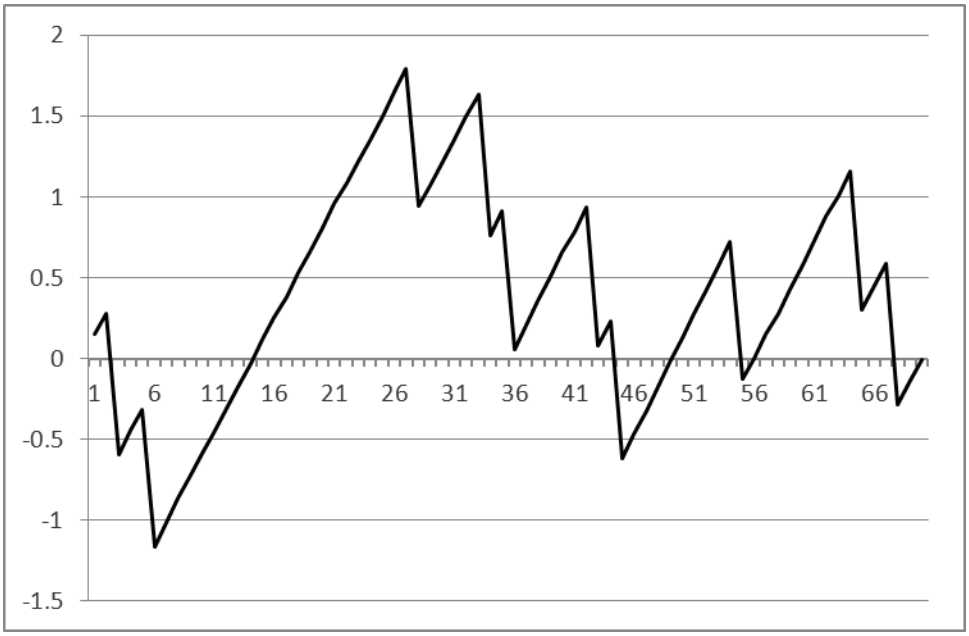
A sub-group risk-adjusted CUSUM analysis evaluating the learning curve for only abdominosacral and pelvic exenterative resections was also performed. For abdominosacral resections, the learning curve for minor complications occurred after the 11th case and for major complications after the 6th case (figure 33).

Figure 33: Major complications RA-CUSUM for abdominosacral resections



Analysis including only pelvic exenterative surgery showed that the learning curve for minor complications occurred after the 14th case and for major complications after the 6th case (figure 34). There was a drop in the learning curve after case 27, which was normalised at case 37.

Figure 34: Major complications RA-CUSUM for pelvic exenterations



1.6 Discussion

This study investigated the learning curve of one colorectal surgery consultant in the performance of exenterative pelvic surgery for locally advanced primary and recurrent rectal cancer. It was demonstrated that the minimum of 14 cases is required to acquire the necessary experience to enhance the overall perioperative complication rate of exenterative pelvic surgery. The IOT, intraoperative blood loss and length of stay were not significantly changed with time. The oncological outcomes remained at the same levels during the period the study took place. When subgroup analysis was performed for abdominosacral resections and pelvic exenterative surgery the learning curve occurred after the 6th case.

Risk-adjusted CUSUM analysis to assess the learning curve for such extensive pelvic surgery does not appear to have been used before. Moriya *et al.* (129) had previously used intraoperative time, blood loss and length of stay to assess the learning curve for pelvic exenterative surgery in 57 patients having surgery for locally recurrent rectal cancer. They divided the patients into two groups based when the surgery was performed. Intraoperative blood loss was reduced from 4,229 litres in the first period to 2,500 litres in the second ($p= 0.00207$). The intraoperative time was reduced from 769 minutes to 682 minutes, but this fall was not statistically significant ($p= 0.38992$). The length of stay was also reduced from 37.5 to 35 days but again not reaching statistical significance ($p= 0.2216$).

One possibility for the progressive improvement in complications reported by the present study may be the better selection of patients for surgery, which had been previously suggested for other types of surgery (191, 277, 282). The majority of the patients with relative contraindications, for example, those with involvement of the external iliac vessels, sciatic nerve and the sacrum above S3, (129) were considered for surgery, early in the experience. However, the higher risk of higher morbidity and unfavourable oncological outcome of these patients have, (129) have led the authors to regard the presence of these features as an absolute contraindication for such surgery. This had contributed to the reduction of abdominosacral resections during the end of the learning curve.

It is also evident from the learning curves for any, and major complications that there was an increase of complications after the 40th case which started to normalise about after the 60th case. This may also be explained by patient selection. As there are no

absolute selection criteria, experience may have resulted in including more challenging cases for surgery by the multidisciplinary meeting. The constant IOT and blood loss throughout the series may be a result of the non-significant increase of plastic reconstruction procedures performed in the later cases. This may have influenced the length of stay as well keeping it constant throughout the series.

The overall complete resection (R0) rate of the present study is comparable with other studies, (48, 132, 134) showing that the early cases were not disadvantaged oncologically. This important consideration may be a reflection of the surgeon's close supervision by the more experienced surgeon at the early cases, although there are no data from the study to support this. The trainer was hands on fully supervising for the first 10 cases and partially supervising for the next 10 cases. However, this study was not designed to evaluate the trainer's influence on the evaluated surgeon's learning curve, and therefore there are no data to support this.

The morbidity reported in this study compares well with the literature (129, 133, 155, 157, 158). A study including 40 patients having abdominosacral resection for recurrent rectal cancer reported an overall complication rate of 60% (24/40 patients). Similarly, Moriya *et al.* (129) demonstrated in a series of 57 patients undergoing exenterative surgery for recurrent rectal cancer, a complication rate of 57% including wound dehiscence (51%) and pelvic sepsis (39%). Complications were more common in patients having higher levels of division of the sacrum. Gannon *et al.* (283) demonstrated an overall complication rate of 43% following exenterative surgery for locally advanced rectal cancer, which is similar to the rate reported by this study. They demonstrated that neoadjuvant chemoradiotherapy, gender, age, type of surgery

and the use and type of plastic reconstruction had no noticeable impact on the complication rate. This experience was the same as that in the present study.

This study has several strengths. First, the patients were managed and operated by the same surgical team eliminating the bias that can result from the involvement of other specialists in the decision-making process and management. Secondly, the operating surgeon was supervised by an experienced pelvic colorectal surgeon, ensuring the patients' safety and the oncological outcome. Thirdly, CUSUM statistical technique has been shown to be more sensitive than standard statistical techniques such as the chi-square test, in examining surgical performance. (284, 285) The risk-adjusted technique also has an advantage over the non-risk adjusted technique, as it takes into account individual risk factors in the individual patient (285).

One of the study's limitations is that by evaluating the learning curve of one colorectal surgeon within one surgical team, it has not been able to compare this to other surgeons. It is also important to stress that the evaluated surgeon had already completed his training and was a fully independent colorectal surgeon before the commencement of his training for this type of operations. Thus the reported learning curve might not be fully representative since there is likely to be some variance between surgeons and therefore needs to be adjusted individually depending on the level of experience. Exenterative surgery for locally advanced primary and recurrent rectal cancer is performed for about 250 patients a year in the UK and several years will be required to assess the learning curve of other surgeons in the same institution. A further limitation of the study might be that complications such as chest infection and DVT might not be directly linked to the operative management. An analysis

based on the type of complication might have been more appropriate, but it would have necessitated a significantly larger number of patients to achieve the same statistical power (286). In addition, a number of patients experienced more than one complication something that this study was not designed to assess. Lastly, the successful management of this group of patients is depended on a team consisted of a number of professionals. Their learning curve and subsequently the team's learning curve may improve with time and influence the outcome. This study was not designed to address this though.

1.7 Chapter's Conclusion

Surgery for recurrent and locally advanced primary rectal cancer is challenging, and training can only be obtained in specialised cancer centres under supervision. Acquiring experience becomes even more difficult as the number of patients operated each year is small. This study has demonstrated that 14 cases are required to gain the training and experience to stabilise the morbidity to an acceptable level. This number should be used as guidance as other factors may influence the number required to gain the desired experience to perform this type of surgery. It is important to understand that this number is likely to differ among individual surgeons and therefore further research is required to validate the results of this study.

Future Considerations

The learning curve of other surgeons should be looked into along with different factors that may influence the learning curve.

CHAPTER 11. Discussion

As described in Chapter 1, despite improvements in the management of primary rectal cancer the incidence of local recurrence rate is still considered high, ranging up to 8-10%. Less than half of the patients will be free from distant metastases and eligible to be considered for salvage surgery of the local recurrence. For these cases, radical surgery in the form of *en bloc* resection of the tumour is required to achieve complete clearance and therefore the best oncological outcome for the patient. Complete clearance (R0) in the absence of distant metastases can result in up to 30% 5-year survival. The type of this surgery is challenging and very demanding.

It was highlighted in chapter 4, which was the first study of this thesis, that the lateral pelvic sidewall is deemed the most challenging part of the pelvis when pelvic exenteration is considered for curative resection of locally advanced primary and recurrent rectal cancer. For decades, there was a debate regarding the value of extended lateral pelvic lymphadenectomy as a supplement of the standard resection of primary rectal cancer, with the Japanese being the biggest supporters of this technique. **This had led to the question about the value of lateral lymohadenectomy as an adjunct to standard surgery for primary rectal cancer.** Lateral pelvic lymph nodes are part of the lateral compartment (figure 2) as it has been described in this thesis chapter 3. **In chapter 4, I investigated the value of extended lateral pelvic lymphadenectomy for primary rectal cancer, using meta-analytical techniques.**

Added Knowledge: Chapter 4 demonstrated that extended (lateral) pelvic lymphadenectomy in patients with primary rectal cancer did not provide any substantive oncological advantage. Sensitivity analysis was performed and showed a small benefit for EL in survival and local recurrence in patients with a Dukes' C but not Dukes' B carcinoma. In addition, extended lymphadenectomy was linked with longer operating time, greater intra-operative blood loss and a higher incidence of urinary and possibly sexual dysfunction.

In the modern era of colorectal surgery, neoadjuvant chemotherapy and chemoradiotherapy have a fundamental role in the management of these patients. Following neo-adjuvant chemoradiotherapy we suggested that the use of EL should be limited to the group of patients with evidence of persistent lateral pelvic lymph node metastasis. The benefit for more advanced rectal cancers should be further investigated. A large randomised study that included 701 patients with advanced rectal cancer was performed by the Japanese group of surgeons, while writing this thesis. They showed a small advantage of EL over non-EL at the range of 4%, though they did not included patients that underwent neoadjuvant chemoradiotherapy. (287)

Future considerations: The meta-analysis highlighted that only very small studies had so far been undertaken to address the specific contribution of neoadjuvant and adjuvant chemotherapy and radiotherapy in avoiding pelvic sidewall lymphadenectomy. Thus, future clinical trials specifically addressing this will be important. Randomised prospective studies should take place to eliminate the limitations of the previously published studies. These should also compare the value of extended lymphadenectomy with chemoradiotherapy.

Following chapter 4, chapter 5 aimed to investigate the value of extended lymphadenectomy in patients undergoing exenterative pelvic surgery for locally advanced primary and recurrent rectal cancer.

Added knowledge: This was the first study to investigate the value of extended lymphadenectomy into this group of patients. This chapter demonstrated that there was no statistically significant oncological benefit in performing extended lymphadenectomy. There was no difference in the perioperative outcomes either.

The risk of significant blood loss and increased intraoperative time have always concerned the surgeons and influenced their decision plan for surgery. As described in chapter 5, exenterative pelvic surgery is long and can result in significant blood loss. The addition of extended lymphadenectomy does not seem to alter these significantly and therefore should be performed when it is necessary and patients are fit for surgery. This chapter demonstrated that the patients that underwent lateral pelvic sidewall lymphadenectomy were younger. However, age alone does not normally influence the decision for extended lymphadenectomy when the patient is deemed fit to undergo an exenterative procedure. In this study, the decision for lateral pelvic sidewall lymphadenectomy was taken by the MDT in the presence of tumour within the lateral compartment or intraoperatively when there were suspicious lateral pelvic sidewall lymph nodes. Tumours within the lateral pelvic compartment have been shown to have poorer prognosis (133, 221, 288). The younger age of the patients in the lateral pelvic sidewall lymphadenectomy group may also support this. Therefore,

the absence of a significant difference between the two groups may indicate, a benefit from performing the procedure.

Future consideration: Larger, multicentre prospective studies to investigate the value of extended lymphadenectomy into this group of patients.

Accurate staging for this group of patients is crucial for planning surgery and maximise the potential for cure. In the effort to predict the tumour's extent and better select patients for surgery, many radiological modalities have been employed such as Magnetic Resonance Imaging (MRI), Diffusion-weighted MRI, Computed Tomography (CT) and Positron Emission Tomography (PET). MRI has significantly evolved in the recent years and has gained the principal place in the pre-operative staging of disease within the pelvis, whereas CT and PET imaging are currently being used mainly to detect the presence of distant disease.

As described in chapter 1, in the absence of distant disease, the patient selection for surgery relies on the MR images, a work that is not often easy due to the presence of scar and fibrotic tissue following radiotherapy and previous surgery. In addition, the postoperative anatomy changes complicate this work even further, often necessitating lengthy discussions between the radiologists and surgeons. Magnetic Resonance Imaging has a fundamental role in staging locally advanced primary and recurrent disease as it can illustrate important anatomical details and enable surgical planning (67, 68). MRI has been shown to be highly accurate in diagnosing tumour invasion into individual adjacent to the rectum anatomical structures but proved to be problematic when assessing the pelvic sidewalls and the female reproductive organs

(69). One more study demonstrated the significant clinical value of MRI in predicting the absence of disease within the individual pelvic organs (71). The same study also reported that the interpretation of the posterolateral structures was challenging especially in the presence of fibrotic tissue. Based on the differences in signal intensity between the tumour and fibrosis, T2 weighted MRI has been shown to be more accurate in discriminating recurrent cancer within a presacral scar than CT (72).

Chapter 6, therefore, was designed to assess the value of the MRI to diagnose tumour invasion within the thesis' seven compartments and whether it can help to predict the oncological outcome.

The study showed that MRI was highly accurate in predicting the presence of disease within all the seven compartments. Apart from the central compartment, MRI was also accurate in excluding the presence of disease in the rest of the compartments. The low specificity for the central compartment should be interpreted with caution, as it was likely a result of the relatively small number of patients without evidence of disease within this compartment.

In the same chapter univariate Cox regression analysis was also employed to assess the MRI's ability to predict the oncological outcome based on tumour invasion within the individual compartments. MRI prediction of tumour invasion within the anterior compartment above the peritoneal reflection was shown to be associated with poorer survival. There was a trend for poorer survival when there was tumour invasion within the peritoneal reflection and the lateral compartment. Even though multivariate Cox regression analysis was not possible due to the relatively small size of the study,

there is evidence to suggest that these patients are at risk. We suggested that in these cases a more aggressive surgical approach should be considered, either in the form of pre-operative boost radiotherapy, more extended resections, intra-operative brachytherapy/radiotherapy or in the form of post-operative cyberknife.

Added knowledge: The study showed that MRI was highly accurate in predicting the presence of disease within all the seven compartments, along with the oncological outcome.

Future considerations: As a result of this work a multicentre trial is underway to validate the diagnostic accuracy of the compartment staging system and its relation to outcomes after beyond TME surgery. The Beyond TME trial (NCT02292641).

Following chapter 6 the question about the value of DW-MRI was raised in the same setting. Diffusion-weighted MR imaging is a relatively new concept in the management of patients with rectal cancer. Even though it has been extensively investigated in other specialties, it hasn't been widely utilised in the field of colorectal cancer. With limited evidence about its potential role in primary and locally recurrent rectal cancer, we designed this study to look into its value in planning exenterative pelvic surgery in this group of patients. This chapter demonstrated that DW-MRI alone had low sensitivity for all compartments except the central. It did, however, have excellent specificity for all the compartments except the inferior. The addition of the diffusion-weighted images increased the overall sensitivity for the lateral compartment; and the overall specificity for anterior compartment below the

peritoneal reflection. Diffusion-weighted MRI was weak in detecting the presence of disease in the majority of the compartments. However, its excellent specificity allowed improving the staging in four patients. At the same time, it led the radiologists to change their MRI reporting and understage two patients in the lateral compartment. Therefore, further research is required to better understand its value, before it can be used to guide clinical practice. It should not be used to change a decision that was made based on the MRI either.

Added knowledge: **DW-MRI should not be used to guide the management of patients with locally advanced primary and recurrent rectal cancer. T2 weighted MRI should remain the gold standard.**

Future considerations: Prospective study investigating the false results and compare them with the histopathology should be performed to identify the reasons of this weakness.

Early diagnosis of the recurrence is also critical as it increases the probability of a curative resection (RO) and consequently reduces the risk of dissemination. Clinical examination supported by a number of radiological modalities such as ultrasound (USS), computerised tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) have been consistently used as part of the routine follow-up for this group of patients. Carcinoembryonic antigen (CEA) has also formed part of the repertoire for early detection of recurrence, initiating more investigation and intensive follow-up when these are negative. This led to the next

part of the thesis, which was designed to answer the question of whether PET is better than other conventional diagnostic tools to identify metastases.

Chapter 8 reviewed the literature to retrieve the studies that investigated and compared the value of PET, compared to other investigations in diagnosing local and distant recurrence. It was demonstrated that PET imaging was more accurate than other conventional diagnostic investigation. Even though PET was shown to be better than CDI, is still far from perfect. One in fifteen patients with distant recurrence may be understaged and proceed with an intention to treat operation, which may result in closure without an attempt to resect. The patients will, therefore, undertake all the associated with anaesthesia risks and experience a delay to commence medical therapy. In addition, PET was shown to overstage 17.7% of the patients' distant recurrences. Therefore, patients may undergo further unnecessary investigation with the associated psychological stress or even worse, denied a potentially curative surgery. It is imperative therefore that the PET images are examined carefully, and the findings are correlated with the results of other radiological modalities and the clinical picture. When there is a strong suspicion of distant recurrence in the absence of any substantial evidence from other radiological modalities or the clinical picture, laparoscopy or CT guided biopsy may be an option.

Added knowledge: PET is more accurate than CDI to detect distant metastases, but the results should be interpreted with caution due to the poor quality of the included studies.

Future considerations: Investigate the value of PET/CT with other more modern CDI.

It is evident that accurate pre-operative staging is vital for the successful management of this group of patients. Chapter 9 was designed to assess the feasibility of fusing the PET with the MR images and explore whether it can improve the accuracy of the local staging. By fusing the two imaging modalities, the limitations of each can be eliminated whereas the strengths could be augmented. For this study, the HERMES workstation was used. The fusion of PET and MR images was feasible with very good image quality. The PET/MRI was shown to be highly accurate in determining the tumour invasion within the pelvis with an overall Area Under the receiver-operating Curve of more than 0.875, suggestive of its potential clinical value. However, at the time of writing this thesis, integrating the two images using a PET/MRI scanner was very costly, and therefore may be deemed prohibitive in everyday clinical practice. The option of fusing the images is readily available and may be more cost-effective and appropriate for every day clinical practice. More research is required though to support this. Surgery for this group of patients is demanding, challenging and require significant information before any decision for further management can be made. The option of fusing the images of PET and MRI may provide the required information to improve the patient selection for surgery without a significant additional cost.

Added knowledge: **Fused PET/MR images is highly accurate in predicting the extent of disease within the pelvis. It may be a valuable added tool in the management of patients with locally advanced primary and recurrent rectal cancer.**

Future considerations: To investigate its value in a prospective setting and compare it to PET/MRI scanner. A cost-effectiveness study should also be performed to explore its role in the everyday clinical practice.

Throughout the thesis, it is evident that exenterative pelvic surgery is challenging and demands several qualities to perform the procedure, not only at the surgical level but also at the team's level. This led to the next and last chapter of the thesis, which was designed and aimed to assess the learning curve of a surgeon, who was fully trained in complex colorectal surgery prior to his training to perform pelvic exenterations, and his team. The risk adjusted CUSUM technique was employed for the purposes of this study. It was demonstrated that a minimum of 14 cases were needed to observe improvement in the overall perioperative morbidity following exenterative pelvic surgery. The intraoperative time, blood loss and length of stay were not significantly changed with time. There was no significant difference in the oncological outcomes either.

This is the first time that risk adjusted CUSUM was used to assess the learning curve for this type of surgery. It was previously used to assess the learning curve for cardiothoracic and laparoscopic colorectal surgery and shown to be more sensitive than other standard statistical methods (284, 285). The risk-adjusted technique has also an advantage over the non-risk adjusted technique, as it takes into account individual risk factors in the individual patient (285).

The progressive improvement in complications reported by the present study may be related to the better selection of patients for surgery, which had been previously suggested for other types of surgery (191, 277, 282). This can be likely attributed to the change of some of the relative contraindications to absolute contraindications while the team's experience increased. The complete resection (R0) rate of the present study is comparable to the published literature (48, 132, 134) showing that the early cases were not disadvantaged oncologically, which is a reflection of the surgeon's close supervision during the initial cases.

Added knowledge: It was demonstrated that a minimum of 14 cases were needed to observe improvement in the overall perioperative morbidity following exenterative pelvic surgery.

It is important to note that this study evaluated the learning curve of one colorectal surgeon within one surgical team. It is also important to stress that the evaluated surgeon had already completed his training and was fully independent colorectal surgeon operating on complex colorectal cases (i.e. Inflammatory bowel disease and pelvic floor surgery) prior to his training for this type of operations. Thus the reported learning curve might not be fully representative of the average trainee since the possible variability among the surgeon was not assessed. In addition, the efficient management of this group of patients depends on the team's performance, which consists of different groups of professionals. Their learning curve and subsequently the team's learning curve may improve with time and influence the outcome. However, this study was not designed to address this.

Future considerations: To investigate the learning curve of other surgeons and explore different factors that may influence the learning curve.

Unanswered Questions and future research: Due to the limited number of patients operated every year in the UK for this type of cancer, the next step would be to create an international multicentre database that will collect prospective data including the MRI, DW-MRI and PET/MRI images' interpretation. This will enable the assessment of these modalities on a bigger scale and validate the results of these studies. It will also allow the evaluation of the interobserver agreement and confirm the reproducibility of these results. Criteria to randomise patients that undergo extended lymphadenectomy should be agreed and perform a randomised controlled study to assess the value of this procedure to this group of patients. A well designed randomised study can provide the highest evidence to provide the answer to this question. The learning curve of more surgeons with different levels of expertise should be assessed, including more factors such as the support from other teams (i.e. plastics, urology, orthopaedics). This will allow a more precise picture of the influencing factors that may have a role in the team's learning curve.

1.1 Summary Conclusion

Exenterative pelvic surgery for locally advanced primary and recurrent rectal cancer is challenging and demands accurate pre-operative staging, which has a key role in the patient selection for surgery. Accurate pre-operative staging allows better planning for surgery and enables better communication between radiologists and surgeons. This thesis showed that MRI is very accurate in predicting tumour invasion within the pelvis and that may be able to predict the patients with poorer prognosis.

Diffusion weighted MRI was not as accurate, but it was demonstrated to increase the accuracy when used with MRI for the lateral compartment, which is the most challenging to interpret and to resect. Therefore, it should be used with caution in this group of patients especially when there is a question regarding the resectability of the lateral compartment. This thesis also showed the fusion of PET with MR images is feasible with very good diagnostic accuracy for all the compartments. The low cost of the fusion is an advantage, but bigger studies are required to confirm this advantage. Extended lymphadenectomy was not shown to provide any significant benefit for primary rectal cancer, and for locally advanced primary and recurrent rectal cancer. Randomised studies are required though to validate this. Finally, a colorectal surgeon requires a minimum of 14 cases under supervision to achieve the experience required to perform exenterative pelvic surgery for locally advanced primary and recurrent rectal cancer. This result may apply to surgeons that have completed their training in colorectal surgery and work as independent colorectal surgeons. More studies including different levels of surgeons are required to assess the different learning curves.

CHAPTER 12: Appendices

1.1 Appendix 1: Pro-forma for MRI reporting of advanced pelvic malignancy

MRI Pro-forma

Patient's age:_____

ID Number:_____ **Date of scan:**_____

Peritoneal Involvement?			Yes	☐	No	☐	Contact ☐
Above the peritoneal reflexion?			Yes	☐	No	☐	
If yes:	Invading:	Sigmoid Colon?	Yes	☐	No	☐	Contact ☐
		Lateral sidewall fascia	Yes	☐	No	☐	Contact ☐
		Iliac vessels high?	Yes	☐	No	☐	Contact ☐
		Ureters high level	Yes	☐	No	☐	Contact ☐
Below the peritoneal reflexion?			Yes	☐	No	☐	
If yes:	Invading:	Prostate?	Yes	☐	No	☐	Contact ☐
		Seminal vesicles?	Yes	☐	No	☐	Contact ☐
		Vagina vault?	Yes	☐	No	☐	Contact ☐
		Uterus?	Yes	☐	No	☐	Contact ☐
		Bladder?	Yes	☐	No	☐	Contact ☐
		Urethra?	Yes	☐	No	☐	Contact ☐
		Pubic symphysis?	Yes	☐	No	☐	Contact ☐

Posterior structures invasion? Yes ☐ No ☐

If yes: Invading Sacral fascia? Yes ☐ No ☐ Contact ☐

Tumour Vertebrae Level
☐ Above S1
☐ Anterior S1

Anterior S2 ☐
Between S1-S2 ☐
Anterior S3 ☐
Between S2-S3 ☐
Lower than S3 ☐

Retro-sacral space? Yes ☐ No ☐ Contact ☐

Tumour Vertebrae Level
☐ Above S1
☐ Anterior S1

Anterior S2 ☐
Between S1-S2 ☐
Anterior S3 ☐
Between S2-S3 ☐
Lower than S3 ☐

Sacrum? Yes ☐ No ☐ Contact ☐

Tumour Vertebrae Level
☐ Above S1
☐ Anterior S1

Anterior S2 ☐
Between S1-S2 ☐
Anterior S3 ☐
Between S2-S3 ☐
Lower than S3 ☐

Lateral structures invasion? Yes ☐ No ☐

If yes: Invading: Ureters? Yes ☐ No ☐ Contact ☐

Internal Iliac vessels Yes ☐ No ☐ Contact ☐

External Iliac vessels Yes ☐ No ☐ Contact ☐

Piriformis-Int Obt Yes ☐ No ☐ Contact ☐

	Lateral pelvic Fascia?	Yes	☐	No	☐	Contact ☐
	Lateral Pelvic Bone?	Yes	☐	No	☐	Contact ☐
	Lateral Lymph Nodes	Yes	☐	No	☐	Contact ☐
	Sciatic nerve	Yes	☐	No	☐	Contact ☐
	Sciatic notch	Yes	☐	No	☐	Contact ☐
	S2 nerve	Yes	☐	No	☐	Contact ☐
	S3 nerve	Yes	☐	No	☐	Contact ☐
Central Recurrence?		Yes	☐	No	☐	
If yes:	High Recurrence >60mm?	Yes	☐	No	☐	Contact ☐
	Low Recurrence <60mm?	Yes	☐	No	☐	Contact ☐
	Mural invasion?	Yes	☐	No	☐	Contact ☐
	Extra-mural Involvement?	Yes	☐	No	☐	Contact ☐
	Sphincter involvement?	Yes	☐	No	☐	Contact ☐
Inferior Compartment Recurrence?		Yes	☐	No	☐	Contact ☐
If yes:	Levator involvement if applicable?	Yes	☐	No	☐	Contact ☐
	Iscio-anal fossa invasion?	Yes	☐	No	☐	Contact ☐
	Perineal scar invasion?	Yes	☐	No	☐	Contact ☐
Evidence of irresectable disease?		Yes	☐	No	☐	
	Sciatic nerve	Yes	☐	No	☐	
	S1 S2 sacrum	Yes	☐	No	☐	
	Lateral pelvic sidewall (bone)	Yes	☐	No	☐	

Summary

Compartments	Yes/No	Organs involved
Peritoneal Reflection		
Anterior above the peritoneal reflection		
Anterior below the peritoneal reflection		
Posterior		

Lateral		
Central		
Inferior		
Number of total compartments involved		

1.2 Appendix 2: PET/MRI fusion reporting pro-forma

PET/MRI Pro-forma

Summary

		Part of fusion technique that contributed the most for the diagnosis	
Compartments	Yes/No	MRI	PET
Peritoneal Reflection			
Anterior above the peritoneal reflection			
Anterior below the peritoneal reflection			
Posterior			
Lateral			
Central			
Inferior			
Number of total compartments involved			

1.3 Appendix 3: Pro-forma for histopathological reporting for advanced pelvic malignancy

Histopathology Report

Patient's age:_____

ID Number:_____ **Date of surgery:_____**

Date of receipt: _____ **Date of reporting:_____**

Pathologist _____ **Surgeon(s) _____**

Sex: **Male** ☐ **Female** ☐

Specimen type: ASR ☐ TPE ☐

Gross Description

Site of Tumour

Maximum tumour diameter _____mm

Distance of tumour to nearer cut end _____mm

Tumour perforation Yes ☐ No ☐

Histology

Adenocarcinoma Yes ☐ No ☐

If No, Other type _____

Differentiation by predominant area Well ☐ Moderate ☐ Poor ☐

Mucinous Yes ☐ No ☐

Signet cell Yes ☐ No ☐

Tumour Invasion

Peritoneal Involvement? Yes ☐ No ☐

Above the peritoneal reflexion? Yes ☐ No ☐

If yes: Invading: Sigmoid Colon? Yes ☐ No ☐

Lateral sidewall fascia Yes ☐ No ☐

Iliac vessels high? Yes ☐ No ☐

Ureters high level Yes ☐ No ☐

Below the peritoneal reflexion? Yes ☐ No ☐

If yes: Invading: Prostate? Yes ☐ No ☐

Seminal vesicles? Yes ☐ No ☐

Vagina vault? Yes ☐ No ☐

Uterus? Yes ☐ No ☐

Bladder? Yes ☐ No ☐

Urethra? Yes ☐ No ☐

Pubic symphysis? Yes ☐ No ☐

Posterior structures invasion? Yes ☐ No ☐

If yes: Invading Sacral fascia? Yes ☐ No ☐

Tumour Vertebrae Level
☐ Above S1
☐ Anterior S1

Anterior S2 ☐

Between S1-S2 ☐

Anterior S3 ☐

Between S2-S3 ☐

Lower than S3 ☐

Retro-sacral space? Yes ☐ No ☐

Tumour Vertebrae Level
☐ Above S1
☐ Anterior S1

Anterior S2 ☐

Between S1-S2 ☐

Anterior S3 ☐

Between S2-S3 ☐

Lower than S3 ☐

Sacrum? Yes ☐ No ☐

Tumour Vertebrae Level
☐ Above S1

Anterior S1 ☐

Anterior S2 ☐

Between S1-S2 ☐

		Anterior S3			☐
		Between S2-S3			☐
		Lower than S3			☐
Lateral structures invasion?		Yes	☐	No	☐
If yes: Invading:	Ureters?	Yes	☐	No	☐
	Internal Iliac vessels	Yes	☐	No	☐
	External Iliac vessels	Yes	☐	No	☐
	Piriformis-Int Obt	Yes	☐	No	☐
	Lateral pelvic Fascia?	Yes	☐	No	☐
	Lateral Pelvic Bone?	Yes	☐	No	☐
	Lateral Lymph Nodes	Yes	☐	No	☐
	Sciatic nerve	Yes	☐	No	☐
	Sciatic notch	Yes	☐	No	☐
	S2 nerve	Yes	☐	No	☐
	S3 nerve	Yes	☐	No	☐
Central Recurrence?		Yes	☐	No	☐
If yes:	High Recurrence >60mm?	Yes	☐	No	☐
	Low Recurrence <60mm?	Yes	☐	No	☐
	Mural invasion?	Yes	☐	No	☐
	Extra-mural Involvement?	Yes	☐	No	☐
	Sphincter involvement?	Yes	☐	No	☐

Inferior Compartment Recurrence?		Yes	☐		No	☐
If yes: Levator involvement if applicable?		Yes	☐		No	☐
Iscio-anal fossa invasion?		Yes	☐		No	☐
Perineal scar invasion?		Yes	☐		No	☐

Metastatic Spread

No of lymph nodes present:_____

No of involved lymph nodes:_____

Apical node involved		Yes	☐		No	☐
Lymphovascular invasion		Yes	☐		No	☐
Perineural invasion		Yes	☐		No	☐
Histologically confirmed distant metastases:		Yes	☐		No	☐

If yes, site: _____

Clearance	**R0**	☐	**R1**	☐	**R2**	☐

1.4 Appendix 4: QUORUM checklist

Heading	Subheading	Descriptor	Reported? (Y/N)	Page number
Title		Identify the report as a meta-analysis [or systematic review] of RCTs	Y	
Abstract		Use a structured format	Y	
		Describe		
	Objectives	The clinical question explicitly	Y	
	Data sources	The databases (ie, list) and other information sources	Y	
	Review methods	The selection criteria (ie, population, intervention, outcome, and study design); methods for validity assessment, data abstraction, and study characteristics, and quantitative data synthesis in sufficient detail to permit replication	Y	
	Results	Characteristics of the RCTs included and excluded; qualitative and quantitative findings (ie, point estimates and confidence intervals); and subgroup analyses	Y	
	Conclusion	The main results	Y	
		Describe		
Introduction		The explicit clinical problem, biological rationale for the intervention, and rationale for review	Y	
Methods	Searching	The information sources, in detail[28] (eg, databases, registers, personal files, expert informants, agencies, hand-searching), and any restrictions (years considered, publication status,language of publication)	Y	
	Selection	The inclusion and exclusion criteria (defining population, intervention, principal outcomes, and study design)	Y	
	Validity assessment	The criteria and process used (eg, masked conditions, quality assessment, and their findings)	Y	
	Data abstraction	The process or processes used (eg, completed independently, in duplicate)	Y	
	Study characteristics	The type of study design, participants' characteristics, details of intervention, outcome definitions, &c,and how clinical heterogeneity was assessed	Y	
	Quantitative data synthesis	The principal measures of effect (eg, relative risk), method of combining results (statistical testing and confidence intervals), handling of missing data; how statistical heterogeneity was assessed;[38] a rationale for any a-priori sensitivity and subgroup analyses; and any assessment of publication bias	Y	
Results	Trial flow	Provide a meta-analysis profile summarising trial flow (see figure)	Y	
	Study characteristics	Present descriptive data for each trial (eg, age, sample size, intervention, dose, duration, follow-up period)	Y	
	Quantitative data synthesis	Report agreement on the selection and validity assessment; present simple summary results (for each treatment group in each trial, for each primary outcome); present data needed to calculate effect sizes and confidence intervals in intention-to-treat analyses (eg 2X2 tables of counts, means and SDs, proportions)	Y	
Discussion		Summarise key findings; discuss clinical inferences based on internal and external validity; interpret the results in light of the totality of available evidence; describe potential biases in the review process (eg, publication bias); and suggest a future research agenda	Y	17
Quality of reporting of meta-analyses				

1.5 Appendix 5: Quality scoring using the NOS scale

Check-list
Selection
1.Assignment for treatment-Any criteria reported? (if yes-1star)
2.How representative was the reference group (HP) in comparison to the general population underg surgery for perforated diverticular disease?
(If yes-1 star, no star if the patients were selected or selection of group was not described)
3. How representative was the treatment group (PRA) in comparison to the general population underg surgery for diverticular disease ?
(If drawn from the same community as the reference group-1 star, no star if drawn from a different sourc selection of group was not described)
Comparability
4.Group comparable for 1and 2 (if yes-2stars, One star was assigned if only the age (1) was reported ev there were no other differences between the two groups and other characteristics had been controlled for star was assigned if the two groups differed or if only the sex was reported.
5.Group comparable for 3 and 4 (if yes-2 stars, one star was assigned if one of these two characteristics not reported even if there were no other differences between the two groups and other characteristics had l controlled for. No star was assigned if the two groups differed
6. Group comparable for 5 and 6 (if yes-2 stars, one star was assigned if one of these two characteristics not reported even if there were no other differences between the two groups and other characteristics had l controlled for. No star was assigned if the two groups differed
Outcome Assessment
7.Clearly defined outcome of interest (yes-1star for information ascertained by record linkage or interview

star if this information was not reported)

8.Adequacy of follow-up (1 star if follow-up >90%)

Comparability Variables:

1= age, 2= gender, 3= ASA grade

4= Emergency or Elective surgery, 5=Presence of abscess/peritonitis

6= Severity of peritonitis

1.6 Appendix 6: Standards of Reporting Diagnostic studies (STARD) checklist

Section and Topic	Item #		On page #
TITLE/ABSTRACT/ KEYWORDS	1	Identify the article as a study of diagnostic accuracy (recommend MeSH heading 'sensitivity and specificity').	
INTRODUCTION	2	State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups.	
METHODS			
Participants	3	The study population: The inclusion and exclusion criteria, setting and locations where data were collected.	
	4	Participant recruitment: Was recruitment based on presenting symptoms, results from previous tests, or the fact that the participants had received the index tests or the reference standard?	
	5	Participant sampling: Was the study population a consecutive series of participants defined by the selection criteria in item 3 and 4? If not, specify how participants were further selected.	
	6	Data collection: Was data collection planned before the index test and reference standard were performed (prospective study) or after (retrospective study)?	
Test methods	7	The reference standard and its rationale.	
	8	Technical specifications of material and methods involved including how and when measurements were taken, and/or cite references for index tests and reference standard.	
	9	Definition of and rationale for the units, cut-offs and/or categories of the results of the index tests and the reference standard.	
	10	The number, training and expertise of the persons executing and reading the index tests and the reference standard.	
	11	Whether or not the readers of the index tests and reference standard were blind (masked) to the results of the other test and describe any other clinical information available to the readers.	
Statistical methods	12	Methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (e.g. 95% confidence intervals).	
	13	Methods for calculating test reproducibility, if done.	
RESULTS			
Participants	14	When study was performed, including beginning and end dates of recruitment.	
	15	Clinical and demographic characteristics of the study population (at least information on age, gender, spectrum of presenting symptoms).	

	16	The number of participants satisfying the criteria for inclusion who did or did not undergo the index tests and/or the reference standard; describe why participants failed to undergo either test	
Test results	17	Time-interval between the index tests and the reference standard, and any treatment administered in between.	
	18	Distribution of severity of disease (define criteria) in those with the target condition; other diagnoses in participants without the target condition.	
	19	A cross tabulation of the results of the index tests (including indeterminate and missing results) by the results of the reference standard; for continuous results, the distribution of the test results by the results of the reference standard.	
	20	Any adverse events from performing the index tests or the reference standard.	
Estimates	21	Estimates of diagnostic accuracy and measures of statistical uncertainty (e.g. 95% confidence intervals).	
	22	How indeterminate results, missing data and outliers of the index tests were handled.	
	23	Estimates of variability of diagnostic accuracy between subgroups of participants, readers or centers, if done.	
	24	Estimates of test reproducibility, if done.	
DISCUSSION	25	Discuss the clinical applicability of the study findings.	

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