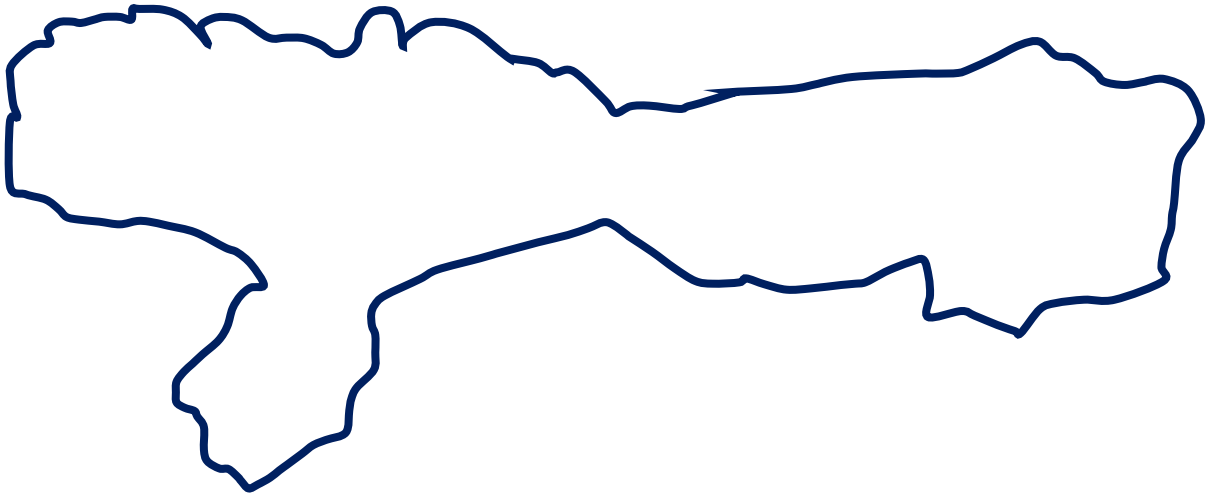
The Rectosigmoid Problem: Defining the Rectum and Optimising Staging of Sigmoid Cancers With Imaging



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Thesis submitted in accordance with the regulations of Imperial College, London, for the degree of Doctor of Philosophy

Dedicated to my wife Charlotte.

Declaration of Originality

I declare that this thesis and the work that it describes is entirely my own. Any assistance received in preparing this thesis has been acknowledged and any sources appropriately referenced.

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Abstract

Introduction

The aim of this study was to research whether imaging could improve the outcomes of sigmoid colon cancer treatment, by better pre-operative staging and consistent differentiation of the rectum from the sigmoid.

Methods

I investigated sigmoid cancer outcomes by systematic review and meta-analysis. I performed a literature search and evidence synthesis on definitions of the rectum, and compared their accuracy in a radiological study. I led a Delphi consensus to agree a definition of the rectum international with colorectal experts. I designed a prospective, ethics-approved joint radiological-tissue study to both investigate the concept of a sigmoid mesenteric waist and validate an imaging-based definition of the rectum. I created and analysed a multi-institutional database to identify prognostic variables for colon cancer and compare Computed Tomography (CT) staging systems.

Results

The pooled local recurrence rate for sigmoid cancer on meta-analysis is high at 10.5%. A wide range of definitions of the rectum are employed by national associations and guidelines. In-vivo radiological comparison of all definitions confirmed they did not accurately localise tumours. Through a Delphi consensus of 132 international experts, the imaging landmark of the sigmoid take-off was agreed to define the rectum. A mesenteric waist was identified at the rectosigmoid junction that could serve as a pathological definition of the rectum. Radiological and specimen analysis validated the sigmoid take-off on imaging as a definition of the rectum.

In 414 patients the local recurrence rate of sigmoid cancer remained high at 12.6%, and was associated with CT-disease features. Identification of tumour deposits and extramural venous invasion on CT were associated with higher rates of recurrence than TNM or T3 substage based CT-systems.

Conclusion

There are a wide range of non-anatomical definitions of the rectum currently in use, which cannot accurately localize tumours. An international Delphi consensus definition of the rectum was the sigmoid take-off, which was validated on specimen analysis. Local recurrence of sigmoid cancer is unexpectedly high. Pre-operative imaging can identify patients that are at higher risk of recurrence.

Publications arising from this thesis

1. **D'Souza N**, Lord A, Shaw A, Kontovounisios C, Sjovall A, Abulafi M, Tekkis P, Brown G. Meta-Analysis of Oncological Outcomes of Sigmoid Cancers: A Hidden Epidemic of R1 "Palliative" Resections. *Eur J Surg Oncol, 2018 Oct 11. pii: S0748-7983(18)31448-3*

2. **D'Souza N**, Shaw A, Lord A, Balyasnikova S, Abulafi M, Tekkis P, Brown G. Analysis of a Novel Staging System for Sigmoid Colon Cancer Based on Tumor Deposits and Extramural Venous Invasion on CT. *JAMA Network Open*. 2019 Dec 2;2(12):e1916987-.

3. **D'Souza N**, De Neree M, Lord A, Shaw A, Abulafi M, Tekkis P, Wiggers T, G Brown The Rectosigmoid Problem. *Surg Oncol. 2018 27:3, 521-525.*

4. **D'Souza N**, Balyasnikova S, Tudkya V, Lord A, Shaw A, Abulafi M, Tekkis P, G Brown. Variation in Landmarks for the Rectum: An MRI Study. *Colorectal Dis. 2018 Oct;20(10):O304-O309*

5. **D'Souza N**, de Neree Tot Babberich MPM, d'Hoore A, Tiret E, Xynos E, Beets-Tan RGH, Nagtegaal ID, Blomqvist L, Holm T, Glimelius B, Lacy A, Cervantes A, Glynne-Jones R, West NP, Perez RO, Quadros C, Lee KY, Madiba TE, Wexner SD, Garcia-Aguilar J, Sahani D, Moran B, Tekkis P, Rutten HJ, Tanis PJ, Wiggers T, Brown G. . Definition of the Rectum: An International, Expert-based Delphi Consensus. *Ann Sur*. 2019 Dec;270(6):955-959.

6. **D'Souza N,** Lord A, Shaw A, Patel A, Balyasnikova S, Tudyka V, Abulafi M, Moran B, Rasheed S, Tekkis P, Coffey JC, Terlizzo M, West NP, Quirke P, Brown G. Ex-vivo specimen MRI and pathology confirm a recto-sigmoid mesenteric waist at the junction of the mesorectum and mesocolon *Colorectal Dis.* 2020 Feb;22(2):212-218

7. **D'Souza N**, Lord A, Shaw A, Patel A, Balyasnikova S, Tudyka V, Abulafi M, Moran B, Rasheed S, Tekkis P, Terlizzo M, West NP, Quirke P, Brown. The sigmoid take-off: An anatomical imaging definition of the rectum validated on specimen analysis. *Eur J Surg Oncol.* 2020 Sep;46(9):1668-1672

8. **D'Souza N**, Day N, Shaw A, Lord A, Rokan Z, Balyasnikova S, Abulafi M, Moran B, Tekkis P, Brown G. Predicting Local Recurrence of Sigmoid Colon Cancer. Submitted for publication.

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Association of Coloproctology of Great Britain and Ireland, Edinburgh 2020

1. The Prognostic Importance of CT Imaging Biomarkers: Predicting Local Recurrence of Sigmoid Colon Cancer in a Multi-Centre Study of 414 Patients
2. Tumour Deposits and Extramural Venous Invasion on CT Predict Disease Recurrence: Analysis of a Novel CT-Staging System for Colon Cancer
3. The Sigmoid Take-Off: an Evidence-Based Definition of the Rectum Endorsed by an International Delphi Consensus of Multidisciplinary Experts
4. Meta-Analysis of Oncological Outcomes of Sigmoid Cancers: A Hidden Epidemic of R1 "Palliative" Resections

European Society of Coloproctology, Vienna 2019

5. Analysis of a Novel Staging System for Colon Cancer Based on Tumor Depth, Discontinuous Tumor Deposits and Extramural Venous Invasion on CT

European Society of Coloproctology, Nice 2018

6. Sigmoid cancer: a hidden epidemic of local recurrence and R1 resections
7. Variation in Landmarks for the Rectum: An MRI Study

Association of Coloproctology of Great Britain and Ireland, Birmingham 2018

8. Failings of Current Definitions for the Rectosigmoid Junction

European Society of Coloproctology, Berlin 2017

9. **IMPRESS**: Improving radical treatment through MRI evaluation of sigmoid cancers
10. **WISE** Study: Surgical Anatomy and '**W**aisting' of the s**I**gmoid **S**p**E**cimen

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I carried out this work in the Department of Gastrointestinal Radiology at The Royal Marsden NHS Foundation Trust during my appointment as a Colorectal Research Fellow at Croydon University Hospital. Professor Gina Brown supervised and edited each manuscript from inception. Professor Paris Tekkis supervised all statistical aspects of each manuscript. He and Mr Muti Abulafi provided feedback on each final draft.

I began my time in research drafting the study protocol for the WISE study, a prospective tissue study that had already been awarded a pump-priming grant. The original purpose of the study was to investigate the possibility of a mesenteric waist on specimen analysis that could predispose to local recurrence. I sought input from my co-authors in their specialist fields, particularly Nick West, Monica Terlizzo and Shahnuwaz Rasheed as well as my supervisors, Professors Brown and Tekkis. I revised the protocol to also test the hypothesis that specimen analysis would validate a pre-operative imaging definition of the rectum. I successfully applied for institutional review board and ethics approval, and the study was badged on the National Institute for Health Research portfolio. During the study, senior research nurse Ceri Evans or I recruited all patients. After surgery, I would liaise with the head MRI radiographer Cheryl Richardson for the specimen to be scanned out of hours during evenings and weekends. I prepped all histopathology specimens on corkboards and took them to the MRI departments where Cheryl Richardson (or one of her colleagues) would perform a bespoke specimen-protocol MRI scan.

Dr Monica Terlizzo, Consultant Histopathologist, photographed all specimens during cut-up in accordance with the protocol. I measured all specimen dimensions on MRI and pathology. As the analysis plan devised by the senior statistician Karen Thomas was exploratory in nature, the initial graphical results were difficult to interpret. I revised the analysis and replotted all graphs to provide a clearer illustration of the dimensions of the mesenteric anatomy. Dr Svetlana Balyasnikova and I

also assessed the sigmoid take-off on the pre-operative MRI scans for 20 patients to compare against anatomical measurements of the bowel specimen.

I performed a literature search as part of my background on the range of definitions of the rectum, and their theoretical and practical limitations. This study also introduced and argued for the use of the sigmoid take-off as an anatomical, imaging definition of the rectum.

I continued research initiated by previous fellows Vera Tudyka and Svetlana Balyasnikova on the performance of different definitions of the rectum on MRI. I completed additional measurements on 63 CT scans of the same patients, performed correlation and Bland-Altman analyses, and then wrote a manuscript.

I performed all stages of a systematic review and meta-analysis of sigmoid cancer outcomes under the close supervision of Paris Tekkis, who taught me how to carry out statistical analysis on STATA. Amy Lord assisted me through all stages of the literature search and data extraction.

I knew that a systematic review would lack granular data on sigmoid cancer outcomes, so I designed a service evaluation for patients with sigmoid cancer that was approved by the Royal Marsden institutional review board. I created a database of all patients with colonic cancer that were discussed in the Royal Marsden MDT since 2012, to complement a previous incomplete database of patients dating back to 2006. Annabel Shaw and I retrieved data from the Royal Marsden hospital database for all patients with sigmoid cancer. I retrieved missing data from local sites (including Croydon, Epsom & St Helier, Kingston Hospital and Chelsea & Westminster) to address incomplete data fields such as missing pathology data and follow up outcomes. Over 200 CT scans were not reported by proforma. I arranged for their transfer back to the Royal Marsden, where l would retrieve them from the picture archiving and communication system (PACS). During my weekly meetings, Gina Brown and Svetlana Balyasnikova re-reported these scans while blinded to clinical information. Creating this database took over 18 months, but now contains detailed data on 414 patients, which continues to be used for research by subsequent fellows.

I had planned a multivariate analysis with Karen Thomas in the service evaluation. To perform a logistic regression analysis of prognostic factors in sigmoid cancer outcomes, I was encouraged by Professor Tekkis to learn how to use STATA for data management and statistical analysis. I attended several Imperial College Postgraduate courses on STATA and spent even more time on statalist helpboards. Under the supervision of Paris Tekkis, and with additional help from Karen Thomas for other STATA queries, I performed all statistical analyses for the service evaluation, and for all other studies in this thesis. Nigel Day succeeded me as the colon fellow. After advice from James Kinross, he obtained additional data on molecular markers, which I included in a revised analysis. Nigel Day then edited my manuscript and submitted it for publication under joint first authorship.

Finally, I compared CT-substaging systems for colon cancer that had been previously described, with our own substaging system based on prognostic factors on CT. Under the supervision of Professor Tekkis, I used Kaplan-Meier survival analysis with Cox logistic regression to demonstrate differences in survival.

This research could not have been completed without a number of people to whom I am deeply indebted. Gina Brown, and Paris Tekkis have been my supervisors and role models for an academic career. Professor Brown's study team, Lisa Scerri, Caroline Martin and Ceri Evans were invaluable sources of expertise and support in helping me set up and run these trials. Other academic surgeons, including Ian Swift, James Kinross, Chistos Kontovounisos and Brendan Moran have helped me write manuscripts, but also given me support and advice about combining careers in research and surgery. In particular, I am very grateful to Muti Abulafi; my life and career have been very different since we met at his M25 course. This thesis would not have been possible without my wife Charlotte, who has always supported me since we first met during a night on-call in Slough, many years ago.

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Chapter 1

Background

Improving Sigmoid Cancer Outcomes

Research is needed to improve colon cancer outcomes. Survival after diagnosis with rectal cancer has dramatically improved over the last 20 years, but equivalent gains have not been seen in colon cancer. Consequently survival outcomes from rectal cancer have begun to exceed those of colon cancer, as seen in national registry data from Denmark (Ostenfeld et al, 2011), Sweden (Birgisson et al), Scotland (ISD Scotland, 2017), and the United States (Siegel et al, 2014). This is not a rare problem affecting a few patients: colorectal cancer is the 3rd most common cancer in both incidence and cause of cancer death in the United Kingdom. Between 2014-2016, 42 000 new cases of bowel cancer were registered each year (Cancer Research UK, 2019), of whom 70% will have cancer of the colon; up to 30 000 patients each year could therefore benefit from better colon cancer treatment.

As the most common site of colon cancer is the sigmoid, it would be a logical starting point to investigate colon cancer outcomes. Local control is essential for reliable cure of cancer; locoregional recurrence will reduce survival and quality of life for patients (Mahvi et al, 2018). But the local recurrence rate of sigmoid cancer is not clear in the literature. A study of 1856 patients in the Stockholm Bowel Cancer registry showed that sigmoid cancers at 37% comprised the single largest group of colonic malignancies and were associated with the highest rate of local recurrence at 11.5% (Sjövall et al, 2007). Only 12% of recurrences were amenable to curative resection. This was one of the first contemporary studies to demonstrate a significant problem with sigmoid tumours. However, significant variation exists between local recurrence rates for sigmoid cancer in recent studies from Sweden (Sjövall et al, 2007) and the United States (Liska et al, 2016) as well as historical studies (Minsky et al, 1988)(Willett et al, 1987). A more systematic interrogation of these results is therefore necessary.

Innovations specific to the treatment of rectal cancer include pre-operative staging by magnetic resonance imaging (MRI), neoadjuvant radiotherapy, the development of surgical techniques such as total mesorectal excision (TME), and pathological quality control/feedback, all of which have

improved rectal cancer outcomes, particularly local recurrence. Yet these innovations have not been extended to sigmoid cancer, the treatment of which is invariably surgery with or without adjuvant chemotherapy (Brown and Koh, 2020). While sigmoid tumours may be thought of as the easier of left sided colorectal tumours, the close proximity of distal sigmoid and rectal tumours below the sacral promontory may result in similar risk of pelvic recurrence. Like rectal cancer, sigmoid cancer may require high quality pre-operative staging using imaging to optimise treatment and reduce recurrence.

The anatomical proximity of sigmoid and rectal tumours has also led to a fundamental obstacle for research. The sigmoid and rectum can be difficult to distinguish from one another, reflected in the lack of a consensus definition of the rectum (McMullen et al, 2005). Tumours in the "rectosigmoid" (NIH, 2017) region in particular will be classified most variably as a result of these different definitions, which may result in significant variation in their management. Pre-operative imaging may illustrate in-vivo anatomical features that may consistently define the rectum and differentiate sigmoid and rectal cancers.

This thesis will investigate whether imaging can improve sigmoid colon cancer outcomes, by examining its role in pre-operative staging and defining the rectum. In this introductory chapter, the evolution and evidence for colonic cancer staging is described, as well as studies of the anatomy of the rectum and sigmoid with their associated mesentery.

Staging: Creating a Roadmap for Personalised Cancer Treatment

Cancer staging is based on assessment of local and distant tumour spread, and determines both treatment strategies and prognosis. Historically, colon cancer staging has been constructed on the principles of rectal cancer staging, beginning in 1932 when Dukes described the anatomical extent of disease on pathology (Dukes, 1932). But the critical aspects of rectal cancer decision making now occur in the pre-operative setting and are based on MRI; this opens up a range of non-operative and operative treatment options. Colon cancer staging is still based on the pathology specimen which permits post-operative treatment strategies and informs prognosis. However, without accurate pre-operative staging based on imaging, there is no basis for neoadjuvant treatment and surgical strategies.

Staging Systems: Dukes to TNM

Cuthbert Dukes created the staging system at St Mark's for rectal cancer (Dukes, 1932), that became the foundation of rectal and colonic cancer staging. This staging classification was based on histopathological examination of the resected bowel cancer specimen to determine depth of mural invasion and lymphatic nodal spread. Dukes revised this system with Bussey 25 years later by reclassifying whether nodal spread involved the apical node (Dukes and Bussey, 1958). Kirklin refined the Duke's criteria by the invasion into and through the muscularis propria (Kirklin et al, 1949). Astler and Coller validated this modification, and then subdivided invasion into and through the rectal wall (Astler and Coller, 1954). Duke's criteria were also revised in 1976 with the addition of stage D, reflecting metastatic disease or extensive local spread (Whittaker and Goligher, 1976). The TNM Classification of Malignant Tumours has replaced Duke's as the classification system within the Royal College of Pathologist's dataset for colorectal cancer resections (Loughrey et al, 2017).

TNM Stage	T	N	M	(Dukes, 1932)	(Astler and Coller, 1954)
0	Tis	0	0	-	-
I	T1-2	0	0	A-B	A-B1
IIa	T3	0	0	B	B2
IIb	T4a	0	0	B	B2
IIc	T4b	0	0	B	B3
IIIa	T1-2 T1	N1 N2a	0	C1 C1	C1
IIIb	T3-4a T2-3 T1-2	N1 N2a N2b	0	C2 C1-2 C1	C1-2
IIIc	T4a T3-T4a T4b	N2a N2b N1-2	0	C2 C2 C3	-
IVa	T1-4	N0-2	M1a	-	-
IVb	T1-4	N0-2	M1b	-	-
IVb	T1-4	N0-2	M1b	-	-

Table 1-1: TNM 8 Classification and Duke's Classification

**Note*: Tis=Carcinoma in situ: intraepithelial or invasion of lamina propria. T1=Tumour invades submucosa. T2=Tumour invades muscularis propria. T3=Tumour invades through the muscularis propria into pericolorectal tissues. T4a=Tumour penetrates to the surface of the visceral peritoneum. T4b=Tumour directly invades or is adherent to other organs or structures. N0=No regional lymph node metastasis N1=Metastasis in 1–3 regional lymph nodes. N1a=Metastasis in one regional lymph node. N1b=Metastasis in 2–3 regional lymph nodes. N1c=Tumour deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis. N2=Metastasis in 4 or more regional lymph nodes. N2a=Metastasis in 4–6 regional lymph nodes. N2b=Metastasis in 7 or more regional lymph nodes. M1=distant metastasis. M1a=metastasis confined to one organ. M1b = metastasis in more than one organ. M1c = metastasis to the peritoneum with or without organ involvement.

TNM is a universal staging system for all cancers, classifying tumours according to tumour size (T stage), nodal disease (N stage) and metastatic disease (M stage). Unlike Duke's, the stage can evaluated by pre-operative or pathological assessment, in which case the TNM stage is prefixed with a c (clinical) or p (pathological) respectively. If a patient has undergone pre-operative therapy, a y prefix is also used. TNM is continually reviewed and updated, as new evidence on the prognostic impact of new variables emerges, and stages 1-4 have been subdivided repeatedly to reflect prognosis. After the first TNM edition was released in 1968, the 8th edition was released in 2016.

Limitations of Pathology Based Staging Systems

An optimum prognostic system should provide homogeneity within the same stage, good discrimination between different stages, and graded linearity in survival by stage. But this has not yet been achieved by pathology-based colorectal cancer staging systems.

On superficial observation, Duke's based staging, which correlates to TNM Stage I, II, III and IV, would seem to meet the above criteria (Figure 1-1). But closer analysis of the results confirms there are increasing large drops in survival with increasing stage: 16% from Duke's A to B, 30% from Duke's B to C, and 40% from Duke's C to D (Figure 1-1).

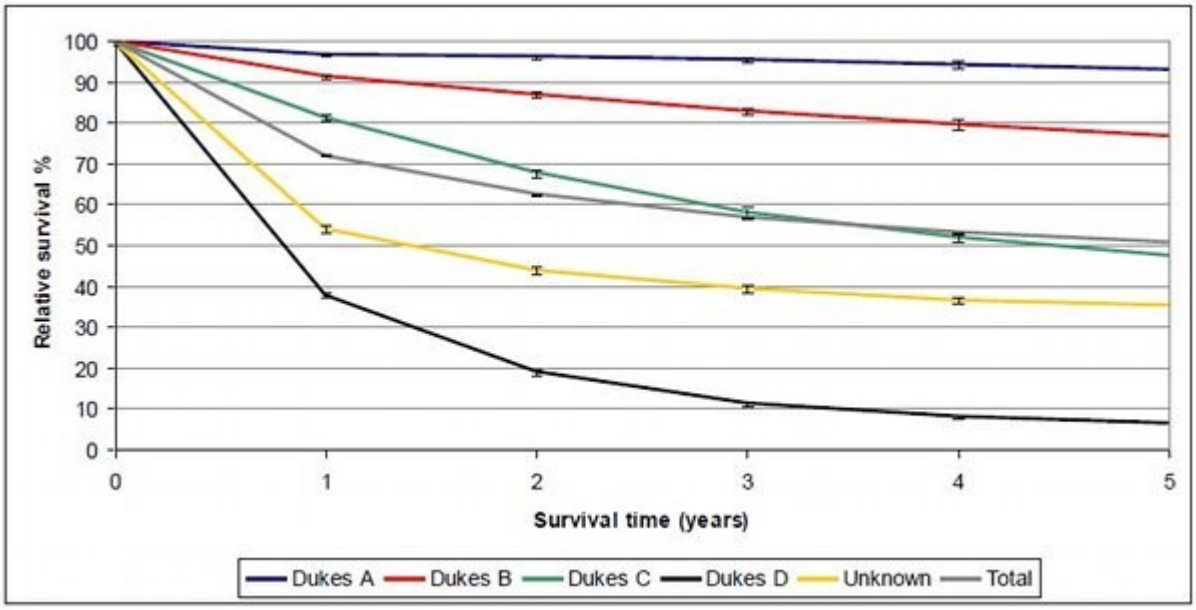


Figure 1-1: Five-year relative survival for colorectal cancer patients (diagnosed 1996-2002) by stage at diagnosis
Note. Image reproduced with permission from the National Cancer Registration and Analysis Service (NCRAS, 2006). *See permissions table, page 212.*

Stage at diagnosis	Number of cases	Percentage of cases (%)	5-year relative survival (%)	Confidence interval (95%)
Dukes A	26,727	8.7	93.2	92.5 - 93.9
Dukes B	74,784	24.2	77	76.4 - 77.5
Dukes C	72,806	23.6	47.7	47.1 - 48.3
Dukes D	28,377	9.2	6.6	6.1 - 7.0
Unknown	106,040	34.3	35.4	35.0 - 35.8
Total	308,734	100	50.7	50.4 - 51.0

Table 1-2: Number of cases (1996-2006) and five-year relative survival of colorectal cancer patients (diagnosed 1996-2002) by stage at diagnosis, England.

Note. Reproduced with permission from the National Cancer Registration and Analysis Service *(*NCRAS, 2006*).* See permissions table, page 212.

Survival does not decrease in a linear, incremental relationship with to the currently-employed stages. This is in part due to heterogeneity within stages, in particular within stage III, as large survival differences exist between between Stages II-IV/Dukes B-D . Merkel et al first described the "prognostic inhomogeneity" of stage III colon cancer in 2001 (Merkel et al, 2001a), and subdivided 1454 stage III patients into 3 prognostically distinct groups (Table 1-3). These findings were confirmed in a further population analysis of 50 042 patients with stage III colon cancer (Greene et al, 2002b), and were incorporated into the revised classification of stage III colon cancer in the 6th edition of TNM (Greene et al, 2002a).

Sub classification	%	5 year OS
III (overall)	100%	49.1%
IIIA: pT1-2 N1	10%	80%
IIIB: pT3-4 N1, pT1-2 N2	50%	60%
IIIC: pT3-4 N2	40%	30%

Table 1-3: subdivision of stage III patients into prognostically different subgroups.

Note. Adapted from Merkel, Susanne, et al "The prognostic inhomogeneity of colorectal carcinomas Stage III: a proposal for subdivision of Stage III." *Cancer: Interdisciplinary International Journal of the American Cancer Society* 92.11 (2001): 2754-2759. OS: overall survival.

More recently, it has been questioned whether nodal disease confounds discrimination between stages. The population data that led to the subdivision of stage III colorectal cancer (Greene et al,

2002b) had also reported that stage IIIA patients had similar survival to Stage II (node negative) patients. This was confirmed in Surveillance, Epidemiology, and End Results Program studies, which reported that 5 year survival for T3N0 (66.7%) and T4a-bN0 disease (60-6-45.7%) was significantly worse than early T1-2 N1 disease (73.7%), suggesting that advanced T stage may carry a worse prognosis than nodal disease (Gunderson et al, 2010). The worse prognosis of patients with stage II vs stage III disease has been verified in Korean (Kim et al, 2015) and Japanese (Hashiguchi et al, 2012) databases, and termed "survival paradox" (Kim et al, 2015).

There remain a number of disease variables that may inform prognosis which are not currently included in TNM criteria. These include patient factors (age, sex, co-morbidity), disease factors (anatomical extent of disease, molecular markers) and quality of multidisciplinary management (assessment and treatment). This may be due to a paucity of good quality evidence for the prognostic association of specific variables, or because other variables remain unknown. At present, the anatomical extent of disease is the most informative prognostic factor, and remains the primary determinant of treatment options for a patient. While traditionally assessed on pathology, rectal cancer trials have demonstrated the importance of pre-operative MRI for prognosis and decision making.

Colonic Cancer Staging: Role of Imaging

Like MRI in rectal cancer, pre-operative imaging of colonic tumours could offer insights into prognostic disease variables to better stage patients. Crucially and unlike pathology-based staging, which changes treatment only in the choice of adjuvant therapy, pre-operative staging can determine pre-operative and intra-operative treatment strategies. At present, the attitude to pre-operative staging in colon cancer is represented well by the authors of one study: "information on T-stage of colon cancer does not change the treatment plan in clinical practice. Consequently, preoperative staging of patients with colon cancer should focus on accurate detection of

locoregional lymph nodes and distant metastases" (Leufkens et al, 2011b). American Society of Colon and Rectal Surgeons guidelines for colonic cancer staging refer only to tumour site and invasion into other structures, to determine the need for non-anatomical resection (Vogel et al, 2017). Apart from assessing resectability, local staging of colon cancers has thus been largely ignored, as the default treatment was surgery with post-operative chemotherapy. However, more recently attention has been renewed on detailed pre-operative imaging to select patients with locally advanced colon cancer for new therapies such as complete mesocolic excision, prophylactic heated intra-peritoneal chemotherapy or neoadjuvant chemotherapy.

Outlined below is the evidence for computed tomography (CT) in staging colon cancer, in addition to pathology, as well as patient factors and quality of multidisciplinary team (MDT) management to create an accurate prognosis.

T stage

The T (tumour) stage in TNM identifies the maximum degree of local invasion of tumour through the bowel wall. T staging has traditionally been performed by measurement during histopathological specimen analysis. Increasing depth of tumour invasion is a well recognised adverse prognostic marker. This was originally established by Duke's and Bussey (Dukes and Bussey, 1958) in rectal cancer in patients without lymphatic invasion. Tumour invasion through the bowel wall may result in intraperitoneal metastatic disease (Hompes et al, 2012), while invasion into the resection margin may result in local recurrence (Loughrey et al, 2014). Locally advanced colon cancer is present in 10-20% of patients (Klaver et al, 2011), which has a substantial impact on prognosis and may require extra-anatomical resection if nearby tissues or organs are invaded.

CT remains the imaging modality of choice for local staging of colonic primary tumours, as well as distant staging (Cunningham et al, 2017). Recent developments in CT technology and the introduction of spiral CT, and interactive multiplanar 3D CT after osmotic bowel preparation have led to better accuracy of CT for T stage, due to more detailed acquisition of colonic tumours, with faster

acquisition times, thinner slices and multi-planar reconstruction (Narayanan et al, 2014). Conventional T staging on CT to differentiate T1 vs T2 vs T3 vs T4 disease is difficult and has limited prognostic effect. CT cannot distinguish layers of the bowel wall, so there is no evidence-based technique to differentiate T1 and T2 disease. T3 disease may be better distinguished from earlier stage lesions because of high contrast between the bowel wall and adjacent fat (Cunningham et al, 2017). The most recent meta-analysis (Nerad et al, 2016) to investigate the diagnostic accuracy of CT T-staging reported a summary sensitivity of 90% (95% Confidence Interval (CI) 83-95%) and specificity of 69% (95% CI 62-75%) from 13 studies differentiating T1-T2 tumours from T3-T4 tumours. The high sensitivity would imply that CT can detect T3 and T4 disease well, but the lower specificity suggests overstaging of T1-2 tumours. Within the meta-analysis, sensitivity was improved for T3-4 disease in studies that used a slice thickness of less than 5mm, (sensitivity 96% (95% CI 92-98%) and specificity 70% (95% CI 56-81%)), or that used CT colonoscopy (sensitivity 97% (95% CI 90-99%) and specificity 81% (95% 65-91%)).

MRI is not commonly used to stage colonic tumours due to motion artefacts from peristalsis or breathing. Only small series from single centres have reported that MRI is accurate in the staging of colon cancer (Nerad et al, 2017, Hunter et al, 2017). Poor inter-observer reliability between experienced gastrointestinal radiologists for MRI staging of colon cancer suggests expertise is difficult (Hunter et al, 2016). When 299 patients with colonic tumours were staged with whole body MRI in the Streamline C trial (Taylor et al, 2019), treatment decisions were 96% congruent with CT-staged pathways decisions. This may reflect the paucity of treatment options for non-metastatic colonic cancer, as agreement with pT stage was only 54%, with 66% of pT4 tumours understaged on CT. Recently MRI has been used successfully in sigmoid cancers, possibly because of reduced motion artefact since the sigmoid is tethered inferiorly to the pelvic brim as it transitions to the mesorectum (Dam et al, 2017).

Endoscopic ultrasound continues to be used in rectal cancer staging, but is not performed for colonic cancer management. One meta-analysis has been conducted on the diagnostic accuracy of commented on endoscopic ultrasound in colonic cancer but in a small number of patients (208) in six studies, all but one of which were conducted over 10 years ago (Malmstrøm et al, 2016).

Lessons from pathology: advanced T3 substage and peritoneal infiltration

Significant heterogeneity in outcomes can be seen within pT3 stage colorectal cancer, which is also the most common T stage, present in approximately 70% of patients treated by surgery (Zinicola et al, 2017). Initial work on extramural spread had demonstrated its impact on prognosis but using different classifications e.g. slight, moderate or extensive (Dukes and Bussey, 1958, Morson et al, 1963) or microscopic vs macroscopic (Cohen et al, 1980). Merkel et al were the first group to publish on extramural spread beyond the outer margin of the muscularis propria measured in millimeters on histology, and demonstrated was an independent predictor of survival in 853 patients (Merkel et al, 2001b). TNM first introduced pT3 substaging into 4 categories in the 2003 TNM supplement (Table 1-4), but it was regarded as optional (Compton, 2003, Wittekind et al, 2012). A meta-analysis on extramural spread has reported that advanced pT3 substage is an independent and significant prognostic factor when measured at 5mm beyond the muscularis propria (Zinicola et al, 2017). On multivariate analysis, advanced pT3 substage is an independent adverse prognostic factor, associated with other prognostic factors e.g. nodal involvement, rates of venous invasion, poorly differentiated tumour (Wong et al, 2008). This may imply that there are other confounding markers that influence tumour biology and oncological outcomes. Despite this, pT3 substage is still not an essential reporting item in TNM 8 (MB et al, 2017).

pT3 Stage	Description on pathology	
pT3	Tumour invades through muscularis propria into • Subserosa • Non-peritonealised pericolic/perirectal tissue	
pT3a	minimal invasion	<1mm beyond muscularis
pT3b	slight invasion	1-5mm beyond muscularis

pT3c	moderate invasion	5-15mm beyond muscularis
pT3d	extensive invasion	>15mm beyond muscularis

Table 1-4: T3 substaging on pathology

Building from the work in rectal cancer, studies of colon cancer have reported that advanced pT3 stage in colon cancer also carries a worse prognosis, with higher rates of nodal and distant metastasis seen in increasing pT3 substage (Yoo et al, 2012), and higher rates of recurrence and correspondingly lower disease free survival and overall survival (Wong et al, 2008, Burdy et al, 2001, Merkel et al, 2001c). Accurate weighting of T stage without over-weighting of N stage in modified staging systems, can lead to better performance in prognosis prediction than TNM (Kong et al, 2018).

In 2007, the prognostic findings of T3 substaging of colonic cancer on pathology were replicated on CT (Smith et al, 2007). Studies of CT accuracy for colon cancer staging subsequently proliferated (Table 1-5). Nerad reviewed 4 studies that investigated T3 substaging on CT based on extramural spread of over 5mm i.e. T1, T2, T3a-b vs T3c-d, T4 (Nerad et al, 2016). In 4 studies of 281 patients, the summary sensitivity was 77% (95% CI, 66-85% and specificity was 70% (95% CI 53-88%); lower sensitivity than TNM staging. The largest study with 19 reporting radiologists described a sensitivity of 87% and a specificity of 69% (Dighe et al, 2012b). The false positive rates may be due to difficulties distinguishing desmoplastic and neoplastic pericolic fat infiltration; radiologists may prefer to "overcall" these lesions rather than risk understaging. More recent studies published (Rollven et al, 2013, Hunter et al, Malmstrøm et al, 2018, Horvat et al, 2018, Park et al, 2019) have reported higher specificity than sensitivity; this may be due to reduced slice thickness and advanced helical or multidetector CT techniques.

Despite the proliferation of papers investigating the diagnostic accuracy of CT in colon cancer by focusing on correlation with pathology, few papers have investigated the prognostic significance of T3 substage on CT. In a series of 126 patients, Smith et al found 3 years relapse free survival was 43% vs 71% in the poor prognosis group ($p<0.01$) (Smith et al, 2007), but a later study from the same

group did not find an association between advanced T3 substage on CT with disease recurrence (Hunter et al). On multivariate analysis of CT and pathology variables in 536 patients with colonic cancers, T and N stage on CT were independent prognostic factors for overall survival and disease free survival (Huh et al, 2012). Although this study did not employ T3 substage, cT3 tumours had worse survival than cT4 tumours.

The evidence is therefore mixed: while advanced T3 substage of colon cancer on pathology led to worse survival (Merkel et al, 2001c), this has only been replicated clearly on CT in one study (Smith et al, 2007). Difficulties in accurate radiological assessment of T3 substage may be an underlying reason. As specificity is frequently higher than sensitivity, radiologists may not reliably identify high risk disease; this is however limited by the small number of radiologists (usually only 2) reporting CT scans in these studies. Further research is required on whether T3 substaging is prognostic, and reproducible by multiple radiologists. The failure of the FOxTROT (Fluoropyrimidine, Oxaliplatin and Targeted-Receptor pre-Operative Therapy for patients with high risk, operable colon cancer) study to answer this question is addressed below in the neoadjuvant therapy treatment section (page 55).

Study	Patients	Radiologists	T3 substage	
			Sensitivity	Specificity
(Smith et al, 2007)	126	2	92%/86%	42%/61%
(Dighe et al, 2010a)	84	2	78%	68%
(Dighe et al, 2012b)	94	19	95%	50%
(Rollven et al, 2013)	28	2	69%/69%	88%/81%
(Norgaard et al, 2014)	86	1	95%	78%
(Wiegering et al, 2015)	275	2	94.9%	53.6%
(Hunter et al)	53	2	60/70%	70/88%
(Malmstrøm et al, 2018)	501	2	65%	89%
(Horvat et al, 2018)	93	2	66%/83%	81%/87%
(Park et al, 2019)	38	2	64%/79%	83%/79%

Table 1-5: Diagnostic accuracy of CT vs pathology for T3 substage.
Sensitivity and specificity reported for reader 1/reader 2 or using summary result if reported by the study.

Peritoneal infiltration

Tumour invasion through the bowel wall results in serosal involvement and localised peritoneal infiltration, which is staged as pT4 disease. When compared to pT3 stage tumours in the absence of nodal disease, pT4 tumours have significantly worse overall survival (72.2% vs 84.7%) in a retrospective study of over 100 000 patients (O'Connell et al, 2004). T4 disease was defined in TNM6 as tumours that perforated the visceral peritoneum (Fleming et al, 1997), but in 2006 this definition was widened to include hyperplastic and inflammatory reactions of the peritoneum (Compton, 2006). Shepherd et al (Shepherd et al, 1997) described and graded local peritoneal involvement (LPI) in a study of 412 specimens.

LPI Grade	Description
1	tumour well clear of closest peritoneal surface
2	mesothelial inflammatory and/or hyperplastic reaction with tumour close to, but not at, the peritoneal surface
3	tumour present at peritoneal surface with inflammatory reaction, mesothelial hyperplasia, and/or ‘‘ulceration’’
4	tumour cells shown free in peritoneum and evidence of adjacent ‘‘ulceration.’’

Table 1-6: Local Peritoneal Involvement (LPI) grade and definition.
Note. Adapted from (*Shepherd et al, 1997*)

T4 tumours were found to have both grade 3 and grade 4 LPI, but tumours with grade 4 LPI had the worst recurrence-free and overall survival. A national study of 889 patients undergoing surgery for colon cancer in Iceland confirmed that that five year cancer free survival was significantly worse for LPI4 at 19% than 42% for LPI3 (Snaebjornsson et al, 2014).

Differentiation of pT4 and pT3 disease on CT is difficult, with few CT studies demonstrating accurate pT4 recognition on CT (Wiegering et al, 2015, Smith et al, 2007, Sammartino et al, 2016). Other studies improved CT accuracy by grouping together “high risk” tumours including pT3 with pT4 tumours (Sibileau et al, 2014, Wiegering et al, 2015). Sibileau identified CT characteristics which distinguished T4a disease with sensitivity and negative predictive value: irregular bowl-shaped external tumour edges, circumferential aspect of tumour and spread to pericolic fact.

While T-staging by histopathology is still regarded as the gold standard, there is significant variation in interpretation of pT4 disease and serosal involvement may not be detected up to 26% of cases (Shepherd et al, 1997, Zeng et al, 1992). This may be due to difficulties in assessment of tumour cells in the mesothelial layer of the serosa. This includes fragility of the mesothelial layer, which can shed during or after surgery; the distortion of normal anatomic layers by a stromal reaction caused by colorectal cancer; and the presence of normal serosal clefts, which can be further distorted by adjacent tumour infiltration, inflammation or fibrosis (Stewart et al, 2011).

N stage

Cancer involvement of the draining lymph nodes is associated with a higher rate of metastatic spread and therefore a poor prognosis. Lymph node assessment is performed during pathological assessment and is the basis of the Duke's Staging System (Gabriel et al, 1935); when present, 5 year survival worsened from 73% (Duke's B) to 7% (Duke's C). The TNM system has continued with these basic principles, with some modifications. Within more recent TNM editions, tumour deposits of non-nodal origins have been classified as N1c within N stage (Brierley et al, 2017).

Nodal assessment of colonic cancer on imaging is poor. In colon cancer guidelines, lymph node assessment is described as "challenging" by the Association of Coloproctologists of Great Britain and Ireland (Cunningham et al, 2017) and ignored entirely by the American Society of Colon and Rectal Surgeons (Vogel et al, 2017). The criteria for positive node identification are inconsistent, and typically rely on size criteria greater than 10mm or border irregularity. Other criteria include lymph node clusters (3 or more), or radiodensity of at least 100 hounsfield units. The sensitivity and specificity of CT for nodal involvement has been estimated at 70-76% and 55-78% respectively in meta-analyses (Leufkens et al, 2011b, Leufkens et al, 2011a, Nerad et al, 2016, Rollvén et al, 2017, Dighe et al, 2010b). A more recent population study from the Netherlands of over 100 000 patients

has confirmed nodal assessment of colonic cancer by CT is inaccurate, correlates poorly with nodal involvement on histology, and may lead to overstaging (Brouwer et al, 2018).

Alternate tumour metastatic routes

Lymph node metastasis has been assumed to be a precursor for distant metastasis, by directly spread from the lymphatic circulation. It has also been assumed that surgical resection is essential to attain a cancer free state. However, as suggested back in 1984 (Cady, 1984) and more recently, by several authors (Bui et al, 2006, Wong et al, 2007, Simunovic and Baxter, 2007), there may be other, as yet undiscovered, confounders to explain the prognostic link between lymph node yield and survival. This unidentified factor(s) that is related to both the exposure (lymph node involvement) and the outcome (patient survival), may have led to an apparent but spurious association between the exposure and outcome. (Simunovic and Baxter, 2007)

An alternative hypothesis would be that lymph node metastases do not seed further distant metastases, but act as an indicator for poor prognosis for surrogate mechanisms that are as yet, poorly understood. While all colorectal sites share a common lymphatic drainage via the cisterna chyli and left subclavian vein to the lungs, the most common site of colorectal metastasis is the liver, which is linked to the portal circulation which drains the colon and proximal rectum. DNA analysis of 213 biopsy samples from liver and lymph node colorectal metastases found they arose from independent subclones, implying different lineage relationships (Naxerova et al, 2017). However, although liver metastases did not share a common origin with lymph nodes, the majority of lung metastases did. It therefore may be possible that lymph nodes are a pathway for colorectal cancer spread to specific distant organs. It may be possible that multiple anatomic routes exist for tumour metastasis, and may be diverse, arising from perineural, perivascular or lymphatic “anatomic highways” (Nagtegaal et al, 2017).

Are tumour deposits the prognostic nodes?

Extra nodal tumour deposits (TDs) are metastatic deposits of tumour within the bowel mesentery without evidence of lymph node involvement. They were fist described in 1935 by Cuthbert Duke's group in their same study on lymphatic spread of rectal cancer (Gabriel et al, 1935). The origin of TDs remains unclear. One common theory is that TDs arise as a discontinuous tumour embolus following extramural venous invasion (EMVI). This may explain the high risk of liver metastases when either EMVI or TDs are detected (Nagtegaal et al, 2017).

The prognostic impact of TDs on local recurrence, disease free survival and overall survival has been demonstrated on meta-analysis (Lord et al, 2017). Despite the worse prognosis of TDs than lymph nodes, their presence when classified as N1c implies a better prognosis than N2 nodal disease (Lord et al, 2017). TDs have been previously classified as lymph nodes, and likely still are, given the wide variation in pathology-detection of TDs between 10-42% (Lord et al, 2017). While TDs have been recognized and included in the most recent editions of TNM (Sobin LH and Ch, 2002, Brierley et al, 2017) , the definition of TDs has changed from size criteria (>3mm) to contour criteria; "if no histological evidence of residual lymph node, classify as tumour deposit if contour irregular, or lymph node if smooth" (Brierley et al, 2017). These have been shown to be non-reproducible, and has led to difficulty and inconsistency in classifying TDs with no effective criteria (Nagtegaal et al, 2011, Nitsche et al, 2011). Observer variation would not only potentially lead to understaging and under treatment in a large number of patients, but also prevents consistency in classification in colorectal trials and audits. Consequently the 5th edition of TNM is still used by the Netherlands and the United Kingdom for colorectal staging.

On imaging, differentiating nodes from TDs theoretically is easier, where the relationship to a vessel can be seen in 3D (Figure 1-2). TDs are known to carry a worse prognosis than involved lymph nodes on pathology (Lord et al, 2017), but no study has yet confirmed this with imaging-detected TDs. The COMET (COncordance in MRI and Pathology Diagnosis of Extranodal Tumour Deposits) study is

prospectively investigating whether TDs can be identified pre-operatively on MRI, and their prognostic impact.



Figure 1-2: Tumour deposit on CT
Note. Discrete deposit of tumour along a vein distant from the primary

M

A staging CT of the chest, abdomen and pelvis is traditionally used to detect metastatic colorectal cancer, which occurs most commonly in the liver, then the lungs, bone and brain (Cunningham et al, 2017, Vogel et al, 2017). The rates of site-specific metastasis vary by the site of the colorectal

primary (Qiu et al, 2015, Riihimäki et al, 2016). Liver metastases may require further characterization on MRI Cunningham et al (2017). The yield of chest CT for lung metastases is low; it is not recommended by European Society for Medical Oncology (Labianca et al, 2013a), but American Society for Colon and Rectal Surgeons guidelines suggest is value lies as a "baseline" assessment of the chest. Detection of peritoneal disease by CT remains problematic; CT can detect larger peritoneal lesions, but will miss smaller lesions less than 0.5cm (Koh et al, 2009).

A more recent meta-analysis has reported higher sensitivity for PET/CT (area under curve (AUC) 0.94) than for CT (AUC 0.83) to detect small distant metastases (Maas et al, 2011); however, increased uptake due to inflammation may cause false positive results. CT also may perform worse in the detection of extrahepatic lesions (sensitivity 53-71% vs PET 70-100%). However, at present American Society for Colon and Rectal Surgeons and ACPGI guidelines still recommend PET-CT as a second line staging investigation only to characterize indeterminate, suspicious lesions from CT (Cunningham et al, 2017, Vogel et al, 2017).

The role of MRI for whole body staging has recently been revisited with promising results. The Streamline-C trial (Taylor et al, 2019) investigated 299 patients with colorectal cancer, who were staged with whole body MRI with equivalent sensitivity (86%, CI 74-94%) for metastatic disease to CT-based staging (82%, CI 69-91%), similar to a previous meta-analysis of 9 studies (Xu et al, 2013) which reported a sensitivity of 86% (95% CI (70-94%).

EMVI

Extramural vascular invasion (EMVI) was described by Dukes in 1958 (Dukes and Bussey, 1958); "*It is well known that in all forms of cancer treated by radical surgery the patient's prognosis depends very much on the extent of local and lymphatic spread and on the likelihood of venous dissemination.".* During pathological analysis, EMVI was defined by Talbot (Talbot et al, 1981) as tumour present

within an endothelium-lined space that is either surrounded by a rim of muscle or contains red blood cells.

EMVI is associated with increased likelihood of developing liver metastases (Sohn et al, 2015) as tumour cells directly access the portal venous route to the liver. EMVI has been found consistently to predict local (Sunderland, 1949) and distant recurrence (Talbot et al, 1980, Krasna et al, 1988, Shirouzu et al, 1991) and worse overall survival (Shirouzu et al, 1991, Talbot et al, 1981, Bokey et al, 1997) in colorectal cancer, as well as specifically colon cancer (Leijssen et al, 2019b). Despite its poor prognosis, it is not part of TNM staging. This is likely due to population-based data that highlights variation in detection of EMVI, suggesting a problem with quality assurance of pathological analysis, particularly by non-specialist gastrointestinal pathologists (Messenger et al, 2011). The Royal College of pathologists have therefore recommended a detection frequency of EMVI of 30% (Loughrey et al, 2014).

EMVI originally was detected only on histopathology, but more recent studies have shown that pre-operative detection using MRI or CT is possible. MRI-detected EMVI carries the same risk for local recurrence and distant metastasis (Bugg et al, 2014, Smith et al, 2008, Sohn et al, 2015) as pEMVI. On meta-analysis of 14 studies, there was significant variation in EMVI prevalence (9-61%), but most studies reported worse oncological outcomes associated with EMVI (Chand et al, 2016). More recently, reports have been published that EMVI can be recognized on pre-operative CT imaging of colon cancer (Hunter et al, Dighe et al, 2010a), and is an independent predictor of synchronous metastases (Yang et al, 2017), disease free survival (Yao et al, 2016) , although diagnostic accuracy is not matched in smaller studies from other centres (McAvoy et al, 2018, Norgaard et al, 2014).

Small vessel EMVI may be missed on CT. In a series of 126 patients (Dighe et al, 2010a), there was poor agreement between 2 observers with poor agreement (kappa = 0.4), sensitivity 61% (CI 66-84%) and specificity 79% (CI 66-84%) . In the 16 patients with EMVI not seen on CT, only microscopic venous invasion (<3mm) was present in 14 patients. Hunter et al found significant variation between

two readers for CT detection of EMVI, with differences in sensitivity (63% vs 47%) and specificity (88% vs 58%) and a low kappa score (0.18) (Hunter et al, 2017). Another retrospective review of 89 CT scans of colon cancer by 2 radiologists reported sensitivity of 18.2% and 66.7%, but specificity of 60.0% and 91.7% (Horvat et al, 2018). EMVI detected by MRI for rectal cancer was also reported on meta-analysis to have better specificity (0.87, CI 0.79-0.92) than sensitivity (0.61, 0.49-0.71). The higher specificity in these studies suggests CT does not miss large vessel EMVI, but the "variability and observer dependence" notes in some studies suggests targeted radiologist training or fellowships may be required to detect these features (Santiago et al, 2016). Despite the poor sensitivity of CT for EMVI, it was associated with worse 3 year disease free survival (49.5% vs 85.8%) in one study of 60 patients (Yao et al, 2016).

Margin involvement

The completeness of tumour removal has long been recognized as a major determinant of treatment success and survival. Predicted circumferential margin involvement (CRM) of rectal cancer on MRI is a critical variable that determines neoadjuvant and surgical strategy. In colon cancer, CRM involvement is not well studied.

The R classification for residual disease, was recommended by American Joint Committee on Cancer in 1977 (Beahrs et al, 1991), and later incorporated into the Union for International Cancer Control TNM classification (Sobin et al, 2010). The R classification denotes the presence of residual tumour after treatment (Table 1-7) at the primary tumour site, but also regional lymph nodes, and/or distant sites. Conventionally R1/R2 is used to describe the completeness of tumour clearance after surgery, regardless of whether metastatic disease is present (Puppa et al, 2011).

R status	Description on Histology
Rx	Presence of residual tumour cannot be assessed
R0	No residual tumour
R1	Microscopic residual tumour
R2	Macroscopic residual tumour

Table 1-7: R classification for residual tumour
Note. Adapted from *Wittekind et al (2002)*

R1 disease can only be classified as present after histological examination for microscopic disease (Wittekind et al, 2002), when the tumour is identified directly at the longitudinal or non-peritonealised margins, also known as the circumferential resection margin (CRM). Involvement may be due to direct extension by the tumour, or by the presence of tumour in other structures such as veins, lymph nodes or tumour deposits. Biopsy of regional tissue or distant sites may also confirm R1 disease.

R2 disease is present when residual tumour is macroscopically visible clinically or pathologically. Without communication between the surgeon and pathologist, R2 disease may be misclassified as R1 disease (Figure 1-3).

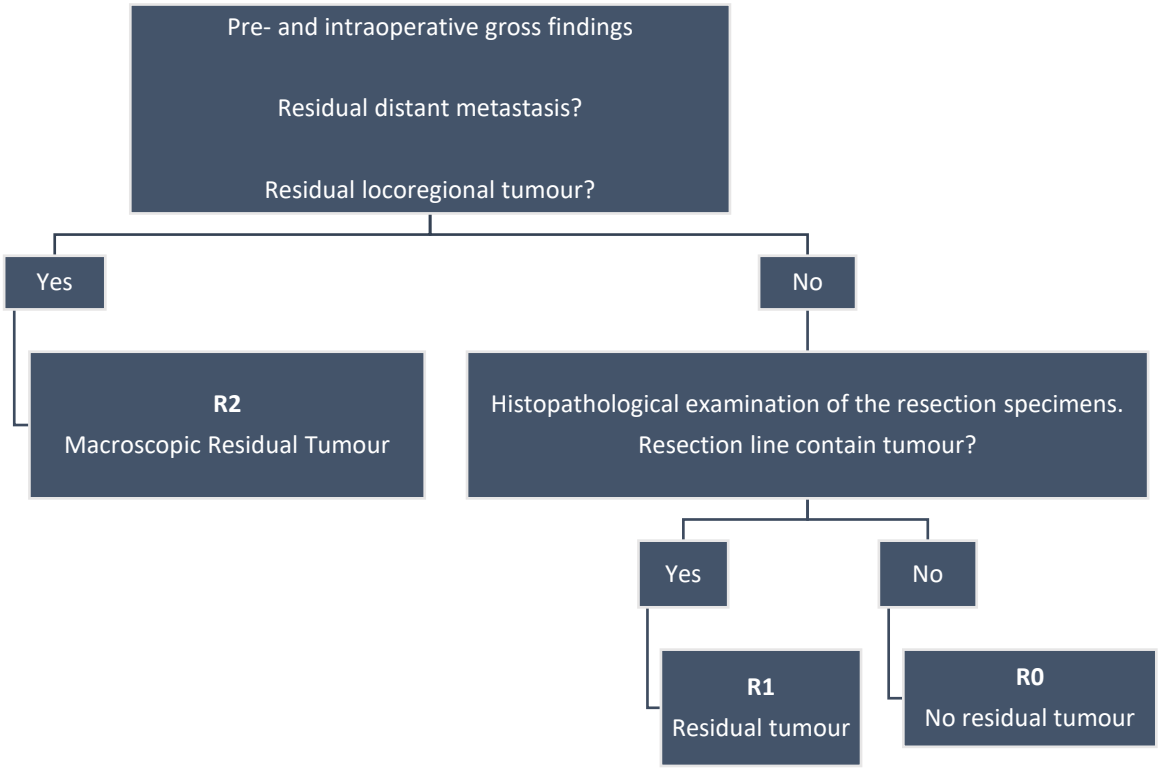


Figure 1-3: TNM residual tumour classification
Note. Adapted from Hermanek P, Henson DE, Hutter RVP, Sobin LH, editors. International Union Against Cancer. TNM supplement 1993. A commentary for uniform use. Berlin: Springer.

Incomplete tumour removal in rectal cancer surgery is an established risk factor for local recurrence (Quirke et al, Wibe et al, 2002b, Quirke et al, 1986, Sebag-Montefiore et al, 2009, Nagtegaal et al, 2002a) and distant recurrence (Hall et al, 1998, Wibe et al, 2002b, Sebag-Montefiore et al, 2009, Nagtegaal et al, 2002a). Consequently, CRM assessment on imaging plays a key role in pre-operative decision making. The introduction of multidisciplinary team discussion was shown in a single institution by Burton et al to reduce the CRM involvement rate from 26% to 3% (Burton et al, 2006b) by identifying patients with poor prognostic features on imaging that would require neoadjuvant therapy. The MERCURY study confirmed that in 11 colorectal cancer centres, MRI could predict a clear CRM in 354 of 408 patients (MERCURY Study Group, 2006). The MERCURY II study (Battersby et al, 2016) demonstrated that CRM assessment on MRI reduced R1/R2 resections by appropriate selection of patients for neoadjuvant radiotherapy and extra-levator or beyond TME surgery. MRI is

recommended for pre-operative staging of rectal cancer in national (ACS, 2017, Cunningham et al, 2017) and international guidelines (Glynne-Jones et al, 2017).

The prognostic implications of CRM involvement in colon cancer is less well studied (Scott et al, 2008, Amri et al, 2015a). It has been suggested that MDT review may reduce margin involvement of colonic cancer by appropriate use of neoadjuvant therapy or multivisceral resection (Amri et al, 2015a, Khan et al, 2015, Klaver et al, 2017), but at present this has not been demonstrated in prospective studies. CT assessment of the CRM has only been investigated in two small, single centre studies, with wide discrepancies in CT sensitivity (33%-84%) for CRM involvement (Burton et al, 2008, Elibol et al, 2016). In the national Dutch Colorectal Surgical Audit, only 1.8% of patients with locally advanced colon cancer (77/4344) were administered neoadjuvant chemotherapy, with a non-significantly increased R0 rate (92% vs 85%, p=0.429), but this was on the basis of advanced T4 stage rather than a predicted involved CRM. Similarly, other small retrospective studies have reported good R0 results with downstaging neoadjuvant chemoradiotherapy for locally advanced colon cancer (Hallet et al, 2014, Cukier et al, 2012 , Qiu et al, 2016, Krishnamurty et al, 2018). The preliminary FOxTROT results did suggest a significant reduction in R1 rates from 10% to 5% with neoadjuvant chemotherapy (Seymour et al, 2019).

Margin involvement after colonic cancer surgery may not be as infrequent as commonly thought. The ascending and descending colon have significant retroperitoneal borders and the mesocolic or “nonperitonealised margin” has now been included as a core item in the most recent Royal College of Pathology Colorectal Dataset (Loughrey et al, 2017). However, as a largely intraperitoneal organ, the colonic CRM is deemed not to be at risk, particularly for transverse or sigmoid segments of the colon which are encased by peritoneum and hang on a mesentery. Colonic mobilization and resection are still regarded as technically easier than a mesorectal excision; but contemporary R1 rates range from 5.3% to 13.3% for all colon cancers (Bateman et al, 2005, Scott et al, 2008, Amri et al, 2015a). However, these reports are often from tertiary “expert” centres, and palliative resections

and emergency surgery is commonly excluded. In England, 25% of patients are diagnosed at emergency presentation with late stage disease, and would therefore not be represented (NCIN, 2015). The Dutch Surgical Colorectal Audit of 41 445 patients with colonic cancer reported R0 rates of 99%, 91% and 87% for patients with non-locally advanced colon cancer, locally advanced colon cancer, and locally advanced colon cancer treated with multivisceral resection respectively (Klaver et al, 2017).

When the colonic CRM is involved by tumour, recurrence is more likely. In a series of 984 colectomies, Amri et al reported a non-significant difference in local recurrence in cases with involved margins (6.3% vs 1.3%, p=0.18) but significantly increased distant recurrence (37.5% vs 13.1%, p=0.005) (Amri et al, 2015a). This may also be due to the adverse disease characteristics associated with R1 margins in this series: T4 disease, LN positivity, high grade tumour histology, EMVI and perineural disease. In a retrospective series of 1100 colectomies, R1 resections for all colon cancers were associated with significantly more overall recurrence (55.5 vs 19% p=0.001), as well as local recurrence (12.2% vs 2%) (Khan et al, 2015). There was significantly worse 5-year disease free survival (32% vs 76%, p=0.001) although on multivariate analysis other significant variables included emergency surgery, T4 stage, lymph node involvement and EMVI. R1 rates were higher for patients undergoing emergency vs elective surgery for rectosigmoid cancer (20 vs 14.2%); the same rates for more proximal sigmoid tumours were 13.7% and 9.2% (Khan et al, 2015). The higher rates of involved margins with rectosigmoid tumours may be because a distal, pelvic sigmoid cancer may invade other pelvic organs, similarly to rectal cancer, and an R1/R2 resection is more likely without pre-operative imaging informing a planned multi-visceral/ exenterative strategy.

Margin involvement can also occur from tumour invasion through the peritonealised colonic surface into other structures that are incompletely resected. At population level in the Netherlands, multivisceral resection of 1595 T4b colonic tumours had a low R0 rate of 87% (Klaver et al, 2017). In a series of 55 patients, T4b colonic tumours were associated with a higher rate of involved margins

when tumours were not resected en-bloc (Leijssen et al, 2019a). This may be due to lack of centralization and low hospital volumes, or because T4b tumours commonly present as emergencies, and are treated by urgent surgery rather than bridging strategies to neoadjuvant therapy and specialist surgery (Klaver et al, 2017).

Some difficulties exist with the current R stage. R classification is entirely contingent on the thoroughness of both clinical and pathological assessment (Wittekind et al, 2002). Studies from the United States have shown that despite its prognostic importance, CRM documentation is only carried out in 26% of patients (Al-Sukhni et al, 2016). There is possibly a knowledge gap amongst surgeons about the use of R1 to denote margin involvement only, and possible omission of R2 documentation of regional or metastatic residual tumour (Wittekind et al, 2009).

Furthermore, it is still unclear what distance from the margin constitutes an R0 resection with low risk of recurrence. Currently, a margin of less than 1mm of tumour clearance is grounds for an R1 classification in the Royal College of Pathology guidelines and the American Joint Committee on Cancer (Loughrey et al, Quirke et al, Birbeck et al, 2002). Some studies have suggested significantly shorter tumour margin distances of <0.1mm (Hwang et al, 2014) or <0.5mm (Park et al, 2014) may be associated with increased local recurrence rates. However, contrasting evidence from Nagtegaal's group states found local recurrence rates were significantly raised (16%) up to 2mm from the CRM (Nagtegaal et al, 2002a), suggesting that underreporting of margin involvement was possible, which was corrected by quality control systems present in their study. A more recent study from France suggested that 0.4mm was an acceptable cutoff, which they calculated by electronic slide upload and computer measurements of CRM distance (Beaufrère et al, 2017). It remains unclear if heterogeneity and error in CRM measurement underlie the differences in disease recurrence, or whether there is another confounding factor.

Disease Factors Not Assessed by Imaging

Further prognostic disease variables cannot be assessed by imaging; these include microscopic disease characteristics (perineural invasion, tumour grade) on pathology (Langman et al, 2017), or molecular variables. When robust evidence exists for these variables, they are included as core data items within the colorectal cancer datasets published by the Royal College of Pathologists (Loughrey et al, 2017), which also form the basis of pathology recommendations in ACPGI guidelines (Langman et al, 2017).

Tumour type & differentiation

Most colorectal cancers are adenocarcinomas. Tumours can also be differentiated into rarer subtypes, including mucinous (10%) and signet ring cell (1-2.4%) carcinomas. Mucinous tumours are associated with advanced stage at presentation and peritoneal dissemination and poor response to chemotherapy (Mekenkamp et al, 2012), but on meta-analysis there is a possible interaction with micro-satellite instability (Verhulst et al, 2012). Signet ring cell tumours are recognized to be an adverse prognostic factor for overall survival and disease free survival when stratified by stage (Yun et al, 2017), with worse 5 year survival than adenocarcinoma (30.1% vs 51.6%) in population data (Sun et al, 2018).

Tumour differentiation of adenocarcinoma is based on the World Health Organisation grading system of 4 subcategories (Table 1-8), dependent on the proportion of gland or tubule formation (Bosman et al, 2010). Poorly or undifferentiated tumours are associated with worse survival (Langman et al, 2017, Halvorsen and Seim, 1988, Compton, 2003).

Grade	Differentiation
1	Well
2	Moderately
3	Poorly
4	Undifferentiated

Table 1-8: WHO grading system of differentiation.
Note. Adapted from (*Bosman et al, 2010*)

Grade-for-grade histologic evaluation has shown to be variable and subject to interobserver variability. A two tiered grading (low grade and high grade) system has been shown to have better

reproducibility and has been recommended by the College of American Pathologists and the Royal College of Pathologists (Compton, 2003), (Loughrey et al, 2014).

After pre-operative therapy, tumour regression may be graded by the degree of fibrosis and absence of tumour cells (Table 1-9). Although all systems are based on rectal cancer specimens after chemoradiotherapy, the FOxTROT study used a 5 point system initially created by Dworak (Dworak et al, 1997) and then modified by Rodel (Rödel et al, 2005), while the American Joint Committee on Cancer and Association of Coloproctologists of Great Britain and Ireland endorse a 4 point system (Langman et al, 2017).

TRG	AJCC (Ryan et al, 2005).	FOxTROT (Rödel et al, 2005),
0		No regression
1	Complete response: no viable cancer cells	Minor regression: less than 25% fibrosis in dominant tumour mass
2	Near-complete response): single cells or rare small groups of cancer cells	Moderate regression: 26-50% fibrosis in dominant tumour mass
3	Partial response: residual cancer with evident tumour regression, but more than single cells or rare small groups of cancer cells (partial response)	Good regression: >50% dominant fibrosis outgrowing tumour mass tumour mass
4	Poor or no response: extensive residual cancer with no evident tumour regression	Total regression: no viable tumour cells, only fibrotic mass

Table 1-9: Tumour Regression Grade (TRG) on pathology systems

Note. AJCC: American Joint Committee on Cancer

Tumour border configuration or "tumour budding"

Microscopic clusters of cancer cells ahead of the invasive front of the tumour are known as "tumour budding", and been shown to be an adverse prognostic factor in univariate and multivariate analysis (Compton, 1999). Loss of cell adhesion may be associated with an invasive behavior to the cells, and may result in lymphatic and distant metastasis and worse survival. Interobserver variability can reach 30% (Jass et al, 1986), but concordance can improve to 90% when specific diagnostic criteria are used (Compton et al, 1997). The evidence was not sufficient for it to be considered as a core data item in the 4th colorectal pathology dataset (Loughrey et al, 2017), but is included in European

Society of Medical Oncology (Schmoll et al, 2012) and National Comprehensive Cancer Network guidelines (NCCN, 2017).

Perineural invasion

Perineural invasion is characterized by tumour invasion and spread along nerve sheaths. This was defined in 1985 as "tumour invasion in, around and through the nerves" (Batsakis, 1985). In 2009, new criteria for the identification of perineural invasion were by the presence of tumour cells surrounding more than 33% of the nerve circumference or within any of the three nerve layers (Liebig et al, 2009). On meta-analysis (Knijn et al, 2016), perineural invasion is correlated with decreased 5 year disease free survival (HR 2.35, 95% CI, 1.97-3.08) and overall survival (HR 1.85, 95% CI, 1.63-2.12). Perineural invasion was seen more commonly in patients with rectal vs colon cancer (20.6% vs 14.1%). In lymph node negative patients with CRC, perineural invasion was associated with significantly worse survival (Liebig et al, 2009). The impact of perineural invasion was found to be equivalent to other factors such as T stage, N stage, LVI status and differentiation grade. It was included as a core data item in the 4th colorectal pathology dataset (Loughrey et al, 2017).

Variation in the presence of perineural invasion has been attributed to the lack of a consensus definition, difficulty in its detection due to inflammatory cells or mucinous pools, and variation in the different densities of innervation in the colon and rectum (Yang et al, 2015). PNI may therefore be expected to be lower in the colon, which is less richly-innervated by autonomic fibers than the rectum.

Molecular Markers

Considerable attention has been paid to molecular testing for biomarkers that can predict response to targeted therapies. As the American College of Pathologists reported, "*many published studies are limited due to early exploratory and retrospective analyses, and those biomarkers, while of potential interest, have not made it to clinical practice*" (Sepulveda et al, 2017). However at present, only epidermal growth factor signalling pathway mutations provide a therapeutic opportunity with

monoclonal antibody therapies (KRAS, BRAF); other molecular markers such as mismatch repair genes (MMR) provide prognostic information.

KRAS and NRAS mutations (exons 2, 3, 4) are found in 35-42% of colon cancers, while mutations in BRAF V600E occur in 7-15% of patients. Both mutations are recognized to predict resistance to epidermal growth factor (EGFR) targeted antibodies (Roth et al, 2009), such as Cetuximab and Panitumumab (Sepulveda et al, 2017). After the National Institute for Health and Clinical Excellence reviewed high quality evidence from observational studies (NICE, 2020), it recommended that all patients with stage IV colorectal cancer suitable for systemic therapy should be tested for RAS (including both KRAS and NRAS) and BRAF mutations. This was based on findings that RAS and BRAF mutations were predictive of response to anti-EGFR.

Mutations or deficiency in DNA mismatch repair genes (MMR deficient) can lead to microsatellite instability (MSI)-high tumours. This prevents the normal induction of apoptosis. MSI-high tumours are found in 15% of CRC, and includes hereditary non-polyposis colorectal cancer (HNPCC) or Lynch syndrome, although the majority are due to sporadic mutations. MMR/MSI identifies patients at low risk of recurrence, with improved overall survival and reduced lymphatic spread and metastasis than MMR proficient tumours (Vilar and Gruber, 2010, Loughrey et al, 2017). Routine testing of deficient MMR status is now a core data item (Loughrey et al, 2017), endorsed by NICE (NICE, 2017), with the purpose of detecting Lynch syndrome. There is some controversy whether MMR deficiency is linked to lack of response to chemotherapeutic regimens based on fluorouracil (Loughrey et al, 2017), but emerging data suggests a role for immunotherapy as a targeted therapy (Sepulveda et al, 2017), although this is not recommended within guidelines at present.

Non-disease factors

The anatomical extent of disease is still inconsistently reported, and new markers for assessment of anatomical spread continue to emerge. However, other factors, including molecular markers may improve prognostic evaluation of colorectal cancer.

Patient factors

Cancer outcomes are not solely dependent on the disease itself, but are affected by a patient's age, sex, comorbidity and immunological status.

Increasing age is a recognized adverse prognostic factor, as is increased comorbidity for overall survival (van Eeghen et al, 2015a, van Eeghen et al, 2015b). Surveillance, Epidemiology and End Results programme data suggest that 40% of patients diagnosed with colorectal cancer have at least one comorbidity; comorbidity and age were associated with reduced overall and disease free survival in Stage I-III cancer (Edwards et al, 2014). Elderly patients are more likely to present as an emergency, with higher stage disease (Iversen, 2012). However, death from other causes is much more likely in elderly patients, thus decreasing overall survival (Edwards et al, 2014, van Eeghen et al, 2015a) from non-cancer causes. Unfortunately, there may also be a negative bias towards aggressive treatment options including chemotherapy for elderly patients, who are poorly represented in clinical oncology trials.

Comorbidity is known to increase death from other causes, but also disease-specific death (van Eeghen et al, 2015a, van Eeghen et al, 2015b). The mechanisms are likely to be multifactorial; patients may be undertreated, have less physiological reserve, may be less likely to adhere to treatment regimes, and there may be multiple direct and indirect interactions between chronic diseases and cancer. A review of the impact of comorbidity confirmed that this worsened cancer prognosis with 5 year mortality hazard ratios ranging from 1.1 to 5.8 (Søgaard et al, 2013). A population study of 12 265 patients with colorectal cancer in Canada reported comorbidity in at least one third of patients (Cuthbert et al, 2018). Fewer patients with comorbidities received guideline prescribed treatment. Patients with colorectal cancer without comorbidity had significantly

longer median survival of 10.7 years vs 4.16 years in patients with cardiovascular disease, 7.25 years in diabetic patients or 6 years in patients with other comorbidities (Cuthbert et al, 2018).

Men have colorectal cancer incidence and mortality rates that are 30% and 40% higher respectively (Siegel et al, 2017) in analysis of Surveillance, Epidemiology and End Results programme data from the USA. This is despite the higher prevalence of right sided cancer in women, which is more likely to present as an emergency, yet still have a better survival outcome (Marks et al, 2018, White et al, 2018). However, a critical literature review of national data revealed minimal differences in survival by stage at diagnosis, suggesting that there were no significant differences in CRC treatment access and efficacy by sex, and that higher CRC death rate in males is likely to be due to higher incidence (White et al, 2018).

Emergency presentation of colorectal cancer is associated with significantly worse survival (McArdle and Hole, 2004), with higher peri-operative mortality, but also overall survival and cancer specific survival due to advanced tumour stage (Kundes et al, 2016). Tumour perforation into the peritoneal cavity in particular is a poor prognostic factor in colon (Petersen et al, 2002) and rectal (Porter et al, 1996) cancer, and classified as pT4b. Further studies have confirmed an association between emergency presentation and worse overall survival on multivariate analysis, even in the absence of nodal disease. (Grande et al, 2013, Moertel et al, 1995).

A patient's immunological status may affect the tumour environment, and therefore disease progression and prognosis. Differences in the host immunological response have been possibly attributed to a patient's genetic background, microbiome and the tumour's microenvironment and own genetic features (Pagès et al, 2018). Its prognostic significance had not been conclusively demonstrated in studies due to variation in the histologic criteria for its presence (Compton, 1999), which needs to reflect the type, functional orientation, density and location of immune cells (Pagès et al, 2018). However, a new consensus standardised "Immunoscore" using digital imaging assessment software has recently been validated, and shown to strongly predict recurrence on

multivariate analysis (Pagès et al, 2018). One more readily available and inexpensive test is the neutrophil/lymphocyte ratio, which assesses inflammation (neutrophilia) and immunity (lymphopaenia), which on meta-analysis is associated with worse overall and disease free survival (Li et al, 2014).

Multidisciplinary Team Quality of Treatment

The quality of treatment administered to patients is the final factor that will affect prognosis. Surgery remains the primary curative treatment option available to patients with colon cancer, but the quality of imaging, pathology and oncological treatment will also affect outcomes. Treatment decisions for each patient are discussed in MDT meetings. MDT working offers benefits to patients, including improved clinical outcomes due to evidence based-decision making with input from a range of experts. MDTs may also benefit clinicians, by providing educational opportunities, and support from other colleagues and reassurance from a corporate MDT decision making process. One systematic review of 27 studies on cancer MDTs found limited evidence for improved survival outcomes, but patients were more likely to receive accurate and complete pre-operative staging, and neo-adjuvant or adjuvant staging (Pillay et al, 2016). This is relevant in MDT treatment of rectal cancer, where pre-operative MRI increased the proportion of patients with local disease control as a result of appropriate selection for neaodadjuvant treatment and curative surgery (Burton et al, 2006b, Palmer et al, 2011). A further six studies on colorectal cancer were reviewed, and most studies reported non-significant survival gains for patients discussed in MDTs (Munro et al, 2015). In the same publication, a review of 586 patients with colorectal cancer reported a reduced hazard of death from colorectal cancer (0.73, 95% CI 0.53-1.00) when patients were discussed in the MDT, although this benefit was largely confined to patients with advanced disease (Munro et al, 2015). While MDTs are time-consuming, resource-intensive and costly, their benefits mean they continue

to be adopted in cancer treatment across the world, most recently in the OSTRiCh group for rectal cancer care in the USA (Dietz and (OSTRICH), 2013).

Treatment decisions in MDT are made prior to surgery based on patient factors and clinical stage on imaging, and following surgery, based on pathology stage. Although specimen analysis on histopathology remains the foundation of colon cancer staging, pre-operative radiological staging may contain equally valuable prognostic information. Radiological staging at present does not significantly alter treatment decisions in colon cancer as there is only one curative option; colectomy. Once alternative treatment options for advanced disease are supported by an evidence base, resources, and local pathways, there will be a need for accurate pre-operative staging to avoid morbidity and mortality from overtreatment by neoadjuvant chemotherapy, complete mesocolic excision, or planned multivisceral resection. The widespread variation in radiologist accuracy for CT staging of variables including T stage and EMVI is documented above. Without reliable CT interpretation of colon cancer, the risk will then be of radiological overstaging; recognized in rectal cancer (Scheele et al, 2018).

Specimen analysis on pathology is regarded as the gold standard for tumour assessment, as measurements under the microscope are seen as reliable. However, deficiencies can exist within pathological staging and reporting (Shepherd and Quirke, 1997). Widespread variation is seen in the assessment of tumour depth of both malignant polyps (Komuta et al, 2004) or advanced tumours with serosal involvement (Klaver et al, 2020), lymph node yield (Lemmens et al, 2006), tumour deposits (Lord et al, 2017), and EMVI (Chand et al, 2016). Key data items may also be missing from "freehand" reports; in a regional study of 1625 patients with colorectal cancer, 76.7% of patients lacked sufficient pathology data to inform decisions on chemotherapy (Morris et al, 2007).

MDT performance can improve with feedback. Feedback to the MDT team on the quality of surgery can improve specimen quality, as seen in the MRC CR07 trial (Quirke et al, 2009). In a randomised trial (Wright et al, 2008), in-person instruction by an expert "opinion leader" improved lymph node

yield from 14.3 nodes to 18.3 nodes (p<0.001). A review of pathologist technique on nodal assessment significantly decreased the proportion with less than 12 lymph nodes examined from 87% to 48% (p<0.0001, (van Steenbergen et al, 2010)). Proforma reporting in pathology has increased completeness of staging information from 31% to 100%. Similarly, the omission of staging information on radiology reports was reduced by proforma reporting from 72% to 4% at a single centre (Taylor et al, 2010). When proforma CT staging reporting of colon cancer was introduced in a study of 1283 reports at 12 United Kingdom centres (Patel et al, 2018), improvement was seen in 10/13 staging items, and the mean completion rate increased from 38.5% to 92.3%. The improvement was greatest for peritoneal infiltration and resectability, which are two key items that inform surgical decision making.

Treatment

"There is a group of low-lying sigmoid tumours which are exceedingly difficult to get at…"(Mayo, 1909)

Rectal cancer treatment is bespoke to each patient and based on their pre-operative MRI stage, as well as patient fitness and stoma acceptance (Figure 1-4). In contrast, the principles of treatment for all non-metastatic colonic cancers remain colectomy, and chemotherapy in cases of nodal involvement on pathology. The evidence for other treatment strategies for colon cancer are described below.

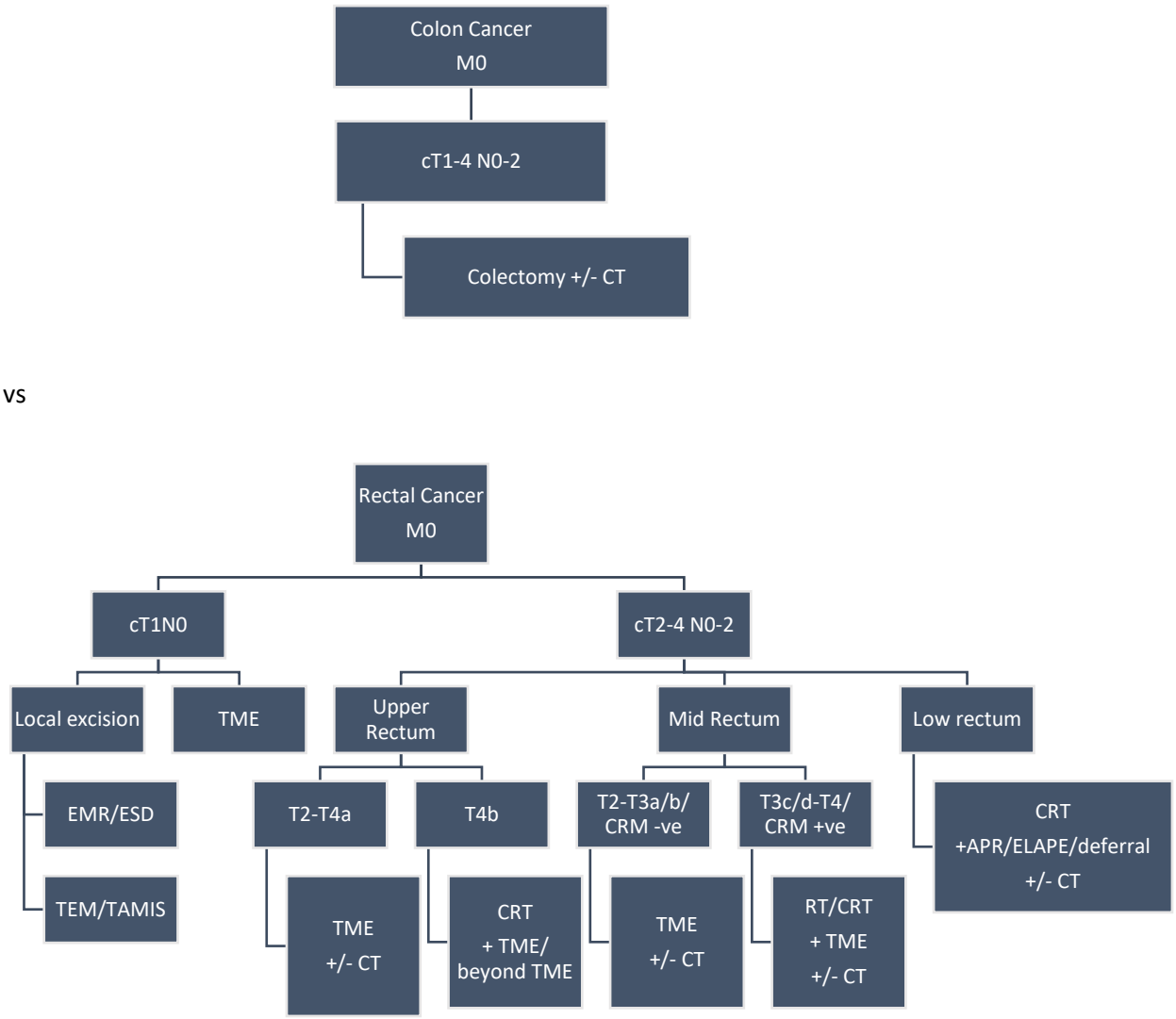


Figure 1-4: Curative treatment pathways for colon vs rectal cancer
Note. TME: total mesorectal excision. EMR: endoscopic mucosal resection. ESD: endoscopic submucosal dissection. TEM: transanal endoscopic microsurgery. TAMIS: transanal minimally invasive surgery. CT: chemotherapy. CRT: chemoradiotherapy. RT: radiotherapy. APR: abdomino-perineal resection. ELAPE: extra-levator abdomino-perineal excision.

Neoadjuvant therapy

Neoadjuvant radiotherapy

Neoadjuvant therapy (radiotherapy and/or chemotherapy) is traditionally used to downstage colorectal cancer pre-operatively. Neoadjuvant strategies are therefore employed mostly for patients with locally advanced disease, to enable an R0 resection and prevent tumour cell shedding during surgery.

Neoadjuvant radiotherapy in the treatment of colorectal cancer is focused almost entirely on rectal cancer. In the randomised Dutch rectal cancer trial 1861 patients (van Gijn et al, 2011) showed a reduction in local recurrence from 11% to 5%. Two further large randomised studies (Sauer et al, 2004, Sebag-Montefiore et al, 2009) demonstrated the benefits of pre-operative treatment with radiotherapy, than post-operative treatment, with lower local recurrence rates (4.4-6% vs 10.6-13%) and less toxicity (short and long term). New evidence in rectal cancer research (Dossa et al, 2017, Renehan et al, 2016, van der Valk et al, 2018) suggests that when pre-operative therapy results in a complete response, surgery may be deferred or even unnecessary. The feasibility of a "deferral of surgery" approach is controversial and still being studied in registries (Renehan et al, 2016, Dossa et al, 2017) and prospective trials (Battersby et al, 2017).

Closer analysis of the landmark rectal cancer trials suggests there may be benefits of radiotherapy to sigmoid cancers (Table 1-10). The German Rectal Cancer Study defined upper rectal tumours above 10cm from the anal verge and found a higher rate of local recurrence: 4.3% (irradiated) vs 10.4% (non-irradiated). The MRC study also found a significant reduction in upper rectal (10-15cm) local recurrence of 1.2% (irradiated) vs 6.2% (selective irradiation). The Dutch Rectal Cancer Trial found a non-significant reduction in local recurrence rates (3.8% to 1.3%) after irradiation in tumours between 10-15cm. None of the studies were powered to investigate the effect of neoadjuvant radiotherapy on upper rectal cancers, and employed a narrow definition of local recurrence, excluding peritoneal or nodal recurrence. Furthermore, each of these studies used various, non-anatomic definitions that may have included patients with sigmoid cancers; it therefore remains unclear whether sigmoid cancers may benefit from radiotherapy.

Study	Study Dates	Definitions	Interventional	LR definition	LR rates
Swedish Rectal Cancer Trial (Folkesson et al, 2005)	1987-1990	UR>11cm N=243	25Gy vs surgery	Pelvis	UR: 8% (rad) vs 12%, *p*=0.3
German Rectal Cancer Trial	1993-1999	UR: 10-16cm N=130	50.4Gy vs surgery	Pelvis	UR: 2.5% (rad) vs 10.4%

(Sauer et al, 2012)					
Dutch TME Trial (Kapiteijn et al, 2001)	1996-1999	UR: 10-15cm. N=551 (31)	25Gy vs surgery	Lesser pelvis	UR: 3.8% (rad) vs 1.3% *p*=0.17
MRC CR07 (Sebag-Montefiore et al, 2009)	1998-2005	UR: 10-15cm N=207	25Gy pre-op vs 45Gy post-op	Intraluminal or pelvic	UR: 1.2% (rad) vs 6.9%

Table 1-10: Local recurrence after radiotherapy to the upper rectum.
Note. LR: local recurrence. R: Rectum, UR: Upper Rectum, Gy: rad: neoadjuvant radiotherapy

Tumours that are localized to the colon pre-operatively are deemed ineligible for neoadjuvant radiotherapy largely because of the risk of toxicity to the small bowel, liver and kidneys. Novel techniques have been developed including three dimensional conformal radiotherapy and intensity-modulated radiotherapy (Hallet et al, 2014, Qiu et al, 2016), that minimize the risk of toxicity. Since then, several small, single centre retrospective studies have reported that pre-operative chemoradiotherapy for locally advanced cancers in the sigmoid colon can lead to excellent R0 results, between 95.2% -100% (Hallet et al, 2014, Cukier et al, 2012 , Qiu et al, 2016), and trends towards improved overall survival and disease free survival (Krishnamurty et al, 2018). A further systematic review (Agas et al, 2019) of mostly retrospective single centre studies has confirmed reduction in local recurrence (OR 0.41, 95% CI 0.21-0.79) and benefits to 5-year disease free survival (OR 2.10; 95% CI 1.21-3.63) or 5-year overall survival (OR 2.00; 95% CI 1.17-3.41) with pre-operative radiotherapy to high risk colon cancers.

The reduction in local recurrence from radiotherapy may not prolong a patient's life. Despite a reduction in local recurrence rates in the Dutch TME trial (van Gijn et al, 2011), there was no overall survival benefit from radiotherapy (49% vs 48%) at 10 years, and a non-significant reduction in cancer-specific death (28% vs 31%). The incidence of secondary malignancies was also found to be higher with radiotherapy at (14% vs 9%), and similar findings(9.5% vs 4.3%) were confirmed by the Swedish Rectal Cancer trial (Birgisson et al, 2005). The risk of non-cancer death is significantly higher after radiotherapy than surgery alone; doubling within the first year of treatment from 4% to 8%

(Colorectal Cancer Collaborative Group, 2001). Toxicity occurs in up to 40% of patients undergoing chemoradiotherapy (Sauer et al, 2004a). The oncological benefits of neoadjuvant radiotherapy need to be weighed against their risks, which may be fatal. This may explain why overall survival is not higher after radiotherapy, despite the reduction in local recurrence. Careful selection of patients for neoadjuvant radiotherapy is therefore essential.

Neoadjuvant Chemotherapy

Pre-operative chemotherapy is another treatment option for colon cancer. The FOxTROT pilot study had promising results with reduced resection margin involvement and post-operative specimen downstaging (Foxtrot Collaborative Group, 2012). It had been hoped that when completed, the international, multicenter, randomised FOxTROT study would provide definitive evidence on the therapeutic benefits of neoadjuvant chemotherapy, but also whether T3 substage assessment on CT is prognostic, and is reproducible by multiple radiologists. The results of FOxTROT were presented first in 2019 (Seymour et al, 2019), reporting a significant reduction in margin involvement (10% vs 5%) and a pathological complete response in 4%, but a non-significant reduction in disease recurrence (13.6% vs 17.2%, p=0.08).

Changes to the methodology of the FOxTROT pilot study, particularly the selection criteria, may have caused the study's negative results. During the FOxTROT pilot study, high risk patients were eligible for pre-operative chemotherapy if their CT-T stage was T4 or T3 with >5mm extramural invasion. However, the decision to broaden the inclusion criteria to all T3 tumours (Foxtrot Collaborative Group, 2012) was based on the results of a "parallel audit" of diagnostic accuracy data from centres involved in the FOxTROT audit (Dighe et al, 2012b). Several reasons were given for the expansion of the inclusion criteria to include all radiologically staged T3 tumours. Firstly, the audit reported that sensitivity of CT for advanced T stage disease was high at 87%, but that pathological analysis of early T3 stage (1-4mm invasion beyond muscularis) tumours reported co-existing "high risk" pathological

features such as nodal involvement, or T4 disease in 9/17 cases. Secondly, the report suggested that CT had a high sensitivity of 95% for all T3 disease and that including these patients would encompass patients with nodal disease and EMVI, who would benefit from chemotherapy. Even if node negative, the audit argued that T3 disease could be an indication for chemotherapy particularly younger patients, based on the QUASAR study (Gray et al, 2007). Finally, the audit suggested that the low specificity of CT for pathological T2 disease (over-reported as T3-4 in 6/12 cases) justified widening the radiological criteria.

It may be argued that these decisions were not logical, and at times conflicting. T3N0 disease in the absence of multiple risk factors is not recognised as an indication for adjuvant therapy in National Comprehensive Cancer Network or European Society for Medical Oncology guidelines (Schmoll et al, 2012). Low specificity of CT for pathological T2 disease was used to justify widening the trial inclusion criteria, but to CT T3 disease only. The original CT-staging of early and advanced CT T stage in the FOxTROT pilot resulted in clearly differentiated groups with good and poor prognoses, which was then supplanted by a mixture of pathological and CT staging that has not been proven in any study. Broadening the advanced T stage group creates the risk of including good prognosis patients in the poor prognosis group and potentially diluting the effects of neoadjuvant therapy; this may explain the negative results of FOxTROT that have been presented to date. An optimal CT-system for identifying high risk tumours is therefore still needed.

Surgery

Radical Mesenteric Excision: Complete Mesocolic or Total Mesorectal

Traditionally, all potentially curable forms of colonic cancer were treated with radical surgical techniques i.e. colectomy to remove tumour with the mesentery of its vascular pedicle. Surgery still remains the mainstay of treatment of colon cancer, and the principles and practice of radical colonic cancer surgery have remained largely unchanged over the last 100 years, since described by Mayo

and Jamieson in 1909 (Jamieson and Dobson, 1909, Mayo, 1909). Even in 1893, Lowson (Lowson, 1893), described mobilization along the white line of Toldt, division of the draining mesentery, and a primary anastomosis; surgical oncological principles that continue to be applied today for colon cancer.

The oncological principles of radical rectal cancer surgery were historically counterbalanced by the accompanying morbidity and mortality. Ernest Miles posited that lymphatic clearance was essential to reduce recurrence as "… removal [of the zone of the upward spread] is just as imperative as is the thorough clearance of the axilla in cases of cancer of the breast" (Miles, 1908). While published local recurrence rates ranged from 20% to 95% (Campos et al, 2012), Miles achieved a reduction to 29.5%, but at the cost of an operative mortality of 42% (Miles, 1908). Peri-operative mortality reduced d to 2.6- 9% after World War II with the introduction of blood transfusion and further still with the advent of electrocautery.

The most fundamental surgical innovation in the treatment of rectal cancer occurred when Bill Heald described total mesorectal excision (TME) in 1982 – "removal of the whole visceral mesentery of the rectum" (Heald et al, 1982). This demonstrated the importance of high quality surgical technique on the basis of anatomical principles. He subsequently published his local recurrence rate of 6% in over 500 patients, reaching 3% in R0 resections (Heald and Moran, 1998). This stood in stark contrast to the accepted local recurrence rate of 20-30% (Kapiteijn et al, 1998, Martling et al, 2000). After the systematic dissemination of TME in regional and national programmes, parallel reductions in the local recurrence rate were demonstrated in the Netherlands from 16% to 9% (Kapiteijn et al, 2002b), 21% to 6% in Sweden (Martling et al, 2000) and 12% to 6% in Norway (Wibe et al, 2002a).

No comparable radical surgical technique for colonic cancer had been described until complete mesocolic excision (CME) was first introduced (Hohenberger et al, 2009). Like TME, it involves removal of the intact draining mesentery and a high vascular ligation at its point of origin. More recently, a consensus statement also described adequate bowel length (Søndenaa et al, 2014) as an

essential component of CME to ensure pericolic nodal excision. Systematic review of CME vs routine colectomy outcomes found a higher rate of complete mesocolic excisions (OR 4.86), with longer bowel in colectomy specimens, longer distance of high tie, and a larger lymph node harvest ((Gouvas et al, 2016) after CME. CME was associated with better overall and distant recurrence rates (11.3% vs 16.8%, p=0.028) and better overall and disease free survival.

Good quality surgery involves clear margins, but also operating in the correct plane to ensure an intact, fascial lined mesenteric package is removed with the anatomical specimen. This will contain all the blood vessels, lymphatic vessels or nodes, or other routes through which tumour may disseminate. Improvement of plane of surgery is possible by surgical training and education (Martling et al, 2005, Kapiteijn et al, 2002a, Kapiteijn et al, 2002b), as well as feedback from histopathologists. The pathologists in the Dutch Rectal Cancer Trial showed a patient's prognosis could be predicted by the quality of TME surgery as evaluated by the completeness of the mesorectal envelope (Nagtegaal et al, 2002a). The mesorectal grading system developed during the CR07 trial categorised planes as good (mesorectal plane), moderate (intramesorecal plane), and poor (muscularis propria plane). The MRC CR07 showed that surgery in the correct plane had lower recurrence with data from over 1000 patients reporting local recurrence rates of 4%, 7% and 13% for surgery in the mesorectal, intramesorecal and muscularis propria groups respectively (Quirke et al, 2009). The mesorectal plane and quality of TME is now a core data item in histopathological reporting of rectal cancer (Loughrey et al, 2017) and within other international guidelines (Glynne-Jones et al, 2017, Burgart, 2020).

In colon cancer, the "mesocolic plane" of the colonic mesentery has been defined as the equivalent of the mesorectal plane. This grading system was formalized during the Medical Research Council Conventional versus Laparoscopic Assisted Surgery In patients with Colorectal Cancer trial (CLASICC) (Guillou et al, 2005), based on the mesorectal grading system from CR07. The categories in this case included good (mesocolic), moderate (intramesocolic) and poor (muscularis propria). A fourth

category was also identified for mesocolic excisions with high vascular ties. Operating within the mesocolic plane requires dissection between the visceral peritoneum (covering the mesocolon) which should remain intact, and the parietal peritoneum (on the retroperitoneum).

After grading the plane of surgery in 399 colectomies, only 1/3 was performed in the mesocolic plane (West et al, 2008). When surgery was performed in the mesocolic plane, there was a significant survival advantage which persisted on multivariate analysis (HR 0.45, 95%CI 0.24-0.85) for stage III cancers (West et al, 2008). Mesocolic plane rate was found to be lower in left sided colectomies in a series of 209 colon cancer specimens (Munkedal et al, 2014). Surgery in the mesocolic plane was found to be more likely (92% vs 40%) with surgeons practising "complete mesocolic excision" than surgeons practising standard resections, although it remains unclear if some variation is due to the expertise of the operating surgeons and pathologists within specialized CME units. However, evaluation of plane of surgery can vary significantly, even between specialist gastrointestinal pathologists (Munkedal et al, 2016).

While TME has become the standard of care in surgery for rectal cancer, CME remains controversial with inconsistent results for lymph node yield, recurrence rates, and disease free survival, and no level I randomised evidence to date (Kontovounisios et al, 2015, Alhassan et al, 2019). The role of CME in sigmoid cancer is complicated by the fact that a high vascular ligation is commonly performed during surgery, as these tumours are often treated by anterior resection instead of sigmoid colectomy. A population based study from Sweden did not find any survival benefits to a higher ligation level despite a higher lymph node yield (Olofsson et al, 2018). A high tie will increase the number of lymph nodes resected, but in randomised trials (Fujii et al, 2018) or the most recent meta-analysis (Zeng and Su, 2018), no clear benefits to survival or recurrence have been demonstrated for rectal cancer.

Technical Performance of Surgery

High quality surgery will improve cancer outcomes. Clear resection margins and more recently specimen quality have been taken as a surrogate marker for the technical performance of surgery, and have been associated with oncological outcomes (Wibe et al, 2002b, Sebag-Montefiore et al, 2009, Quirke et al, 2009, Nagtegaal et al, 2002b). But a more direct assessment of high quality surgery comes from intra-operative technical assessment. Excellent or substandard performance has been demonstrated to affect outcomes. Analysis of 176 case videos of TME surgery from the prospective, multi-institutional ALACART trial by a blinded researcher found that a laparoscopic total mesorectal excision performance tool could measure intra-operative surgical performance with reliability and validity (Curtis et al, 2020). Better performed surgery was associated with optimal (mesorectal) fascial plane of surgery in specimens (93% vs 59%, $p = 0.002$) and lower 30-day morbidity (23% vs 50%, $p = 0.03$). Only medium-term oncological outcomes were available (median follow up 2.9 years), but surgeons in the upper vs lower quartiles of performance had fewer locoregional recurrences (0% vs 6.3%, $p = 0.18$) and better overall survival (96.6% vs 87.5%, $p= 0.2$). These differences were not statistically significant, which may be due to insufficient follow up or lack of power.

Another study (Stulberg et al, 2020) scored the technical skills of 17 surgeons by a single video of a right hemicolectomy, by 10 or more reviewers, and found that surgical technical performance correlated with clinical (rather than oncological) outcomes. There was a significant difference in rates of any complication (15.5% vs 20.6%, $p = 0.03$), unplanned reoperation (4.7% vs 7.2%, $p = 0.02$), and a composite measure of death or serious morbidity (15.9% vs 21.4%, $p = 0.02$).

These studies have demonstrated that intra-operative performance can affect short-term post-operative morbidity, and specimen quality. It is also possible that they may therefore affect longer term oncological outcomes, although this has not yet been assessed. Tools to assess intra-operative performance could be used for formative assessment during or after training, or summative

assessment for the purpose of credentialing. Further investigation into the applicability of these tools (e.g. the predictive validity of the laparoscopic total mesorectal excision performance tool) are required before its formal adoption (Curtis et al, 2020). Creating tools that are less time and resource intensive may also be necessary to encourage their broad uptake, particularly in a training setting.

Multivisceral or Exenterative Surgery for Colon Cancer

Locally advanced colorectal cancer is present in 10-20% of patients; 4-5% of patients will have locally invasive disease into surrounding structures, classified as T4b (Govindarajan et al, 2006, Landmann and Weiser, 2005).

Locally advanced rectal cancer that invaded into adjacent structures was historically considered incurable, with 5 year survival of less than 5% (Solum et al, 2004). However, by centralizing treatment at tertiary referral units with specialist expertise, there have been improvements in clinically significant morbidity (12-27%) and 30 day mortality (0%) and 3 year survival after R0 resection (Heriot et al, 2008, Chew et al, 2017, Pelvex Collaborative, 2019). This has likely arisen from better patient selection with imaging and multidisciplinary involvement, appropriate neoadjuvant treatment strategies and improved surgical techniques for pelvic exenteration and reconstruction.

In contrast, the staging and treatment of locally advanced colonic cancer has not evolved. The sigmoid is the most common colonic tumour site (46%) that requires multivisceral resection in some series (López-Cano et al, 2010). Local recurrence rates for colonic cancer are significantly higher when resections are not performed en-bloc (69% vs 28), resulting in lower overall survival rates at 5 years of 17% vs 49% (Gall et al, 1987, Hunter et al, 1987). Surveillance, Epidemiology, and End Results Program data confirmed a survival advantage when T4b colonic tumours were treated by multivisceral, en-bloc resections (HR 0.89, 0.83-0.96) (Govindarajan et al, 2006)).

Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

Strategies to prevent or treat peritoneal dissemination of colon cancer will improve colon cancer outcomes. Intra-peritoneal spread may occur as a result of tumour cell "exfoliation" after invasion through the bowel wall, or iatrogenically at the time of surgery from lymphatics, blood vessels or even the tumour itself. Peritoneal carcinomatosis is found at the time of primary surgery (Jayne et al, 2002, Koppe et al, 2006) in 8%, and after surgery in 4-19% of patients (Koppe et al, 2006).

Traditionally, peritoneal carcinomatosis was viewed as incurable metastatic disease, and supported with palliative treatment options as survival was limited to 7 months if untreated (Arjona-Sánchez et al, 2014, Sadeghi et al, 2000). With palliative chemotherapy, the median survival extends only to 5-15 months (Jayne et al, 2002, Lemmens et al, 2011) although survival was improved to 23.9 months in more recent studies using FOLFOX i.e. folinic acid, fluorouracil and oxaliplatin (Elias et al, 2009). Quality of life with peritoneal metastases is often very poor as a result of bowel obstruction and ascites.

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) have been used to treat peritoneal carcinomatosis. Median survival with CRS and HIPEC is 32-65 months (Elias et al, 2009, Franko et al, 2010, Mahteme et al, 2004), and found to be significantly better than chemotherapy alone on meta-analysis (Mirnezami et al, 2014). Despite considerable morbidity (23 to 44%) and mortality rates (0-12%), cytoreductive surgery and HIPEC is associated with improved survival for patients with peritoneal carcinomatosis versus palliative or systemic chemotherapy treatment options.

Preventive approaches to peritoneal metastases can be divided into two strategies. The first is a pre-operative approach based on imaging, with cytoreductive surgery and HIPEC performed at the time of primary tumour resection. The alternative is an adjuvant approach based on pT4 disease on histology, where patients are administered HIPEC with or without cytoreductive surgery in the immediate or delayed post-operative period, or at a planned relook one year later.

The evidence for an adjuvant approach was most convincingly built up in early studies before 2000, but not replicated in contemporary studies. Three phase III trials demonstrated significantly improved 5 year overall survival (62% vs 41%) after administration of intra-peritoneal chemotherapy to 286 patients on meta-analysis (De Bree et al, 2002). More recent studies of adjuvant and second-look approaches have not reported the same benefits. The COLOPEC trial offered post-operative adjuvant HIPEC therapy by laparoscopy without cytoreductive surgery, for high risk tumours based on pT4 stage (Klaver et al, 2019b). There was no significant difference in peritoneal carcinomatosis, but the optimum patient selection criteria, timing of HIPEC, mode of delivery and efficacy of HIPEC remain unknown. The ProphyloChip study randomised 150 high risk patients (minimal peritoneal disease resected with the primary, history of ovarian metastases or perforated primary tumour) to surveillance or relook with cytoreductive surgery and HIPEC (Goere et al, 2018). Peritoneal disease was diagnosed in 52% of patients undergoing relook laparotomy, but again there was no significant difference in disease free survival or overall survival at 3 years in the surveillance vs second look groups respectively.

These most recent studies suggest that adjuvant treatment with HIPEC may fail to improve survival. Surgery may be technically difficult due to adhesions, which may lead to unequal distribution of HIPEC within cavity (Arjona-Sanchez et al, 2018), especially with the laparoscopic approach in the COLOPEC trial which would also preclude effective cytoreductive surgery. While some clinicians have suggested that an oxaliplatin-based HIPEC regime may be ineffective, it may also simply be true that HIPEC does not have a significant therapeutic effect on peritoneal carcinomatosis as suggested by abstract of the PRODIGE-7 trial (Quenet et al, 2018). Prediction of peritoneal relapse using pathology specimens also precludes the possibility of intra-operative therapy. At the time of post-operative treatment, residual microscopic disease may be encased by fibrin and more resistant to treatment.

A prophylactic approach may therefore hold promise, but at present, there is no evidence for a pre-operative treatment strategy. This approach is currently under investigation in the Italian

Promenade trial and the Spanish HIPECt4 study on the basis of advanced tumour stage on imaging (Sammartino et al, 2016, Arjona-Sanchez et al, 2018).

Adjuvant therapy

Adjuvant chemotherapy for colon cancer

Adjuvant chemotherapy is used after surgery for colon cancer to reduce the risk of disease recurrence. The survival benefits of adjuvant chemotherapy in stage III colon cancer was demonstrated first in 1990. A pooled analysis of 20 800 patients from carboplatin and fluorouracil (FU)-based adjuvant treatment studies in colon cancer reported that 80% of colonic cancer recurrence was seen within the first three years (Sargent et al, 2009). Chemotherapy conferred a significant reduction (HR 0.61) in recurrence only in the first two years after surgery; this possibly conferred a survival benefit that resulted in 10% improvement in eight year overall survival in stage III patients (Sargent et al, 2009).

Adjuvant fluorouracil (5FU) chemotherapy is indicated for fit patients with stage III (i.e. nodal disease on pathology specimen) colonic cancer in international guidelines (Table 1-11). The addition of oxaliplatin to fluoropyrimidine chemotherapy reduces recurrence risk further in stage III patients (André et al, 2004, Kuebler et al, 2007, Haller et al, 2011). Additional toxicity (principally neutropenia and paraesthesia) in the oxaliplatin treatment groups led to more treatment discontinuation.

However, pooled RCT data of 12 834 patients in the International Duration Evaluation of Adjuvant Therapy collaboration, (Grothey et al, 2018)) demonstrated reduced toxicity (particularly to sensory neuropathy) and improved quality of life with abbreviated three month (rather than six month) oxaliplatin-based CAPOX (capecitabine and oxaliplatin) regime, whilst maintaining an equivalent three year disease free survival (83.1% vs 83.3%) for lower risk groups (not T4 or N2 disease). Oral

forms of fluorouracil such as capecitabine have been shown to be as effective as intravenous administration with fewer adverse events (Twelves et al, 2005), and are approved by NICE.

	Stage II	Stage III
NICE (NICE, 2020**)**	Consider in high risk	Recommend capecitabine + oxaliplatin for 3 months or oxalitplatin + 5-FU and folinic acid (FOLFOX) for 3 to 6 months or single-agent fluoropyrimidine (e.g. capecitabine) for 6 months
SIGN (SIGN, 2016**)**	Consider in high risk	Recommend 5FU +/- oxaliplatin. Oxaliplatin based regime if higher risk and fit.
ASCO (Costas-Chavarri et al, 2019**)**	Consider in high risk	Recommend
ESMO (Labianca et al, 2013a**)**	Consider in high risk	Recommend 5FU + oxaliplatin

Table 1-11: Guidelines and indications for chemotherapy
Note. NICE: National Institute for Health and Care Excellence. SIGN: Scottish Intercollegiate Guideline Network. ASCO: American Society of Clinical Oncology. ESMO: European Society for Medical Oncology. 5FU= 5-fluorouracil.

Chemotherapy is not currently recommended for patients with stage II colon cancer (NICE, 2011a), and is only offered after discussion in patients meeting high risk criteria (Table 1-12). Trials of adjuvant chemotherapy in stage II cancer have failed to conclusively demonstrate a significant benefit to disease free survival or overall survival (Figueredo et al, 2004, Gill et al, 2004, 1999, Andre et al, 2009, Kannarkatt et al, 2017). However, the evidence on this topic is mainly limited to non-systematic pooling of trial data and case series, with only one randomized controlled trial (O'Connell et al, 1997). Within these trials, patients with high risk features including EMVI or TDs, have not have been consistently identified by pathologists. It is therefore unclear which patients with high risk stage II disease may benefit from chemotherapy.

	Shared indications	Guideline-specific
NICE (NICE, 2011a)	pT4 Poorly differentiated Perforation	MSI, tumour budding
ASCO (Benson, 2005, Costas-Chavarri et al, 2019)		MSI, MMR proficient
ESMO (Labianca et al, 2013b)		Obstruction

	Lymphovascular invasion
ACPGBI (Gollins et al, 2017)	Perineural invasion
	LN <12-13

Table 1-12: Indications for chemotherapy in Stage II patients

Note. NICE: National Institute for Health and Care Excellence. ASCO: American Society of Clinical Oncology. ESMO: European Society for Medical Oncology. ACPGBI: Association of Coloproctologists of Great Britain and Ireland.

Summary of treatment options for colon cancer

Personalised colorectal cancer treatment is based on the numerous anatomical and non-anatomical risk factors captured by the staging process. In rectal cancer, personalised care has resulted from innovations in image-guided treatment, neoadjuvant treatment, surgical technique and pathological feedback. Unfortunately, these same innovations have not occurred in colon cancer. While CT staging holds promise, the use of TNM-based systems do not hold prognostic information, and the reliability and diagnostic accuracy of T3 substaging varies. Neoadjuvant chemotherapy did not improve outcomes in the FOxTROT study, and neoadjuvant radiotherapy has not been adequately investigated. The standard surgical technique remains colectomy; the benefits of CME are only reported in retrospective studies, and adjuvant or second look HIPEC failed to improve outcomes in randomised studies. Finally, pathological feedback with regards to margin status is established in colon cancer, but the circumferential resection margin is less well studied in colon cancer, and mesocolic plane of surgery is not commonly audited and requires further investigation.

The situation may therefore appear somewhat bleak for colon cancer. But there are knowledge gaps that may yield new therapeutic targets. A reliable and prognostic system of CT staging for colon cancer needs to be established to identify high risk patients. Neoadjuvant chemotherapy may improve outcomes if given to appropriately selected patients. CRS and HIPEC may improve outcomes if performed at the time of primary tumour resection. Surgery itself for colon cancer may be improved; by intra-operative assessment to improve technique, and by feedback from the MDT

about the plane of surgery in resected specimens. Complete mesocolic excision may yet be found to be an appropriate surgical option for selected advanced colonic tumours.

Sigmoid colon cancer may not seem to be the logical site of colonic cancer to study first. Unlike rectal cancer, sigmoid colon cancer is commonly seen as the “easy” left sided cancer to remove with clear margins. A tumour situated at the apex of a long mesenteric loop is technically and oncologically more straight-forward to treat with surgery. Access to an extra-pelvic sigmoid tumour and its draining mesentery is less challenging than a distal sigmoid tumour within the pelvis, and certainly less than a bulky rectal tumour low down within a narrow pelvis. It is technically not possible for the mesenteric extension of the tumour to cause a positive margin by reaching the retroperitoneum. Generous longitudinal margins can often be achieved without the need for splenic flexure or mesorectal excision.

Yet, on a preliminary literature review, oncological outcomes for sigmoid cancer are unclear, and local recurrence rates may be unexpectedly high. Some of the strategies from rectal cancer may also be applied to it’s nearest colonic neighbor;, unlike other sites of colon cancer, sigmoid cancers are possible targets for neoadjuvant radiotherapy, based on pre-operative imaging. Mesorectal excision may also be necessary for distal sigmoid tumours extending into the rectum. Complete mesocolic excision may be appropriate for locally advanced sigmoid tumours, and exenterative surgery may also be necessary for locally invasive pelvic sigmoid cancer.

Research into these strategies is required to create an evidence base for personalized treatment of sigmoid colon cancer. But more fundamentally, controversy still surrounds the means by which a rectal cancer is distinguished from a sigmoid cancer. This single, seemingly uncomplicated variable is the basis directing patients along very different treatment pathways, in particular with regards to eligibility for neoadjuvant therapy. Before sigmoid colon cancer outcomes can be investigated, the question that must first be addressed is where does the sigmoid end and the rectum begin?

Personalised Cancer Treatment: is the tumour in the sigmoid or rectum?

Anatomy & Embryology: Importance of the Mesentery

Elucidating the anatomy of the large bowel and in particular the transition between the rectum and sigmoid, requires embryology to be revisited. Particular attention to mesenteric development may also establish an anatomical basis for oncological resection of colonic cancer.

Embryology of the Sigmoid

During the intestinal rotation in the body stalk in the 5th week of life in utero, the small and large bowel are suspended outside of the abdominal cavity on a mesentery attached to the posterior abdominal wall. On their return to the abdomen on the 10th week, the mesentery of the descending and ascending colon fuse with the parietal peritoneum on the posterior abdominal wall, anchoring them to the retroperitoneum. The sigmoid retains its free mesentery, as does the transverse colon becomes attached to the greater omentum.

There is no embryological basis to differentiate the sigmoid from the upper rectum, as both are derived from the hindgut. They are supplied by sigmoid and superior rectal arteries branches of the inferior mesenteric artery, and drained by the sigmoid and superior rectal branches of the inferior mesenteric vein.

Embryology of the Sigmoid Mesentery

During the presentation of his cadaveric case series to the Royal College of Surgeons, Hunterian Professor Sir Frederick Treves suggested that the right and left mesocolon were frequently absent in

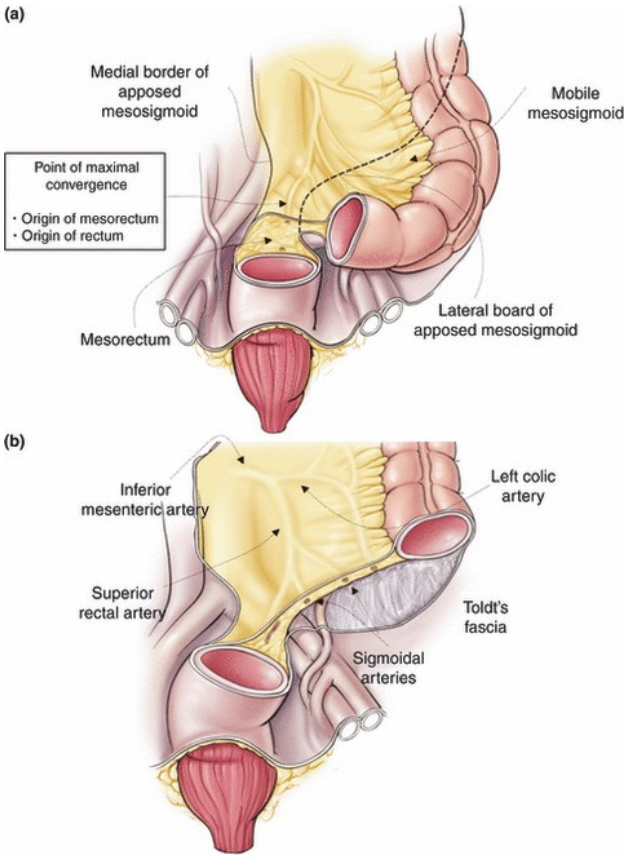
up to 76% of patients (Treves, 1892). He posited this was a result of “obliteration” through a process of “fusion” with the retroperitoneum (Culligan et al, 2012). This anatomical conception of the mesentery took hold, and is commonly documented in anatomical textbooks (Moore et al, 2013, Drake et al, 2009).

Despite the acceptance of the concept of an obliterated mesentery in anatomy textbooks, the teachings of Carl Toldt form the anatomical basis of colectomy in surgical practice. Toldt suggested that rather than disappearing, the mesentery of the right and left colon persist in apposition to the retroperitoneum. Toldt described the mesentery in separation from the posterior abdominal wall by a connective tissue plane (Congdon et al, 1942), later named by Goligher as “Toldt’s fascia”. When Congdon revisited the concept of Toldt’s fascia, he “incises between the fascia of fusion [Toldt’s fascia] and the lamina mesenteriae propria [mesentery] to avoid injury to the vessels and nerves which abound in the lamina.” (Congdon et al, 1942). Mobilisation of the ascending and descending colon from the retroperitoneum requires dissection in this plane.

Professor John Coffey and his group in Limerick have published extensively on mesenteric anatomy, based on the principles of Toldt. A prospective anatomical study of the mesentery in 107 patients undergoing resection by Culligan et al demonstrated a continuous mesocolon from the ileocaecal to rectosigmoid junctions in patients undergoing total colectomy (Culligan et al, 2012). The group went on to suggest that the mesentery in fact remains contiguous from the duodenum to the rectum, and is separated from the retroperitoneum by a continuous fascial layer (Coffey and O'Leary, 2016). Similar findings were demonstrated by this group in a cadaveric study, which found the persistence of the posterior mesocolic lining of mesothelium using electron microscopy (Culligan et al, 2014). This finding was previously found in another anatomical and histopathological study of cadavers and bowel specimens (Gao et al, 2013), which illustrated the fascial composition of loose connective tissue and dissection planes with microscopy.

A Sigmoid Mesenteric Waist Identifies the Rectosigmoid Junction?

Dissection in the mesenteric-based planes during resection of the intestine has been described in rectal cancer with TME (Heald and Ryall, 1986), and more recently in colon cancer in complete mesocolic excision (Hohenberger et al, 2009). Along the mesentery, there are points where dissection may be technically challenging and hazardous. This was previously found to be the case in the low rectum where involvement of the circumferential resection margin was common at the insertion of the levators and puborectalis, due to the paucity of surrounding mesenteric tissue (Salerno et al, 2008, Shihab et al, 2010) .



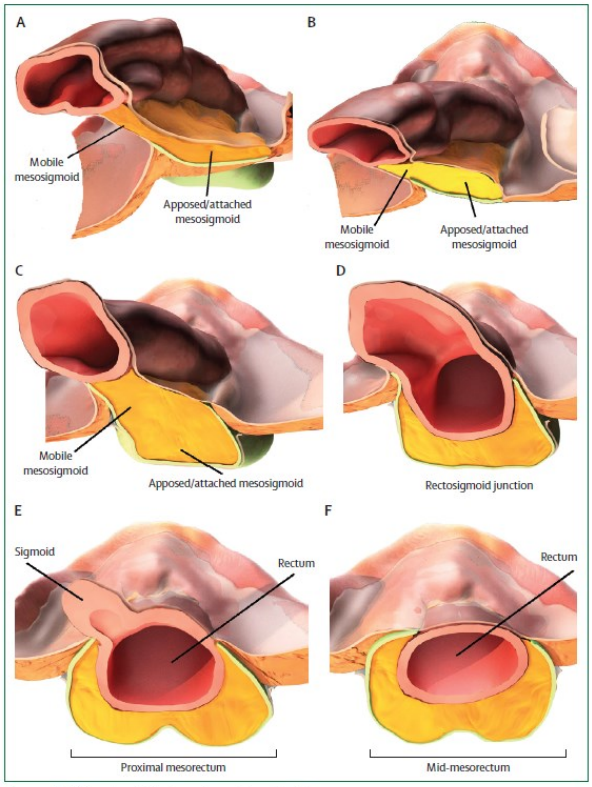


***Figure 4*: Axial (craniocaudal) views of mesosigmoid and mesorectum**
(A) Upper mesosigmoidal, (B) mid-sigmoidal, (C) distal mesosigmoidal, (D) rectosigmoidal, (E) proximal, and (F) mid-mesorectal levels.

Figure 1-5: Sigmoid mesocolon in continuity with mesorectum
Note. Left: (Culligan et al, 2012), *image reproduced with permission of the rights holder, John Wiley and Sons.* Right: (Coffey and O'Leary, 2016), *image reproduced with permission of the rights holder, Elsevier. See permissions table, page 212.*

Coffey's group demonstrated the continuity of the sigmoid mesocolon with the left mesocolon proximally, and the mesorectum distally (Figure 1-5) in a study of 134 resected bowel specimens (Culligan et al, 2012). This study reported that the mesosigmoid tapered distally, and converged maximally at the pelvic brim, at which point the apposed component of the mesosigmoid is shortest in transverse diameter, deemed the "point of greatest proximity" (Culligan et al, 2012). After this point, they found the mesentery widens to become the mesorectum, and that this level corresponded with the coalescence of the taenia coli (Figure 1-5).

A preliminary audit of abdominoperineal excision specimens by Quirke et al also found is a narrowing in the cross-sectional surface area in the sigmoid mesentery at the pelvic brim (Figure 1-6).

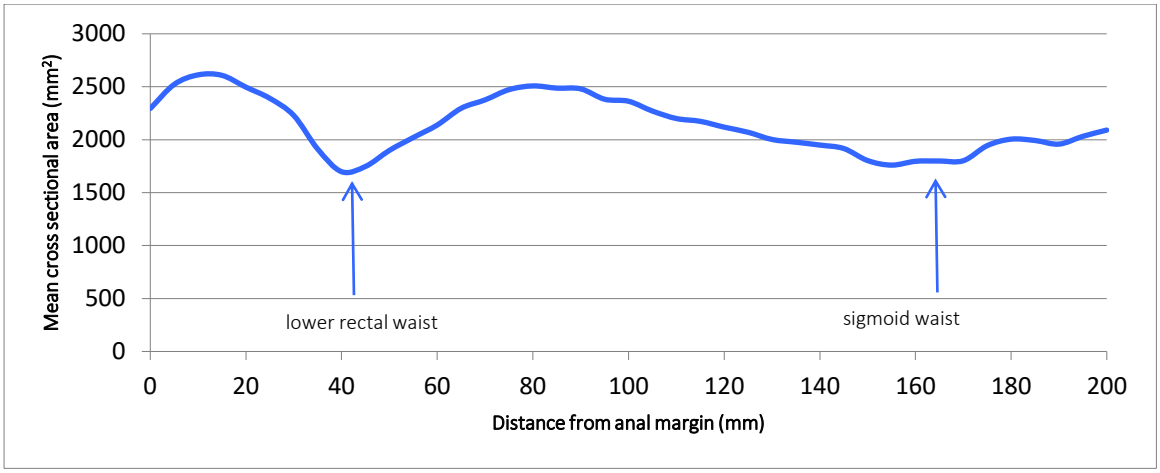


Figure 1-6: Graph of mesenteric surface area demonstrating sigmoid waist
Note. Unpublished data from Philip Quirke and Nicholas P West, reproduced with permission.

This finding suggests that the "point of the greatest proximity" occurs at a waist or narrowing in the sigmoid mesentery at the pelvic brim. The oncological implications of a tapering sigmoid meso-colon may be similar to the low rectal waist. The concept of the low rectal waist was established after an anatomical study (Salerno et al, 2008) into the high positive margin rates during abdomino-perineal excision (Eriksen et al, 2004). Salerno et al demonstrated the presence of a low rectal mesenteric "waist", i.e. narrowing of the surface area, present at the level of puborectalis, where the

mesorectum converges after tapering down from the edge of the levators. This provided an anatomical explanation for the increased risk of positive margins and tumour/bowel perforations from tumour resections at this level. If a sigmoid waist is present, it may be a cause of higher local recurrence rates. The U-shaped sigmoid mesocolon is frequently long at is apex, and consequently most surgeons are unconcerned about a positive resection margin for tumours at this point. However, if the sigmoid mesentery narrows sufficiently, it may be a source of margin involvement as for the low rectal waist.

Quirke's data suggests the waist occurs at 16cm, in the sigmoid mesentery, while Coffey's group believed that the mesenteric waist was at the recto-sigmoid junction. Further investigation into the anatomical dimensions of the mesentery of the rectum and sigmoid may distinguish one from the other and enable an anatomical definition of the rectum.

The Rectosigmoid Problem

A clear and standardised definition of the start of the rectum has not yet been established. Previous definitions were employed based on the modalities available at the time. The third sacral segment was the traditional landmark used by anatomists: this was probably seen in relation to the coalescence of the taenia coli. The most common anatomical definition using a colonic landmark is the coalescence of the taenia coli, accompanied by the cessation of the appendices epiploicae. While this may be appreciated intra-operatively, this landmark is not visible to the endoscopist or the radiologist pre-operatively. Metric measurements came into practice when endoscopic visualisation of tumours became possible, but before cross-sectional imaging was available. Thus, in current practice most colorectal teams resort to a definition using arbitrary measurements from the anal verge.

In national guidelines and research studies, endoscopic measurements have been preferred to anatomically driven definitions. The evidence for specific metric measurements is unclear, although

at least one definition (12cm) was based on patterns of recurrence (Nelson et al, 2001), although the data informing this decision was mostly from retrospective single centre studies. Practising colorectal surgeons have shown variation in their definition of the proximal border of the rectum; a survey of 120 surgeons found that 35% used the anterior peritoneal reflection as the landmark, while another 30% used the distance from the anal verge (McMullen et al, 2005).

Distinguishing the sigmoid colon from the rectum is important in planning pre-operative staging techniques, neo-adjuvant treatment strategies and surgical approaches which differ substantially between sigmoid cancer and rectal cancer. If a rectal tumour has been misclassified as a sigmoid tumour, the patient will have been inadequately staged, and not been considered for pre-operative downstaging (chemo)radiation, potentially decreasing their chance of a complete resection and worse survival. Misclassification is inevitable, not just because of variation in the length of the rectum, but because studies of radiotherapy in upper rectal cancer (Table 1-10) used different measurements to define the rectum. At the time of surgery, surgeons may be surprised to find that a tumour classified as “sigmoid” (>12/15cm) may be a rectal cancer (Piscatelli et al, 2005). This may result in a sub-optimal operation if performed by a non-specialist rectal surgeon. If the decision is made on-table to proceed with an anterior resection instead of a sigmoid colectomy, the patient will not be counselled for the different functional outcomes and higher anastomotic leak rate.

Now that the rectosigmoid junction has been recognised as a distinct segment of colon (ICD-O; C-19) by the International Classification of Diseases, further heterogeneity in management and outcomes could result, to the detriment of patients and research. A population study from the United States of rectosigmoid tumours reported that neoadjuvant chemoradiation reduced CRM positivity from 11% to 8% (p=0.01) and improved 5 year overall survival from 72 to 77% (HR 0.79, 95% CI 0.69-0.90) compared with upfront surgery (Venigalla et al, 2018). Other single-centre series have reported recurrence rates with tumours of the upper rectum, using measurements of 10 or 12cm from the

anal verge, that are lower (Lopez-Kostner et al, 1998), or similar (Rosenberg et al, 2010) to tumours of the mid-rectum. Another single centre study reported that stage III rectosigmoid cancers had similar outcomes to rectal cancer (Park et al, 2008). But optimal management of rectosigmoid tumours remains unclear because of variation in its definition. Databases such as Surveillance, Epidemiology, and End Results Program may use their own definition of rectosigmoid tumours as "10-15cm from the anal verge" (NIH, 2017), or rely on local criteria from the hundreds of local hospitals that contribute data.

As a consequence of important advances in diagnostic and staging techniques over the past decades and the emergence of neoadjuvant therapeutic options, it is timely to focus on an updated and uniform definition of the rectum.

Chapter 2

Hypotheses

Hypotheses

Aims

The aim of this research was to investigate whether imaging could improve outcomes from sigmoid colon cancer; by optimising pre-operative staging, but also by consistently distinguishing the rectum from the sigmoid.

Hypotheses

1. Sigmoid colon cancer outcomes are unknown, but could be improved by pre-operative staging with imaging (objectives 1, 7, 8).
2. An imaging based definition of the rectum is necessary to accurately distinguish the sigmoid and rectal cancers (objectives 2-6).

Objectives

1. Investigate outcomes of sigmoid cancer in the literature by meta-analysis (Chapter 4).
2. Conduct a literature search and evidence synthesis on definitions of the rectum (Chapter 5).
3. Investigate the validity of current definitions using in-vivo patient anatomy on radiology (Chapter 6).
4. Establish an international consensus definition of the rectum (Chapter 7).
5. Characterise the anatomy of the mesentery at the rectosigmoid junction to investigate the presence of a sigmoid mesenteric waist (Chapter 8).
6. Validate an imaging definition of the rectum using specimen anatomy (Chapter 9).
7. Investigate contemporary rates and risk factors for local recurrence of sigmoid cancer (Chapter 10).
8. Analyse CT staging systems for colon cancer (Chapter 11).

Chapter 3

Methods & Materials

Methods

This chapter outlines the methods used for the studies I conducted that involved identifiable patient data. Methodology specific to other studies is described within the relevant chapter.

Staging of Sigmoid Cancer

Inclusion and Exclusion Criteria

Patients with sigmoid colon cancer were identified from a prospective record of colorectal cancer multi-disciplinary team (MDT) meetings at the Royal Marsden Hospital. This included all patients with colorectal cancer referred from Epsom & St Heliers (52%), as well as patients with advanced malignancy from Croydon University Hospital (27%). Further referrals of patients with advanced malignancy are taken from a local network of Kingston Hospital, St George's Hospital, and Chelsea & Westminster (10%). The Royal Marsden also receives tertiary national and international referrals (11%) of patients with advanced pelvic malignancy, and referrals specifically for adjuvant treatment for patients that had already undergone surgery at the local centre.

Treatment plans were individualised after MDT discussion. The study start date was set at January 2006, when modern, high resolution, multi-detector CT scanners became commonplace. The study end date was January 2015, so patients had at least 3 years of follow up data, commencing from the date of surgery. Surgical technique and peri-operative management were not standardised across institutions, although follow up for all included English National Health Service patients was performed at the Royal Marsden and was standardised as per the National Institute for Health and Care Excellence guidelines for colorectal cancer (NICE, 2011b). The study met Reporting Recommendations for Tumour Marker Prognostic Studies (REMARK) (Altman et al, 2012).

Patients were included for analysis if they had non-metastatic adenocarcinoma arising in the sigmoid colon on CT scan, and underwent colonic resection. The distal landmark of the mesorectal-mesocolic

junction on imaging was used as the distal landmark to distinguish sigmoid from rectal tumours. The proximal sigmoid-descending colon junction was appreciated by the cranial transition from the sigmoid hanging ventrally or medially, to its fixed lateral and retroperitoneal position. There were 780 patients with sigmoid cancers discussed in the MDT over this period.

Exclusion criteria included metastatic disease at presentation (20.6%), disease that was later found not to be colorectal cancer (8.7%), early tumours removed with endoscopic treatment only (3.3%), or synchronous tumours (1.9%). Patients that were managed palliatively without resection of their primary tumour (8.7%), and patients that died within 30 days of surgery (0.9%) were also excluded. If no follow up data was available for international or national patients that returned to their referral hospital after surgery, they were excluded (4.0%). In total, 414 out of the 780 patients with sigmoid tumour (53.1%) were included in the study (Figure 3-1).

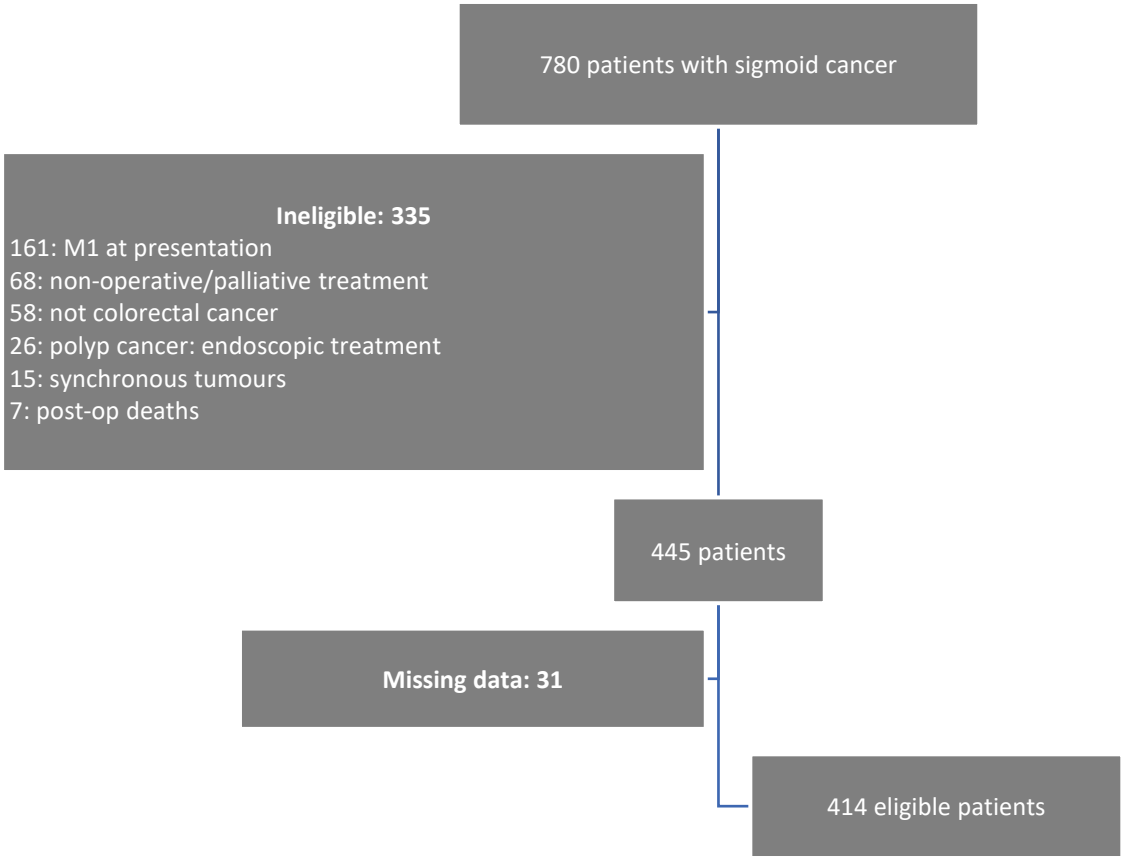


Figure 3-1: Study flowchart

Ethical Approval

Local ethical approval was obtained from the Royal Marsden Committee for Clinical Research (SE636). The need for participant informed consent for retrospective analysis was waived by the committee.

CT Technique

CT scans were performed at a number of National Health Service and international institutions, on multidetector CT scanners from a range of manufacturers. Standard CT abdomen-pelvis protocols with 1mm slice intervals were employed in nearly all cases. During standard staging CT scans within the local referral network, patients were kept nil by mouth for at least 2-4 hours prior to examination, and given oral contrast prior to CT scan. Rectal enemas were rarely administered. Intravenous iodine-based contrast is standardly administered. Images from United Kingdom trusts are reconstructed at 1-3 mm slice thickness, and undergo multiplanar reconstruction; this was not possible in fewer than 10% of cases. External CT data varied significantly in slice thickness, use of contrast, and image reconstruction. Data on CT reports from the local hospital were extracted when reported by specialist gastrointestinal radiologists on standardised CT reporting proformas for colon cancer developed by the Royal College of Radiologists (Patel et al, 2018). They were otherwise re-reported by two specialist gastrointestinal radiologists with more than five years of experience while blinded to the clinical information. Identification on CT of features of advanced colonic disease required multiplanar reconstruction on CT multidetector scanners.

Data Items

Data was extracted on basic demographics such as age, sex, emergency presentation, and pre or post-operative treatment (i.e. radiotherapy or chemotherapy). CT data was recorded on T stage (including T3 sub-staging by depth of spread), nodal disease, discontinuous tumour deposits (TDs),

extra-mural vascular invasion (EMVI) and peritoneal infiltration localised to the tumour site (i.e. not disseminated).

Local tumour stage

Endoscopically detected tumours that were not visible on CT were classified as T1 tumours.

Tumours confined to the bowel wall were classified as T2 tumours.

Lesions were classified as T3 on CT when tumour extended through the muscularis propria with a broad-based bulging or nodular configuration in continuity (Figure 3-2). T3 substage was measured in millimetres beyond the muscularis propria and classified as T3a (less than 1mm), T3b (1-5mm), T3c (5-15mm) and T3d (over 15mm), as per TNM guidelines for colorectal cancer (Edge and Compton, 2010). Tumour spread beyond the muscularis propria can be measured on multi-planar reconstruction of the tumour (Rollvén et al, 2013, Dighe et al, 2012b, Hunter et al, Smith et al, 2007).

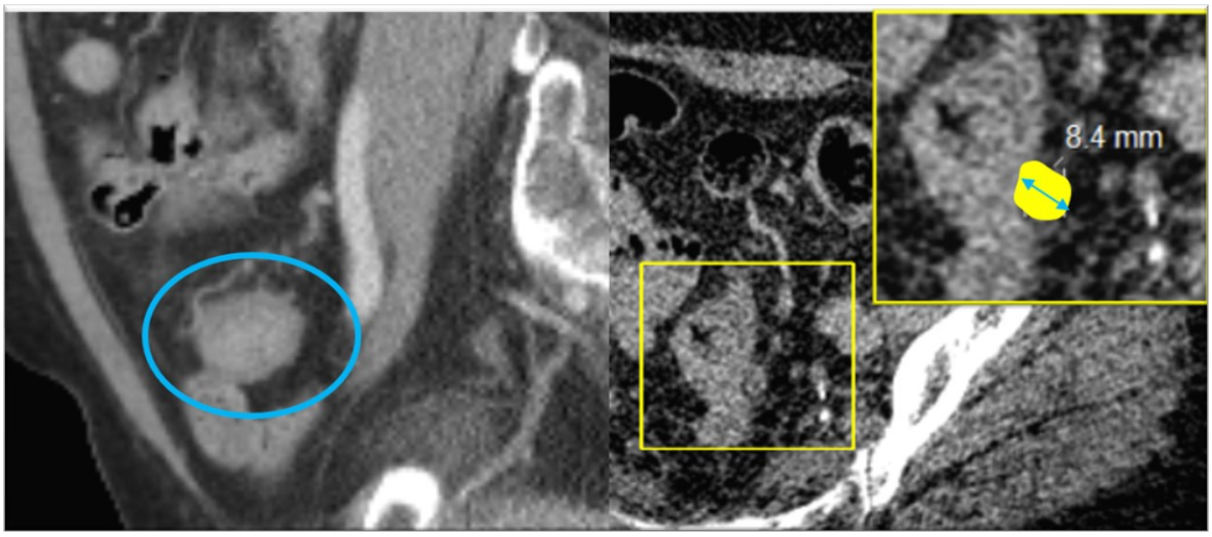


Figure 3-2: T3 Substaging on CT
Note. Left: early T3a lesion (<5mm extension beyond muscularis propria). Right: advanced T3c lesion (>5mm extension beyond muscularis propria).

T4a disease was recognised on CT when the anti-mesenteric border demonstrated infiltration of over 5mm through the muscularis propria. T4b disease was seen when tumour infiltrated adjacent organs.

Lymph node involvement

Lymph nodes were deemed to be involved by cancer if they measured more than 5mm on short axis diameter. N1 disease was present if 1-3 nodes were enlarged, and N2 disease was present if more than 4 nodes were involved.

Extra-mural venous invasion (EMVI)

EMVI was detected when tumour directly invaded veins beyond the muscularis propria (Dighe et al, 2012b, Hunter et al). On CT, the draining colonic veins can be identified as tubular structures in continuity on adjacent slices on multiplanar reconstruction. Linear or serpiginous extension of the primary tumour into the peri-colonic veins can be seen, as the tumour infiltrates and expand the vessel, creating an irregular contour (Figure 3-3). As this can be a subtle finding in smaller veins, it is likely only larger-vessel EMVI is detected on CT.

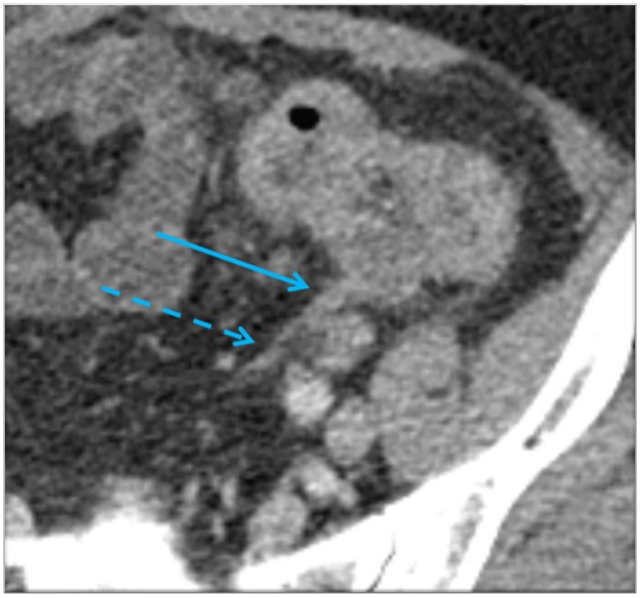


Figure 3-3: Extramural venous invasion (EMVI) on CT

Discontinuous tumour deposits (TDs)

TDs are deposits of cancer cells that are discontinuous with the primary tumour and not associated with a lymph node. They can be distinguished from smoothly enlarged round lymph nodes on CT, as they are more likely to have an irregular contour and mixed signal density. While both TDs and lymph nodes may appear to have an irregular contour, TDs will interrupt the course of a vein (best seen on multiplanar reconstruction, while lymph nodes will lie alongside a vein (Figure 3-4).

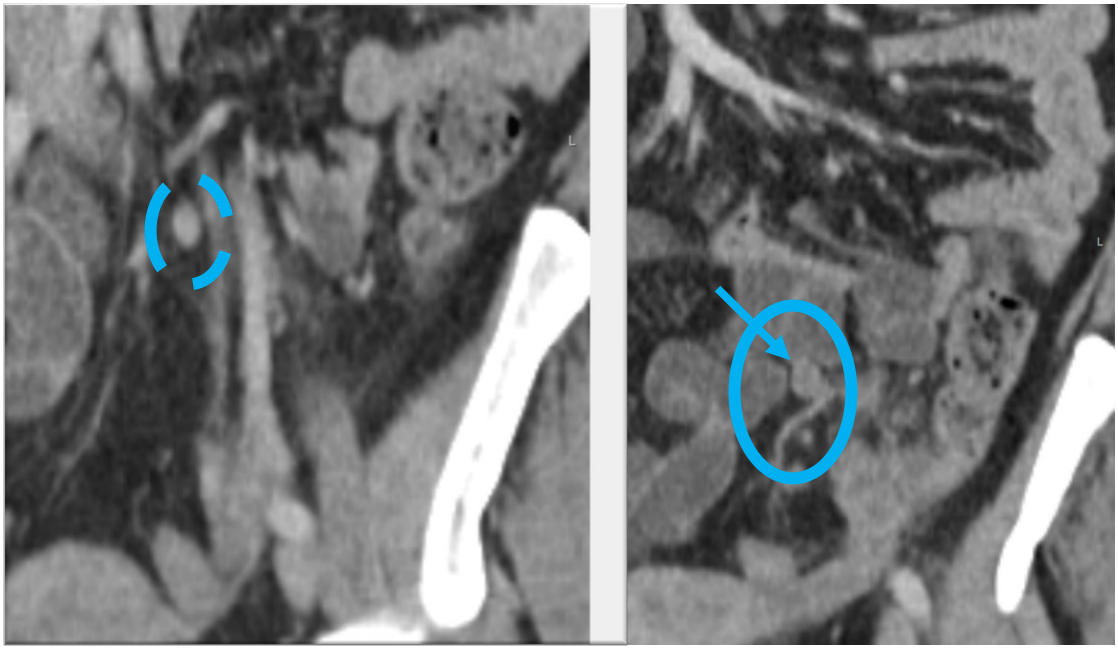


Figure 3-4: Lymph node vs tumour deposit on CT
Note. Left: round nodule, possible lymph node. Right: nodule interrupting course of draining vein, likely tumour deposit.

Pathological variables of T stage, nodal disease, tumour deposits, differentiation grade, extra-mural vascular, peritoneal disease and circumferential resection margin status were recorded on the standard dataset issued by the Royal College of Pathologists and extracted (Loughrey et al, 2014). Data was extracted on recurrence and death from clinical notes. Recurrence site was confirmed on imaging, and re-classified as local recurrence (LR) or distant recurrence (DR).

All included patients had complete data for radiological staging. Local institutions were contacted to seek missing data, particularly on patient follow up. Missing data for pathological variables was quantified. Patients lost to follow up had their duration of follow up quantified as the period between the date of surgery and date of the last clinic appointment or scan.

Outcomes

Disease Recurrence

Data on post-operative cancer recurrence at follow up was recorded and analysed, including the anatomical location of the recurrence. Disease recurrence was based on CT findings suggestive of disease relapse, with MDT confirmation even if biopsy confirmation was not performed eg in the palliative setting.

Local Recurrence

Local or locoregional recurrence was classified as any intra-abdominal tumour regrowth outside of the liver as confirmed by biopsy or clinical suspicion on imaging. While there has been increasing interest in locally recurrent rectal cancer, there is limited data or practice guidelines on locally recurrent colon cancer (Brown and Koh, 2020). Studies of locoregional recurrence of colon cancer have used different definitions, where some studies only include intraluminal anastomotic recurrences (Obrand and Gordon, 1997), and other studies exclude peritoneal or retroperitoneal recurrence (Sjövall et al, 2007). A classification system for locoregional recurrence of colon cancer that has been used by advanced colorectal malignancy groups from the Netherlands, Australia and the United States (Elferink et al, 2012, Brown and Koh, 2020, Liska et al, 2016) was followed:

1) Peri-anastomotic: In the immediate vicinity of the primary anastomosis
2) Peritoneal: Away from the primary tumour site but within the peritoneum
3) Retro-peritoneal: Posterior to the peritoneal cavity extending up to the pre-aortic region
4) Pre-sacral: Anterior to the Sacrum

5) Mesenteric: Within the sigmoid mesentery along draining venous vasculature

Distant Recurrence

Distant recurrence was classified by site if solitary eg liver, lung, nodal, otherwise as oligometastatic disease.

Death

Death was recorded from hospital notes or practitioner letters. If a cause of death was recorded, it was noted. Deaths were ascribed to cancer if disease recurrence had been reported.

The date of last follow up was noted from the last entry in the patient's hospital notes; this included the patient's last attendance in the colorectal clinic, but also extended to any clinic appointment, letter from general practitioner, or investigation including blood tests or imaging.

Statistical Analysis

Statistical analysis was planned by medical statisticians within the Royal Marsden Hospital, and conducted under their supervision. No sample size calculation was performed; this was determined by the number of patients meeting the inclusion criteria. Frequency tables were compiled of all prognostic variables and outcomes. Continuous variables were compared using a two-tailed T-test. Median survival was compared using the Wilcoxon rank-sum test. Categorical variables were compared using Fisher's exact test. Statistical significance was set as $p<0.05$ in 2-tailed tests. Clinically relevant covariates were chosen *a priori* to test higher order interaction. Age was recategorized (<55, 55-70, 70-85, >85) based on clinically relevant infection points for survival. Model building employed backwards stepwise selection ($p<0.2$) with sequential elimination of nonsignificant predictor variables ($p>0.05$), and likelihood ratios to test variable inclusion/exclusion decisions. Kaplan-Meier survival plots were calculated for recurrence free survival. Cox multi-regression analysis was used to derive univariate and multivariate hazard ratios for recurrence from

pre-operative variables. Survival analysis was defined for recurrence free survival as time to event in months from date of surgery to date of local recurrence, distant recurrence, or death from colorectal cancer. Observations were censored at the date of last follow up or date of death as a result of non-colorectal cancer. For local or distant recurrence, time to recurrence was measured from the date of surgery to date of recurrence; patients with no recurrence were censored at the date of last follow up or death. Statistical analysis was performed on STATA version 13 (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC).

Radiological & Specimen Analysis of the Sigmoid Mesentery

Inclusion and Exclusion Criteria

Eligible patients were prospectively identified during the colorectal cancer multidisciplinary team meeting at the Royal Marsden Hospital. Patients were included if they were above 18 years, were due to undergo rectal cancer surgery that included the anterior peritoneal reflection and consented to take part in the study. Exclusion criteria were patients that could not undergo MRI, had undergone previous rectal or sigmoid colon surgery, or underwent surgery that did not include the anterior peritoneal reflection or the sigmoid mesentery.

Ethical Approval

This study was designed with patient involvement after meeting with the South West London Bowel Cancer Support Group. The study received research ethics committee approval from the Health Research Authority in the United Kingdom (IRAS no 220869) as well as from the Royal Marsden Committee for Clinical Research (local institutional review board, CCR4686).

MRI Technique

Patients underwent routine pre-operative MRI scans of their rectum reported on a standard proforma by two gastrointestinal radiologists with over 10 years' experience. The pre-operative MRI

determined patient eligibility i.e. requirement for low rectal resection. Surgery was performed using a mesenteric-based technique by one of two consultant colorectal surgeons, each with over 10 year's experience. In cases of locally advanced low rectal cancer, a beyond TME approach was utilised.

Immediately following surgery, specimens were opened along the anterior peritoneal surface, washed out and immersed in formalin for a minimum of 48 hours. Formalin-fixed specimens underwent MRI scanning whilst fixed to a corkboard along their longitudinal axis using wooden toothpicks (Figure 8-2, page 134). Cod liver oil tablets were sutured to the anterior peritoneal reflection to act as a marker. Specimens were scanned in a 3T Phillips MRI Imaging system. Axial slices were taken at 3mm intervals, in addition to coronal and sagittal views.

Histopathological Technique

Following the MRI scan, specimens were returned to formalin for a minimum of 7 days. The specimen was subsequently sliced at 5mm intervals as per Royal College of Pathologists guidelines (Loughrey et al, 2014). Photographs were taken of these cross sectional slices using a high definition camera mounted on a tripod with a ruler for calibration (Figure 8-2, page 134).

Measurements on pathology photographs were performed using Digimizer software and on MRI using the Sectra picture and archiving communication system (Sectra PACS Workstation IDS7, Sectra AB, Linköping, Sweden).

Statistical Analysis

Statistical analysis was planned by medical statisticians within the Royal Marsden Hospital. After extensive discussion about the sample size between the study authors and medical statisticians, it was agreed that such an investigation would only be exploratory; as such, a sample size of 20 was calculated based on a previous imaging/specimen study of the low rectal waist (Salerno et al, 2008a). The costs and availability of MRI scanning slots, extra cut-up time in pathology and Fellow availability to process samples was also taken into account during sample size calculation.

Endpoints were summarised using graphical methods and descriptive statistics including Pearson's Correlation Coefficient and Bland-Altman plots. Statistical analysis was performed on STATA version 13 (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC).

Chapter 4

Sigmoid Colon Cancer Outcomes in the Literature

D'Souza N, Lord A, Shaw A, Abulafi M, Kontovounisios C, Sjövall A, Tekkis P, Brown G. **Meta-analysis of oncological outcomes of sigmoid cancers: A hidden epidemic of R1 "palliative" resections.** *Eur J Surg Oncol. 2019 Apr;45(4):489-497. doi: 10.1016/j.ejso.2018.09.028. Epub 2018 Oct 11*.

Aim

As the oncological outcomes of sigmoid cancer are not well known, this study aimed to investigate the local recurrence rate of sigmoid cancer, as well as distant recurrence and disease-free survival, and explore reasons for the variation in these rates.

Methods

Study Selection

A systematic review and meta-analysis was planned and conducted according to PRISMA guidelines (Moher et al, 2009). The review was prospectively registered on the PROSPERO database (CRD42017069326).

A literature search in Pubmed was performed on the 4th of February 2017 since inception. A combination of search terms (Appendix 1) was created by the lead author (ND'S), who has previously authored meta-analyses including Cochrane Reviews, after discussion with research librarians. When studies were not available through online journal access, the study authors were contacted by e-mail directly. We supplemented the search results by checking the reference lists of relevant and included studies.

The primary outcome was local recurrence after surgical treatment of sigmoid or rectosigmoid cancer. The secondary outcomes were distant recurrence or disease free survival after surgical treatment of sigmoid or rectosigmoid cancer.

Inclusion/exclusion criteria

Studies were eligible for inclusion if they described the primary or secondary outcomes. Studies were excluded if they included less than 50 cases, did not describe the primary or secondary outcomes for sigmoid cancer, or grouped sigmoid cancer with other sites (e.g. sigmoid and rectal

cancer, or left sided colon cancer). Studies published in a language none of the authors or their colleagues could translate were excluded.

Data extraction

Data was extracted independently by 2 authors (ND'S, AL) and disagreements resolved by consensus. Data was extracted on the following fields following a pilot: first author, year of publication, study design, number of participants, number of males and females, mean age of participants, local recurrence rate and sites, distant recurrence rate and sites, disease free survival (median and 5 year), TNM stage, grade of differentiation, lymphatic or venous invasion, emergency presentation. Individual patient level data was not sought since most studies were over 10 years old.

Assessment of Methodological Quality

Study quality was assessed by the Newcastle Ottawa Score (Wells GA, 2001) (Appendix 2). Studies with scores of less than 4 were at high risk of bias, 4-6 of moderate risk of bias, and over 7 at low risk.

Statistical Analysis

Meta-analysis using the random effects model was performed using MedCalc for Windows, version 15.0 (MedCalc Software, Ostend, Belgium). The weighted summary proportions for local and distant recurrence, and disease free survival were calculated under the random effects model. Categorical variables for local and distant recurrence were analysed using ANOVA. Study heterogeneity was assessed by I^2 (Higgins and Thompson, 2002).

Results

The search terms identified 1323 studies (Figure 4-1). Studies were filtered by title and abstract to exclude irrelevant publications. Full texts were retrieved for 83 articles, of which 71 were excluded. The reference lists of included studies were searched to identify a further 5 eligible studies that were included in the analysis. In the final analysis, 17 eligible papers were included with 5953 patients (Table 4-1). The data for sigmoid cancers was frequently present as a subgroup for overall colon cancer. Consequently characteristics of patients with sigmoid cancer were not described in all studies and could not be reported here.

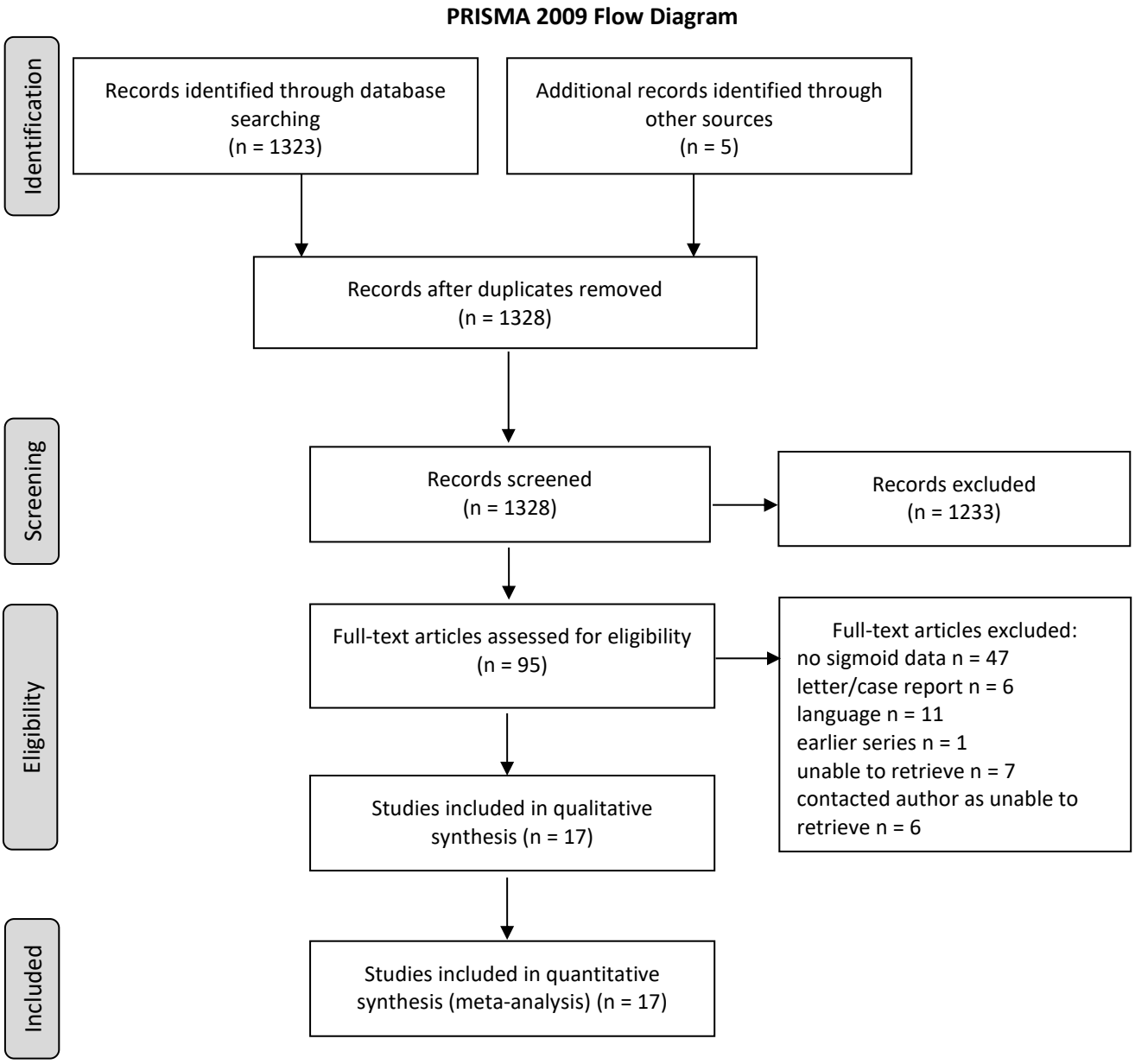


Figure 4-1: PRISMA flowchart for meta-analysis

Author	Country	Study period	Study design	No pts	Adjuvant therapy	LR (%)	DR (%)	5 year DFS
(Amri et al, 2015b)	USA	2004-2011	Retro*	238	unclear	32 (13%)	45 (19%)	
(Di Cataldo et al, 2007)	Italy	1992-2001	Retro*	102	unclear	14 (14%)		
(Harris et al, 2002)	USA	1980-1993	Retro*	397	yes	14 (4%)		
(Jagoditsch et al, 2000)	Austria	1984-1997	Retro*	270	unclear			83%
(Kraemer et al, 2001)	Singapore	1989-1999	Retro*	422	yes	25 (6%)	74 (18%)	
(Lautenbach et al, 1994)	US	1967 - 1991	Retro*	136	unclear	17 (13%)		
(Leung et al, 2004)	Hong Kong	1993-2002	Random+	403	yes	18 (4%)	56 (14%)	77%
(Liska et al, 2016)	USA	1994-2008	Retro*	433	yes	15 (3.5%)		
(Manfredi et al, 2006)	France	1976-2000	Retro*	566	yes	109 (19%)	152 (27%)	
(Marinello et al, 2015)	Spain	1992-2010	Retro*	450	yes	32 (7%)		81%
(Michelassi et al, 1988)	USA	1965-1981	Retro*	230	no	21 (9%)		
(Minsky et al, 1988)	USA	1965-1978	Retro*	115	no	24 (21%)	9 (8%)	
(Olson et al, 1980)	USA	1960-1970	Retro*	85	no	17 (20%)	17 (20%)	
(Park et al, 2016)	Inter-national	2004-2008	Retro*	678	yes	17 (2.5%)		81%
(Radespiel-Tröger et al, 2004)	Germany	1984-1996	Retro*	535	no			80%
(Sjövall et al, 2007)	Sweden	1996-2000	Retro*	682	unclear	79 (12%)		
(Willett et al, 1987)	USA	1970-1977	Retro*	211	no	55 (26%)	70 (33%)	

Table 4-1: Study characteristics
Note. Abbreviations: * Retro = retrospective. + Random = randomised. LR = local recurrence. DR = distant recurrence. DFS = disease free survival.

Primary outcomes

The pooled local recurrence rate was 10.5% in 15 studies with 5148 patients (95% CI 0.07 – 0.14, Figure 4-2). Heterogeneity measured by I^2 was 94%.

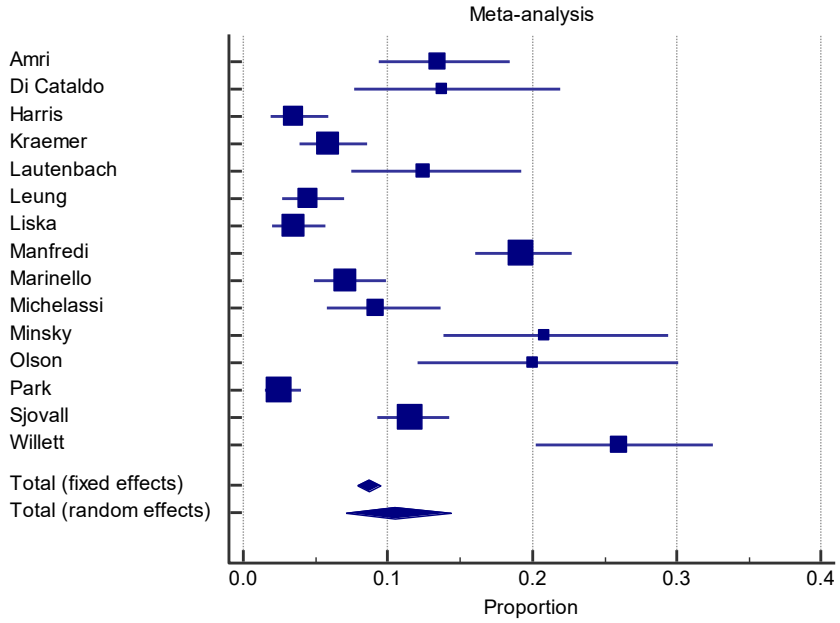


Figure 4-2: Forest plot of 10.5% pooled local recurrence

Secondary Outcomes

The pooled distant recurrence rate was 19.5% in 7 studies with 2040 patients (95% CI 0.14 – 0.25, Figure 4-3). Heterogeneity measured by I^2 was 90%.

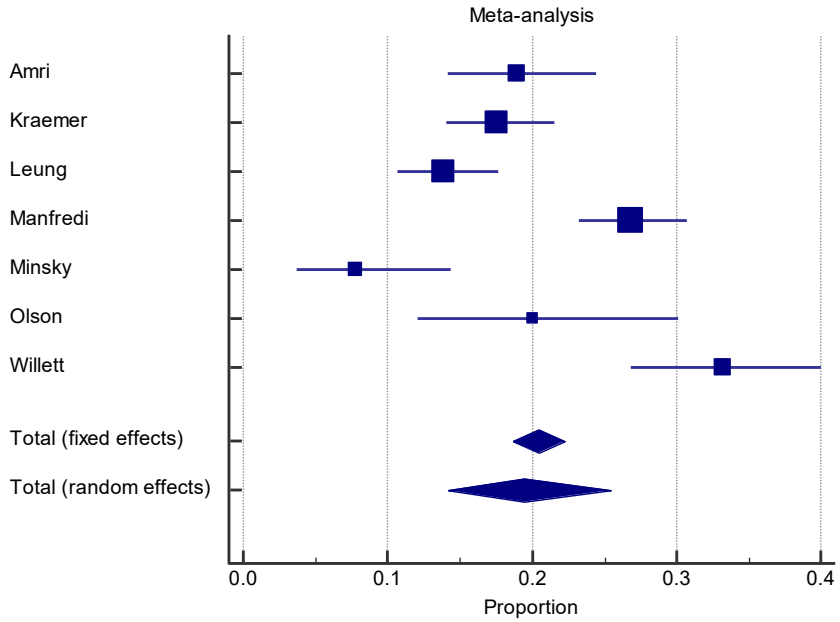


Figure 4-3: Forest plot of 19.5% pooled distant recurrence

The pooled 5 year disease free survival was 80.4% in 5 studies with 2336 patients (95% CI 78.6%-82.1%, Figure 4-4). Heterogeneity measured by I^2 was 12.17%.

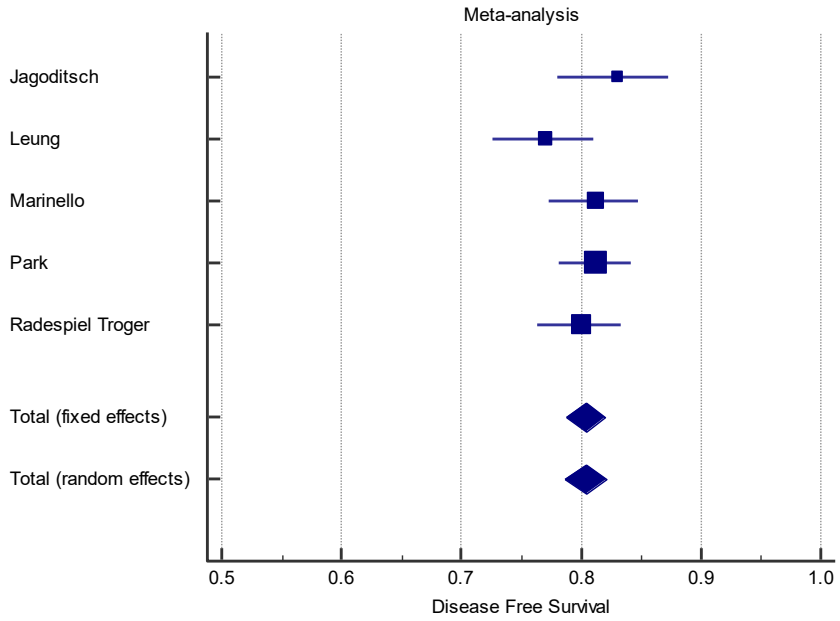


Figure 4-4: Forest plot of pooled 80.2% 5 year disease free survival

Subgroup analysis for study date showed a downwards trend for local recurrence with later studies, that was statistically significant after logistic regression analysis (p=0.02). No significant change in distant recurrence was found in relation to study date (p=0.96, Figure 4-5).



Figure 4-5: Local and distant recurrence vs study start date
Note. Local recurrence (left) and distant recurrence (right).

Studies in which patients were given adjuvant therapy (Figure 4-6) had lower rates of local recurrence (*p=0.006)*, but not distant recurrence (p=0.944).

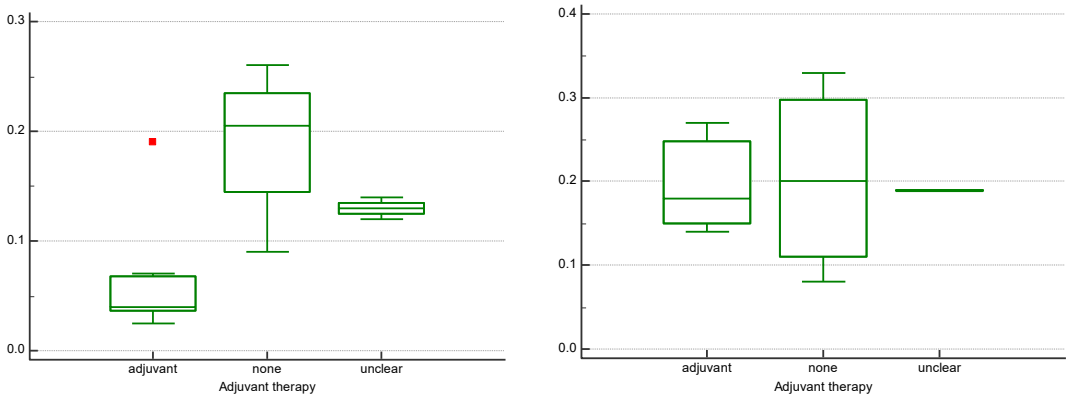


Figure 4-6: Local and distant recurrence vs adjuvant therapy
Note. Local recurrence (left) and distant recurrence (right).

No significant difference was found with subgroup analysis by country with ANOVA. No further subgroup analysis could be carried out due to the paucity of data on other prognostic features in the included studies. Data on stage, TNM classification, differentiation and EMVI was available for 4 studies. Data on hazard ratios was available for 2 studies.

Assessment of Methodological Quality

The median Newcastle Ottawa Score of the included studies was 4 (range 2 to 7) out of a maximum possible score of 9, and therefore rated as moderate. Details of the quality assessment are reported in Appendix 2.

Data on R1 resections was only given in three papers (see Table 4-2). R1 or non-curative operations were described in the study flow in 13 studies, but only included in the analysis of one study (Liska et al, 2016). R1 rates varied from 15-20%. Up to 54% of patients were excluded with R1 resections and other exclusion criteria with no breakdown. We wrote to the corresponding authors for papers written since 2005 for further data on their R1/R2 resection rates.

Author	R1 rates quant-ified	R1 or non-curative resections described?	If described, were R1s/non-curative excluded	What were R1/non-curative rates
(Amri et al, 2015b)	0	no		4.3% R1/R2*
(Di Cataldo et al, 2007)	0	no		No response*
(Harris et al, 2002)	0	yes	yes	28% max†
(Jagoditsch et al, 2000)	1	yes	yes	15%
(Kraemer et al, 2001)	0	yes	yes	unclear
(Lautenbach et al, 1994)	0	yes	yes	unclear
(Leung et al, 2004)	0	no		
(Liska et al, 2016)	1	yes	yes (R1 not R2)	R1 4%
(Manfredi et al, 2006)	1	yes	yes	19.7%

(Marinello et al, 2015)	0	yes	yes	No response*
(Michelassi et al, 1988)	0	no		
(Minsky et al, 1988)	0	yes	yes	37% max†
(Olson et al, 1980)	0	yes	yes	54% max†
(Park et al, 2016)	0	yes	yes	No response*
(Radespiel-Tröger et al, 2004)	0	yes	yes	
(Sjövall et al, 2007)	0	yes	yes	4.5%-12.8%*
(Willett et al, 1987)	0	yes	yes	no

Table 4-2: Description of R1 resection rates and non-curative surgery
Note. †Total number of excluded patients with possible R1 resections *Study authors contacted for additional data

Discussion

This systematic review found the local recurrence rate of sigmoid cancer ranged from 2.5% to 26% in the 17 included studies. Given the heterogeneity of outcomes reported, it is unclear what is the true local recurrence rate of sigmoid cancer; but a variety of methodological and clinical issues suggest it may be even higher than 10.5%. The poor quality of studies from selection bias and inappropriate exclusions, omission of prognostic staging data, and utilisation of different definitions of the sigmoid highlights the need for further research.

One study reported R1-2 resections in 20% of patients and classified these cases as "palliative"(Manfredi et al, 2006). Another study excluded "palliative" cases (28% overall) and consequently had a 100% R0 rate (Harris et al, 2002). Other studies excluded "palliative" operations, but it is unclear whether the pre-operative intent of surgery was curative. Correspondence with one study author (Sjövall et al, 2007) confirmed that despite detailed breakdown of the "radicality" of surgery (i.e. whether margins were clear) by surgeon and pathologist in a national registry, the intent of surgery is not captured.

The practice of labelling R1 resections as palliative was commonplace in rectal cancer surgery 30 years ago (Heald and Ryall, 1986). Radical surgery in rectal cancer is rarely performed with palliative intent. The practice of deeming an operation as "palliative" after surgery or histology has revealed involved margins is no longer continued. In part, this is because better pre-operative staging in rectal cancer has enabled both patient selection and the optimal approach for curative surgery. This may involve referral for specialist surgery (exenterative, multivisceral, low rectal) in combination with pre-operative therapy. A similar approach has not been adopted in colon or sigmoid cancer. he pooled rate of 10.5% is higher than the contemporary local recurrence rates in rectal cancer between 3%-5% (Bonjer et al, 2015, Jeong et al, 2014) described in randomised trials, although a direct statistical comparison between rectal and sigmoid cancer outcomes was not performed.

Other patients at high risk of recurrence were excluded in some studies. This includes patients who had undergone emergency surgery (Park et al, 2016, Leung et al, 2004), or who had neoadjuvant or adjuvant treatment (Park et al, 2016, Radespiel-Tröger et al, 2004). Other studies only analysed results from sigmoid colectomies not anterior resections for sigmoid cancer (Amri et al, 2015b), potentially excluding distal sigmoid cancers at the pelvic brim which are at higher risk of recurrence.

Variation in the definition of local recurrence may lead to an underestimate of its incidence. One study did not classify peritoneal, mesenteric/retroperitoneal and omental disease within the category of local recurrence (Amri et al, 2015b). When those sites were included, the local recurrence rate increased from 1.9% to 13%.

Clinical Practice Issues

The different guidelines used to classify cancers as rectal or sigmoid may have led to their misclassification. Only 41% (7/17) of the studies described their criteria for localising cancer to the sigmoid. Some studies may have classified distal sigmoid tumours as rectal tumours, therefore

excluding a subset of sigmoid tumour that would have a high recurrence rate. This could certainly be true in studies that classified all cancers below 18cm (Marinello et al, 2015) or 15cm (Liska et al, 2016, Sjövall et al, 2007, Park et al, 2016) as rectal and excluded them. "Rectosigmoid" tumours (ICD-10 C19) were excluded in 3 studies (Amri et al, 2015b, Olson et al, 1980, Radespiel-Tröger et al, 2004), again potentially removing a subset of sigmoid cancers that may have a high recurrence rate.

The introduction of adjuvant and neoadjuvant therapies in later study periods may have reduced the number of recurrences. The distant recurrence rate was not lower in studies with adjuvant therapy; but these studies began recruitment in 1976, 1989 and 1993. Distant recurrence rates were not described in more contemporary studies that employed adjuvant therapy. Patients that develop unresectable distant recurrence may have synchronous local recurrence, which may be missed by radiologists, or not recorded by their clinical team.

Study quality

The median Newcastle-Ottawa Score of 4 indicated that study quality was moderate. Only one study employed a randomised methodology (Leung et al, 2004), while the other studies were retrospective observational studies. The most frequent quality issues were the exclusion or failure to describe R1 resections (15/17), the omission of TNM staging data for sigmoid cancers (13/17) and the high or unclear loss to follow up (12/17).

Many studies had either a high loss to follow up, or did not describe loss to follow up. Some international referral centres for cancer would use telephone follow up if record linkage was not possible. This less rigorous form of follow up permits the possibility of undetected recurrent cancer.

As nearly all studies were retrospective, institutions may have only submitted their data for publication if it showed a low local recurrence rate.

Strengths and weaknesses

This systematic review was conducted according to recommended guidelines, and has revealed that sigmoid cancer outcomes are worse than previously thought. The poor methodological quality of the studies yields useful insights into conduct of future research, but led to heterogeneity which means the exact scale of the problem remains unknown, and precluded a direct comparison to rectal cancer outcomes. A direct comparison with rectal cancer outcomes was not performed in this meta-analysis, but may not be possible given the heterogeneity in the definitions of sigmoid and hence rectal cancers. No staff in the author's institutions were found that spoke the languages of the studies that were excluded. None of the studies excluded on the basis of language were cited in any included study.

Guidelines for Future Research

Future research should not exclude patients with R1 resections, or adverse pre-operative prognostic factors. Studies should describe the modality and landmarks used to localise the tumour. The International Classification of Diseases code for "rectosigmoid" location should not be employed. Tumour stage should be given. Follow-up techniques and losses should be described in order to determine whether recurrent disease may have been missed. Local recurrences should be classified as to the anatomical area (e.g. anastomosis, mesentery, peritoneum, retroperitoneum, nodes, sacrum). The outcomes and treatment of patients with local recurrence should also be described. Treatment outcomes for sigmoid cancer should be held to the same standard as those of rectal cancer.

Conclusion

Sigmoid cancer has a high pooled local recurrence rate of 10.5%, which is higher than contemporary published local recurrence rates of rectal cancer. A large number of papers fail to describe or include R1 resections of sigmoid cancer, which are frequently described as palliative. Classification of sigmoid tumour was either not defined, or inconsistently defined. The variation in sigmoid cancer local recurrence rates is due to a lack of quality in study methodology and reporting standards. High quality studies that include R1 resections are needed to determine the actual recurrence rate of sigmoid cancer.

What does this study add to the literature?

The local recurrence rate from sigmoid cancer is high.

Only 7/17 studies described their landmarks for sigmoid tumours, which varied substantially, and rectosigmoid studies were excluded in other studies.

Published series commonly exclude patients at high risk of recurrence e.g., patients undergoing emergency surgery, patients with R1 resections.

Chapter 5
The Sigmoid Take-Off

D'Souza N, tot Babberich MD, Lord A, Shaw A, Abulafi M, Tekkis P, Wiggers T, Brown G. **The rectosigmoid problem.** *Surg Oncol* 2018 Sep 1;27(3):521-5.

Aim

The aim of this study was to find a validated, reliable definition of the rectum to differentiate sigmoid from rectal tumours.

Methods

The primary endpoint was to establish the range of definitions in the literature, and investigate anatomical evidence for or against their use.

Results

An overview of the different definitions of the rectum is seen below in Table 5-1 and Figure 5-1.

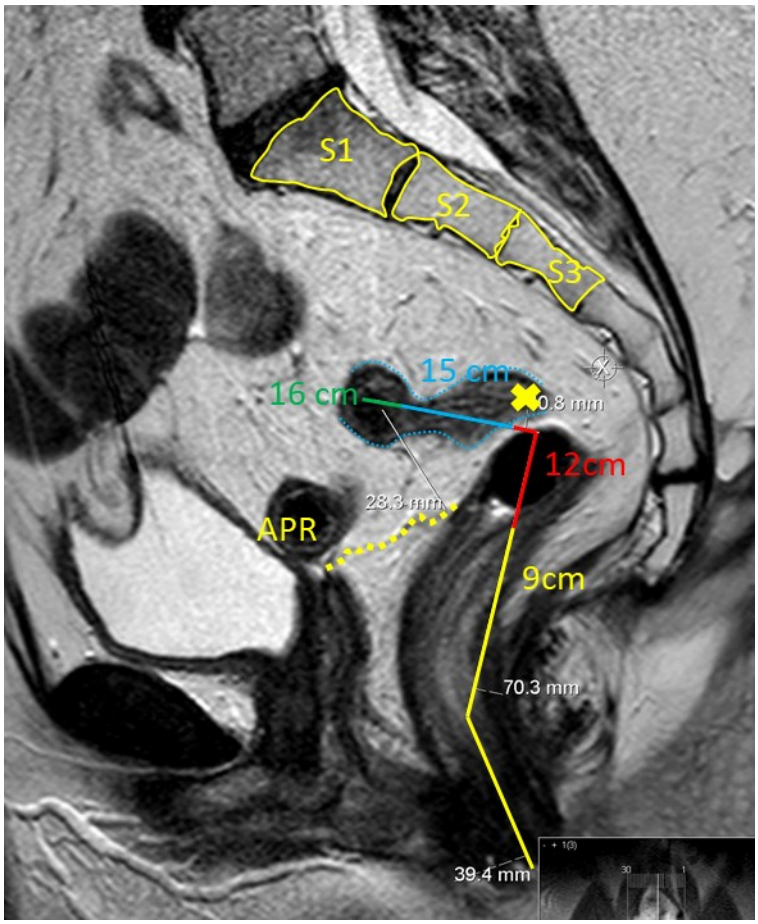


Figure 5-1: Illustration of current definitions of the rectum
Note. Metric measurements from the anal verge, sacral bony landmarks, anterior peritoneal reflection (APR) and the sigmoid take-off (yellow cross) in relation to the rectum and sigmoid.

These definitions employ either endoscopic measurements, or anatomical landmarks. Metric measurements have also been used to differentiate the upper, middle and low rectum by 5cm increments from the anal verge by MRI (Taylor et al, 2008). Anatomical definitions are bony, colonic, mesenteric or vascular landmarks that may be seen on pre-operative imaging, at the time of surgery, or on post-operative histology. Organisation including the American Society of Colon and Rectal Surgeons (Monson et al, 2013), TNM (Wittekind C, 2001), Dutch Colorectal Cancer Group (Kapiteijn et al, 2001) utilise a combination of landmarks to define the rectum.

Mayo described "the third sacral vertebra" as the point of the rectosigmoid junction. However, he believed that this was the landmark for the "ending of the mesenteric attachment" of "the terminal portion of the sigmoid" (Mayo, 1909).

There is wide variation from country to country for the upper limit of the rectum (Table 5-1), which guides patient selection for radiotherapy.

Landmark	Guidelines/Source	Landmark Type
Sacral Promontory	Swedish Rectal Cancer Trial (Swedish Rectal Cancer Trial, 1997) TNM staging (Wittekind C, 2001) United States ASCRS guidelines (Monson et al, 2013)	Anatomical: bone
Third sacral segment	Anatomy textbooks (Drake et al, 2009)	Anatomical: bone
Second sacral segment	Japan—upper rectum (Dennosuke, 1983) Dutch rectal cancer trial (Kapiteijn et al, 2001)	Anatomical: bone
Anterior peritoneal reflection	Japan— lower rectum (Dennosuke, 1983)	Anatomical: bowel
Coalescence of taenia coli, cessation of appendices epiploicae	Anatomy textbooks (Drake et al, 2009) United States ASCRS guidelines (Monson et al, 2013)	Anatomical: bowel
Mesocolic-mesorectal transition	Intra-operative study (Memon et al, 2009) Specimen study(Culligan et al, 2012)	Anatomical: mesentery
16cm	Germany (Wagner and Hermanek, 2013) TNM staging(Wittekind C, 2001) German Rectal Cancer Trial (Sauer et al, 2004)	Metric: endoscopy
15cm	United States ASCRS guidelines (Monson et al, 2013) United Kingdom guidelines (ACPGBI, 2007) European ESMO guidelines (Glimelius et al, 2013) UICC Manual (Glynne-Jones et al, 2015)	Metric: endoscopy

	Dutch rectal cancer trial (Kapiteijn et al, 2001) MRC CR07 trial (Sebag-Montefiore et al, 2009)	
12cm	United States NCI Guidelines (Nelson et al, 2001) Spain (Grávalos Castro et al, 2010) ACOSOG Z6051 trial (Fleshman et al, 2015)	Metric: endoscopy
9cm	South Korea (Hwang et al, 2014)	Metric: endoscopy

Table 5-1: Definitions of the rectum from national guidelines, published literature or trial criteria for neoadjuvant therapy Note. ASCRS = American Society of Colon and Rectal Surgeons. ESMO= European Society for Medical Oncology. NCI= National Cancer Institute. *ACPGB =: Association of Coloproctologists of Great Britain and Ireland. UICC = Union for International Cancer Control*

Problems with current definitions

Bony Landmarks

The third sacral segment has traditionally been held as the landmark for the beginning of the rectum, although there is little evidence from the literature to validate this practice. Two studies reported a shorter distance to the sacral promontory than to the coalescence of the taenia (Wasserman et al, 2016, Yun et al, 2008), implying bony landmarks can only be a surrogate marker for a variable colonic transition point.

The Mesorectal-Mesocolic Transition

The mesorectal-mesocolic transition has been described in studies of intra-operative anatomy, and specimen analysis of the rectum. The transition may be detected intra-operatively at “the point that the surgeon felt there was mobility of the colon away from the vertebral column” (Memon et al, 2009). This is obviously a subjective and non-reproducible test, but nonetheless fits Culligan’s description of the transition from the sigmoid mesocolon to the mesorectum, which corresponded to the transition from the sigmoid colon to the rectum, and the coalescence of the taenia coli (Culligan et al, 2012).

Anterior Peritoneal Reflection

The anterior peritoneal reflection has previously been described as a landmark for the beginning of the rectum. However, the mesorectum continues laterally and posteriorly above the anterior peritoneal reflection. It would be more accurate to state that the anterior peritoneal reflection delineates the intraperitoneal and extraperitoneal rectum. The mean distance to the anterior peritoneal reflection from the anal verge by rigid endoscopy ranges from 8.8-13.7cm (overall range 7-21cm) in men, and 8.1-12.3cm (overall range 5.5-17cm) in women (Table 5-2). The mean distances measured by MRI were similar at 9.9-10.9cm (overall range 6.4-14.2cm) in men, and 9.2-10.9cm (overall range 7.0-13.6cm) in women (Table 5-2).

Study	AV-APR distance (range) in cm				Modality	Country
	Men	*n*	Women	*n*		
(Wasserman et al, 2016)	13.7 (10, 21)	41	12.3 (8.5, 17)	30	RP	USA
(Memon et al, 2009)	11.0 (9, 17)	27	11 (8, 15)	33	RS	Australia
(Yun et al, 2008)	8.8	23	8.1	23	RS	Korea
(Najarian et al, 2004)	9.7 (7, 16)	50	9 (5.5, 13.5)	50	RP	USA
(Yiqun et al, 2016)	10 (6.5, 13.0)	188	10.4 (8.1, 13.6)	95	MRI	China
(Gollub et al, 2013)	10.9	126	10.9	54	MRI	Europe, USA
(Paparo et al, 2014)	9.9 (6.4,14.2)	39	9.2 (7.0, 12.1)	27	MRI	Italy

Table 5-2: Distance *from the anal verge to anterior peritoneal reflection*
Note. RP = rigid proctoscopy, RS = rigid sigmoidoscopy.

Coalescence of the Taenia Coli

The coalescence of the taenia coli cannot be seen on CT or MRI. Detection of this anatomical landmark is therefore dependent on the operating surgeon. The overall (mean) distance to the coalescence of the taenia in all patients measured by rigid endoscopy ranged from 12-37cm (18.6-25.5cm) in men, and 13-44cm (17.6-25.4) cm in women (Table 5-3). The variation in distance to the

coalescence of the taenia coli implies that there is either a wide degree of variation in the length of the rectum, or intra-operative error is likely during direct visual assessment. The latter may be due to the coalescence of the taenia coli over a distance rather than a particular point. Some studies have shown that the coalescence of the taenia does not occur at the level of the sacral promontory (Memon et al, 2009, Wasserman et al, 2016).

Study	AV-CTC mean distance (range) in cm				Country
	Men	*n*	Women	*n*	
(Wasserman et al, 2016)	25.5 (17, 37)	41	25.4 (16, 44)	30	USA
(Memon et al, 2009)	20.3 (12, 35)	27	18.8 (13, 26)	33	Australia
(Yun et al, 2008)	18.6	23	17.6	23	Korea

Table 5-3: Distance from the anal verge to the coalescence of taenia coli
Note. CTC = coalescence of taenia coli. AV = anal verge

Valves of Houston

John Houston described the transverse rectal valves, and made special note of the middle valve, also called Kohlrausch's valve, said to correspond to the anterior peritoneal reflection (Houston, 1987). The superior rectal valve is anecdotally said to mark the rectosigmoid junction, although in fact this was never mentioned by Houston himself (Cohen, 1968).

The valves of Houston were investigated in an anatomic study of 18 cadavers, and barium enemas in 36 volunteers (Shafik et al, 2001). Valves numbered two to three in 29/36 patients. The variation in the number of valves was confirmed in a further endoscopic study of 400 patients, the number of valves numbered three in only 45.5% of patients (Abramson, 1978). Approximately 25% of patients had less than 2 or more than 3 valves.

Metric Measurements

Measurements by MRI or using predefined distances will inevitably result in incorrect tumour localisation for some patients. The distance to landmarks within the rectum has been shown to vary for patients by sex (Wasserman et al, 2016, Gollub et al, 2013, Yiqun et al, 2016), height (Yun et al, 2008, Wasserman et al, 2016) and weight (Wasserman et al, 2016, Najarian et al, 2004) by rigid proctoscopy or MRI (Baatrup et al, 2009). There is also likely to be additional variation by ethnicity, as there was a shorter distance to rectal landmarks in studies from Korea and China than in studies from Australia and the United States. Tumour localisation is more inaccurate when measurements are made using colonoscopy (Louis et al, 2010, Piscatelli et al, 2005) rather than rigid sigmoidoscopy (Schoellhammer et al, 2008).

An alternative landmark: the sigmoid take-off

An alternative anatomical landmark is the sigmoid take-off. This radiological landmark identifies the junction of the sigmoid mesocolon with the mesorectum, and therefore the sigmoid colon with the rectum. The rectum and mesorectum are fixed posteriorly to the pre-sacral fascia up until the mesorectal apex. Above this point, the sigmoid mesocolon becomes mobile and lifts ventrally off the sacrum, leading to the horizontal sigmoid. This landmark has been used in practice at the Royal Marsden Hospital MDT, and is anatomically consistent with the point of "mobility of the colon away from the vertebral column" described by (Memon et al, 2009) signifiying the mesorectal-mesocolic junction reported by (Culligan et al, 2012).

On cross-sectional imaging (CT or MRI), the sigmoid take-off can be identified on 2 views (Figure 5-2). On axial views, it can be seen as the ventral projection of sigmoid, when the upper mesorectum, tethered to the sacrum by the recto-sacral/pre-sacral fascia, transitions to the mesocolon. On sagittal views, this projection can be seen as a horizontal sweep. A divergence in the

blood supply can be seen at the sigmoid take-off. Proximally the spidery sigmoid arteries supply the sigmoid through its fan-shaped mesocolon. Distally, the superior rectal artery bifurcates and supplies the rectum through its cylindrical fatty envelope.

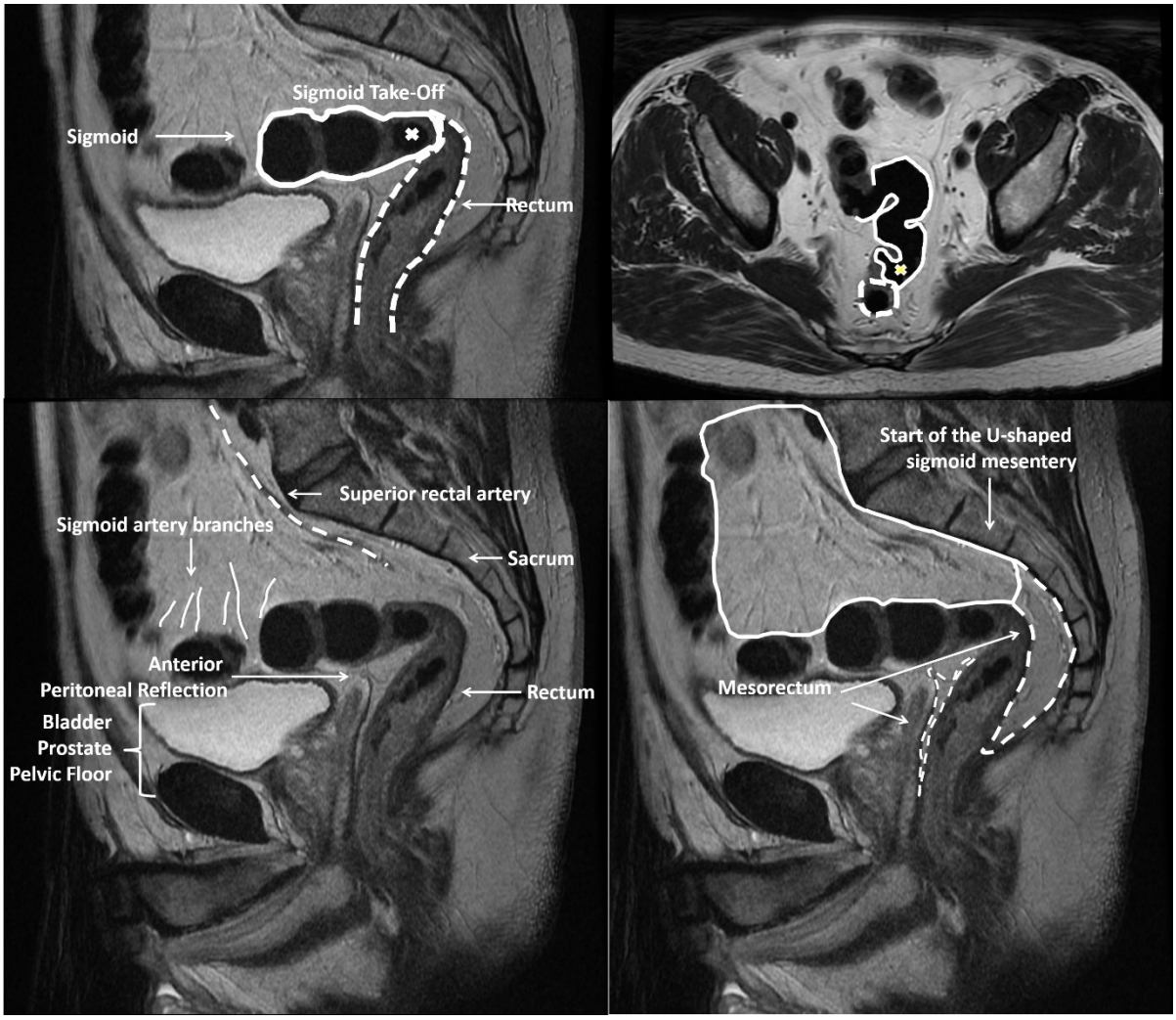


Figure 5-2: Anatomical relationships of the sigmoid take-off on CT
Note. Clockwise from top left: sagittal and axial views of the sigmoid and rectum (dashed outline), U-shaped sigmoid mesocolon illustrated, spidery sigmoid vessels vs larger calibre superior rectal artery dashed) highlighted.

Discussion

There is a wide number of published definitions of the rectum, and eight different definitions are used in national guidelines and research trials. But rectums are different lengths. Even using one consistent metric measurement will incorrectly localise some sigmoid tumours to the rectum and

vice versa, confounding clinical and oncological outcomes. The plurality of definitions in use poses a problem for researchers, clinicians and patients. To achieve best care for rectal cancer, a harmonised definition of the rectum is needed to standardise research and treatment.

The sigmoid take-off is a definition of the rectum with a logical, anatomical basis. As an imaging definition, it is inherently reproducible, although subject to interpretation (or misinterpretation). Any suspected tumours of the sigmoid or rectum will have cross-sectional imaging routinely performed, on which the take-off may be identified. However, its validity and reliability have not been investigated.

Conclusion

Understanding the optimal treatment for cancers near the upper rectum or lower sigmoid cannot be accomplished without an unambiguous, accurate and reproducible landmark to which the location of the tumour can be related. Future research should aim to establish an acceptable, validated definition of the rectum for use in both research and clinical practice.

What does this study add to the literature?

Eight definitions of the rectum are in use by national guidelines and research studies, none of which have been validated by in-vivo or cadaveric studies of anatomy.

The sigmoid take-off identifies the mesorectal-mesocolic transition on cross-sectional imaging, and could be used to define the rectum.

Chapter 6

Variation in Landmarks for the Rectum on MRI

D'Souza N, Balyasnikova S, Tudyka V, Lord A, Shaw A, Abulafi M, Tekkis P, Brown G. **Variation in landmarks for the rectum: an MRI study.** *Colorectal Dis. 2018 Oct;20(10):O304-O309.*

Aim

This aim of this study was to investigate whether commonly used definitions for the rectosigmoid junction can reliably identify the corresponding bowel as rectum or sigmoid on MRI.

Methods

Endpoints

The primary endpoint was to identify corresponding the segment of bowel as rectum or sigmoid for the following landmarks: metric measurements from the anal verge of 12, 15 and 16cm; bony landmarks of the sacral promontory, third sacral segment (S3).

The secondary endpoints were to: measure the distance of the anal verge to the sigmoid take-off to identify the variation in height of the rectosigmoid junction; identify corresponding segment of bowel as rectum or sigmoid for each sacral landmark with reference to the sigmoid-take off; compare distance from the anal verge to the sigmoid take-off on MRI and CT.

Inclusion and Exclusion Criteria

100 consecutive patients who underwent high-resolution staging MRI of the pelvis for rectal cancer at the Royal Marsden Hospital were selected between 01.01.2012 and 31.12.2012.

MRI technique

MRI was performed on a 1.5 Tesla system using a spine array and a phased array body coil. High spatial resolution T2 weighted axial and sagittal MRI images were obtained with 3 mm slice thickness. High-resolution MR are defined as voxel size less than 1.5 and sufficient signal to noise ratio.

Magnetic resonance images were processed by a single investigator (SB), blinded to clinical data. An expert GI radiologist (GB) corroborated measurements to confirm quality assessment

The sigmoid take-off was used to identify the rectosigmoid junction in all patients and measure the length of the rectum. The distance of the sigmoid take-off from the anal verge was measured by curvilinear distances corresponding to the lumen of the rectum. It was compared to the standards lengths of the rectum and to bony landmarks, using rectilinear measurements as straight lines from the anal verge.

Statistical Analysis

Descriptive statistics were used for rectal length. When CT scans were also available, measurements were compared against MRI using Student's t-test, and compared on a Bland-Altman graph using MedCalc for Windows, version 15.0 (MedCalc Software, Ostend, Belgium).

Results

Of the 100 included patients, 44 were female. The mean age was 61 (range 26-92). Height, weight, body mass index and ethnicity were not recorded.

The mean length of the rectum from the anal verge, measured by the distance of the sigmoid take-off from the anal verge was 12.6cm (standard deviation 1.8cm, 95% CI 12.3 – 13.0cm), ranging from 9.4 to 19.0cm (Figure 6-1).

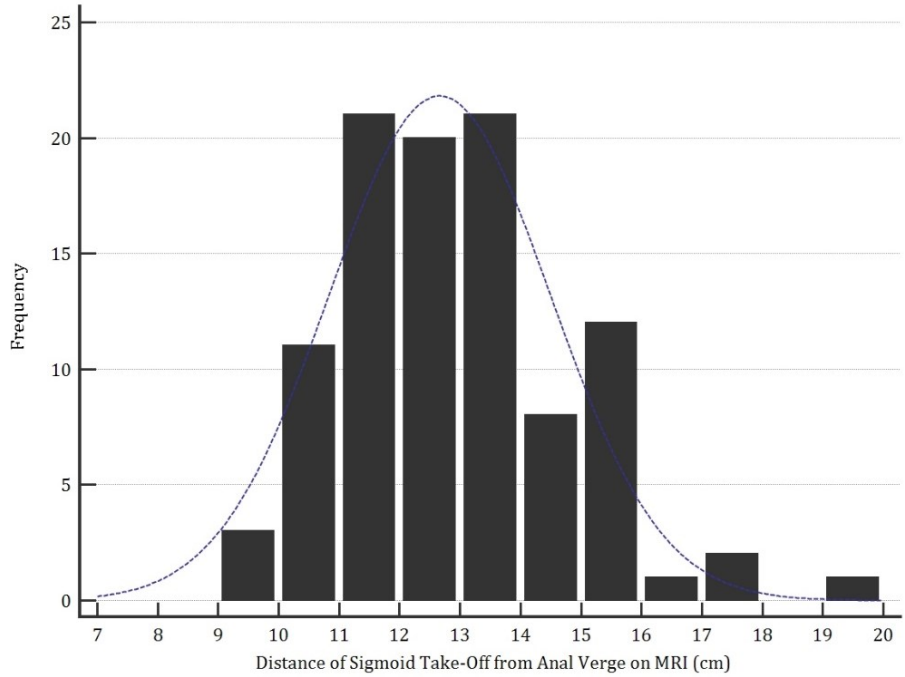


Figure 6-1: Histogram of rectal length

Definition of Rectum	Type	Sigmoid	Rectum
Sacral Promontory Swedish Rectal Cancer Trial (Swedish Rectal Cancer Trial, 1997) TNM staging (Wittekind C, 2001) USA guidelines (ASCRS) (Monson et al, 2013)	Anatomical: bone	100 (100%)	0 (0%)
Third sacral segment Anatomical teaching (Mahadevan, 2011)	Anatomical: bone	28 (28%)	72 (72%)
16cm Germany guidelines (Wagner and Hermanek, 2013) CAO/ARO/AIO-94 trial (Sauer et al, 2004) TNM staging (Wittekind C, 2001) SEER staging (National Cancer Institute, 2019)(National Cancer Institute, 2019)(National Cancer Institute, 2019)(National Cancer Institute, 2019)(National Cancer Institute, 2019)(National Cancer Institute, 2019)(National Cancer Institute, 2019)(National Cancer Institute, 2019)(National Cancer Institute, 2019)(National Cancer Institute, 2019)	Metric: endoscopy	96 (96%)	4 (4%)
15cm United States guidelines (ASCRS) (Monson et al, 2013) United Kingdom guidelines (ACPGBI, 2007) European guidelines (ESMO) (Glimelius et al, 2013) UICC Manual (Glynne-Jones et al, 2015) Dutch rectal cancer trial (Kapiteijn et al, 2001) MRC CR07 trial (Sebag-Montefiore et al, 2009)	Metric: endoscopy	84 (84%)	16 (16%)
12cm USA guidelines (NCI (Nelson et al, 2001)) Spain guidelines (Grávalos Castro et al, 2010) ACOSOG Z6051 trial (Fleshman et al, 2015)	Metric: endoscopy	35 (35%)	65 (65%)

Table 6-1: Sigmoid colon or rectum identified by traditional definitions of the rectum

Note. ASCRS = American Society of Colon and Rectal Surgeons. ESMO= European Society for Medical Oncology. NCI= National Cancer Institute. *ACPGBI = Association of Coloproctologists of Great Britain and Ireland. UICC = Union for International Cancer Control. NCI = National Cancer Institute. SEER = Surveillance, Epidemiology and End Results Program.*

At 12, 15 and 16cm from the anal verge, the rectum had ended and the sigmoid had already commenced in 35%, 84% and 96% of cases respectively (Table 6-1). The position of the rectosigmoid junction was compared to sacral bony landmarks (Table 6-1). At S3 and the sacral promontory, the sigmoid had commenced in 28% and 100% of cases respectively.

The length of the rectum was measured in 59 patients on CT scans using the sigmoid take-off, and compared to the MRI rectal length; no significant difference was found (Table 6-2, Figure 6-2).

Rectal Length	**CT**	**MRI**
Mean	12.4*	12.4*
Standard Deviation	1.77	1.82
Minimum	9.2	9.4
Maximum	17.8	17.5
Median	12.2	12.5
Interquartile Range	2.43	2.50

Table 6-2: Comparison of measurements of rectal length on CT vs MRI using the sigmoid take-off

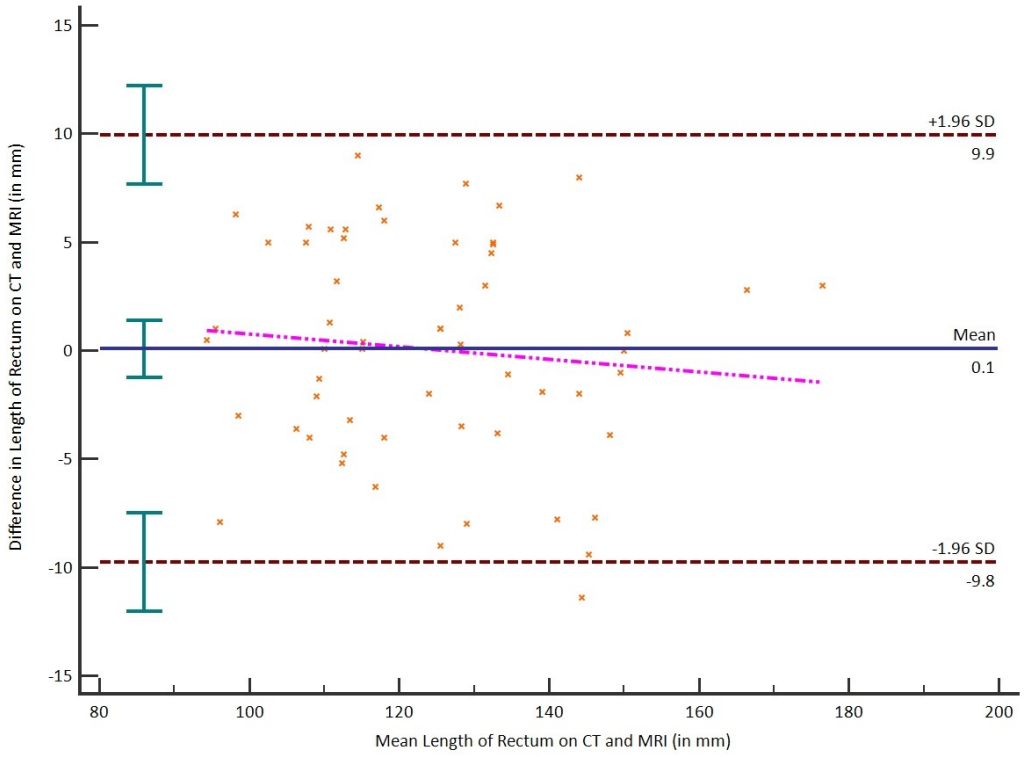


Figure 6-2: Bland-Altman plot of difference in length of rectum on CT and MRI

Discussion

Our results demonstrate that standard definitions of the rectum will misclassify tumours of the sigmoid colon will frequently as rectal cancer. This occurred more frequently with increasing distance from the anal verge, or higher sacral landmarks.

We found a wide variation in length of the rectum from 9.4 to 19cm, which has been reported in other studies (Park et al, 2008, Memon et al, 2009, Wasserman et al, 2016, Yun et al, 2008). Arbitrary landmarks will not account for this variation in patient anatomy and rectal length, and therefore frequently do not localise the rectosigmoid junction accurately. As a result, patients with distal sigmoid cancers have almost certainly been included in the study populations of key trials in rectal cancer. German (Sauer et al, 2004), Dutch (Kapiteijn et al, 2001) and American (Fleshman et al, 2015) rectal cancer studies used distances from the anal verge of 16cm, 15cm and 12cm respectively as their boundaries for the rectum. However, within our study population the rectum had ended

before these landmarks in 96%, 84% and 35% of patients. Tumours above these levels will therefore in fact be sigmoid cancers in 96%, 84% and 35% of cases.

Patients with sigmoid cancer will therefore have been included in rectal cancer trials of neoadjuvant radiotherapy in significant numbers (Sebag-Montefiore et al, 2009, Sauer et al, 2004, Kapiteijn et al, 2001, Swedish Rectal Cancer Trial, 1997). Although there is mixed evidence for neoadjuvant radiotherapy (Kapiteijn et al, 2001, Burton et al, 2006a, O'Neill et al, 2008, Sebag-Montefiore et al, 2009) in sigmoid cancer, these research studies were carried out to investigate the effect of neoadjuvant therapy on rectal cancer, and the results will therefore be confounded.

A potential criticism of this study would be the use of MRI instead of proctoscopy to measure distance from the anal verge. However, a previous study has described the difference in measurements on MRI and proctoscopy as less than 1cm (Keller et al, 2014). We did not corroborate our MRI lengths with proctoscopy, although previous in-vivo studies have confirmed a wide variation in rectal length using rigid endoscopy (Memon et al, 2009, Wasserman et al, 2016, Yun et al, 2008). The mean length of the rectum on MRI in this study is consistent (12.6cm vs 12.5cm) with the largest in-vivo study of rectal length in 175 patients (Park et al, 2008). One previous in-vivo intra-operative study found there was almost no difference in distance from the anal verge to the sigmoid take-off with the coalescence of the taenia coli (1cm in men, no difference in women (Memon et al, 2009)). Only 1 radiologist performed MRI distance assessment, but this has been shown to have excellent inter-observer correlation by previous studies (Jacobs et al, 2017, Meylemans et al, 2014). Cross-sectional imaging is performed in all non-emergent patients with colorectal cancer. Although we employed MRI to identify the sigmoid take-off, in practice CT could also be used. To fully validate the sigmoid take-off to define the rectum will require an international consensus, histological correlation, and demonstration of inter-observer agreement.

Conclusion

Definitions of the rectum that rely on arbitrary measurements from the anal verge, or reference to bony landmarks, will tend to overestimate the length of the rectum.

What does this study add to the literature?

Current definitions of the rectum based on metric measurements or bony landmarks cannot accurately localise tumours to the rectum or sigmoid. The mean length of the rectum in 100 patients was 12.6cm, ranging from 9.4cm to 17.5cm on MRI; metric measurements will frequently misclassify distal sigmoid tumours to the upper rectum.

Chapter 7

An International Consensus Definition of the Rectum

D'Souza N, de Neree Tot Babberich MPM, d'Hoore A, Tiret E, Xynos E, Beets-Tan RGH, Nagtegaal ID, Blomqvist L, Holm T, Glimelius B, Lacy A, Cervantes A, Glynne-Jones R, West NP, Perez RO, Quadros C, Lee KY, Madiba TE, Wexner SD, Garcia-Aguilar J, Sahani D, Moran B, Tekkis P, Rutten HJ, Tanis PJ, Wiggers T, Brown G**. Definition of the Rectum: An International, Expert-based Delphi Consensus.** *Ann Surg. 2019 Dec 1;270(6):955-9.*

Aim

The primary aim of this study was to achieve an international consensus on the definition of the rectum from the sigmoid colon. The secondary aim was to establish the variation in the existing definitions of the rectum.

Methods

On the basis of definitions of the rectum currently used in the literature, a Delphi consensus survey was conducted using an online tool (surveymonkey.com). The Delphi technique is a widely used consensus method that allows a large group of individuals to achieve consensus on a complex problem effectively by structuring the group communication process (Hsu and Sandford, 2007). A 70% level of agreement was required to achieve consensus within a maximum of 3 rounds.

Sampling

The survey was disseminated by e-mail to leading academics and practitioners known to the senior authors from all colorectal multi-disciplinary team (MDT) specialties (surgery, radiology, medical oncology, clinical oncology and pathology) (Figure 7-1) to ensure there was representation from experts across the colorectal multidisciplinary team with a high degree of knowledge and experience. Participants were encouraged to invite further specialists on this topic to join the Delphi survey. Members of the national associations of colorectal surgeons in Great Britain and the Netherlands were also invited to participate in the survey.

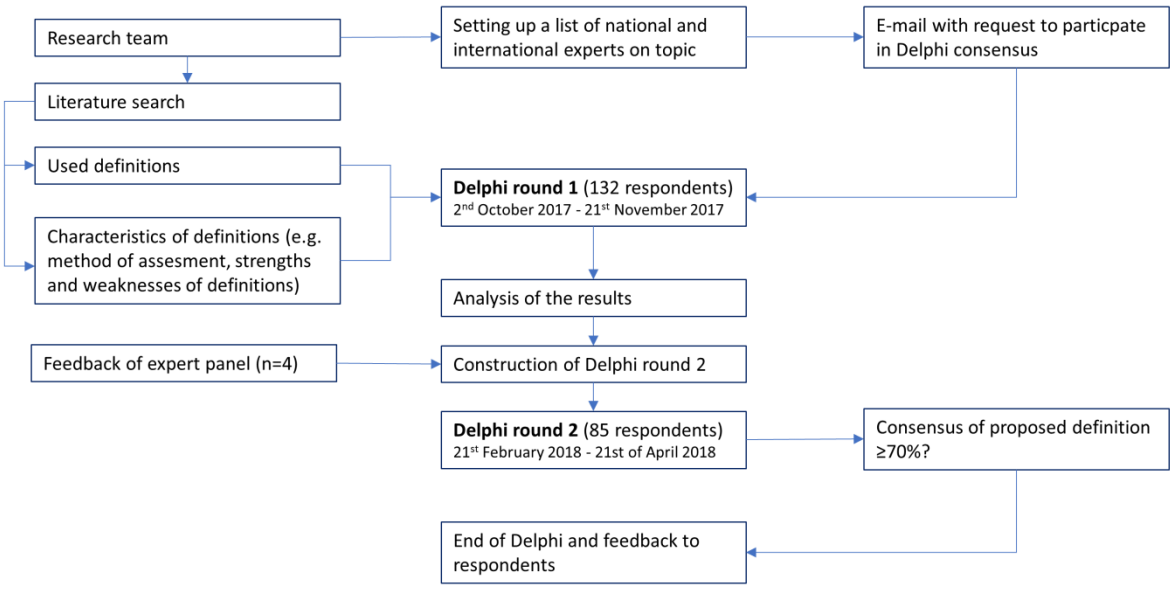


Figure 7-1: Delphi consensus flowchart

Definitions of the Rectum

Experts were surveyed on a range of published definitions of the rectum (Table 5-1, page 106). These included measurements from the anal verge (12, 15, 16 or 20cm) or anatomical landmarks (sacral promontory, anterior peritoneal reflection, coalescence of taenia coli, junction of mesorectum and mesocolon). Experts were also given the option of describing other landmarks they themselves used.

Round 1

In the first round, participants were invited to indicate their existing preferences for the definition of the rectum. Survey questions included their opinion about the importance of a consistent definition of the rectum, which modalities were available to participants in their institutions to define the rectum, and which modalities and landmarks they pragmatically used to define the rectum. A brief summary of evidence of the strengths and weaknesses of the landmarks were provided. Participants were then asked to restate their preferences for the ideal modality and landmark to define the rectum. Two e-mail reminders were sent to non-responders. Round 1 opened on the 2nd October 2017 and closed on the 21st November 2017.

Round 2

Only participants from the first round were invited to the second round. A panel of four experts, all colorectal surgeons with extensive experience, were consulted in advance to provide feedback on the survey. After incorporating their comments and obtaining their approval, the updated version of the survey was e-mailed. Participants were informed of the results of the first round. The participants were asked if they would agree as to which was the most popular 'ideal modality and landmark' of the rectum from the previous round. They were then given a summary of evidence for the most popular definition. Finally, they were asked to restate their preferred definition.

Logistic regression analysis was performed on STATA (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC) to investigate whether participant specialty or country affected voting. Round 2 opened on 21st February 2018 and closed on the 21st of April 2018.

Results

Round 1

There were 132 experts who responded to the invitation to take part in the survey and completed 89% of all survey questions. The majority of respondents (60%) were colorectal surgeons. All members of the MDT responded including surgeons (specialist rectal, general, surgical oncologist or retired), gastroenterologists, radiologists (specialist colorectal or general), medical oncologists, radiation therapists (clinical oncologists), and pathologists (Figure 7-2). All 6 continents were represented in the survey (Figure 7-2), with the bulk of participants from the countries of the survey authors (36% United Kingdom, 31% Netherlands).

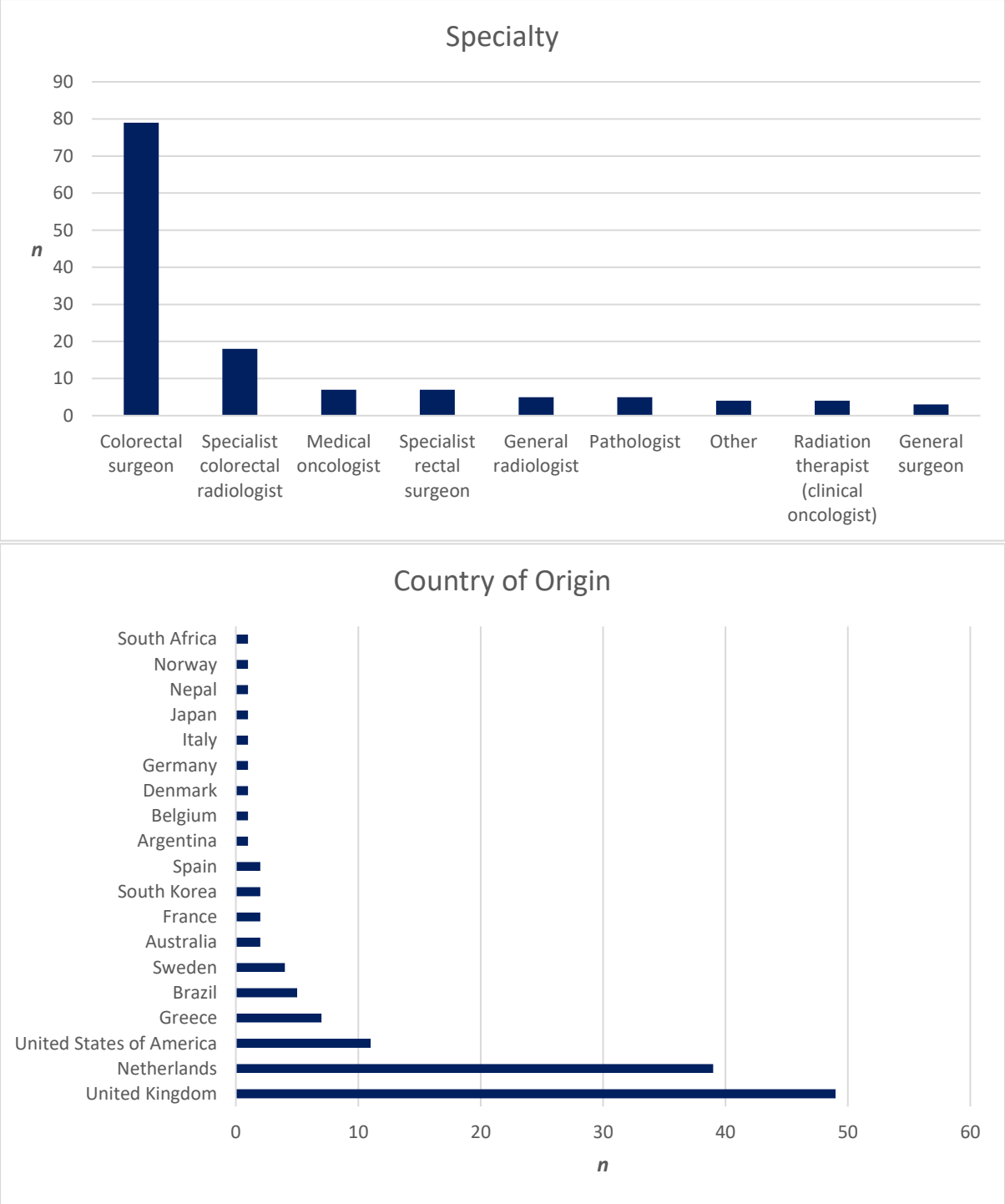


Figure 7-2: Participant background by MDT specialty and country

Over 90% of clinicians thought it was important to define the proximal extent of the rectum. The most common reasons were to determine eligibility for neoadjuvant therapy (75%), to counsel patients about their functional and oncological prognosis (43%), and to ensure adequate volumes of rectal cancer surgery (27%).

MRI was the most commonly available modality to define the rectum (98%), followed by flexible endoscopy (86%) and CT (80%). Pragmatically, MRI was used in over 67% of institutions to define the rectum, followed by rigid endoscopy (10%) and flexible endoscopy (8%). Other modalities mentioned included intra-operative findings, CT, histology, and barium enema.

Over 11 different pragmatic definitions were used in every day clinical practice (Figure 7-3). The most commonly employed definitions were 15cm from the anal verge (36%), the anterior peritoneal reflection (15%) and the sacral promontory (12%). The most common other definition of the rectum specified tumours arising below the line extending from the sacral promontory to the pubic symphysis.

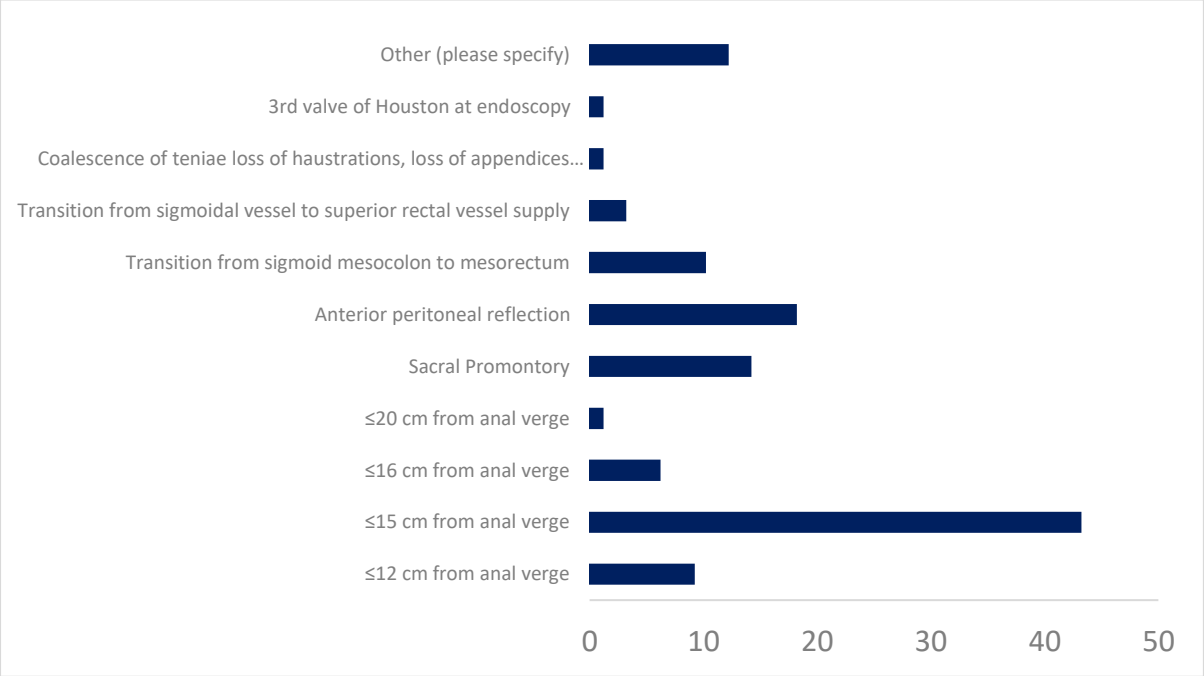


Figure 7-3: Pragmatic definitions (in daily use by experts) for the rectum

After a summary of published evidence for and against different landmarks, the preferred modality to define the rectum was MRI (73%), followed by intra-operative findings (13%) and rigid endoscopy (6%).

Of the imaging definitions of the rectum, the most commonly chosen definition was junction of mesorectum and mesocolon seen on imaging as the “sigmoid take-off” (56%), followed by 15cm from the anal verge (14%) and the sacral promontory (10%).

Round 2

85 participants from round 1 took part in round 2 and completed 91% of all survey questions (Figure 7-4). The majority (62%) were colorectal surgeons. All other representative members of the colorectal MDT were involved in round 2.

The geographic breakdown was similar to the first round, with all continents represented. The Delphi consensus definition of the rectum was agreed by 81% of participants to be the sigmoid take-off. A further 87% of participants were satisfied the sigmoid take-off could define the rectum. In total, 81% of participants believed the sigmoid take-off could be used within their own institution. No association between participant specialty, or country regarding their choice of definition was found upon logistic regression analysis.

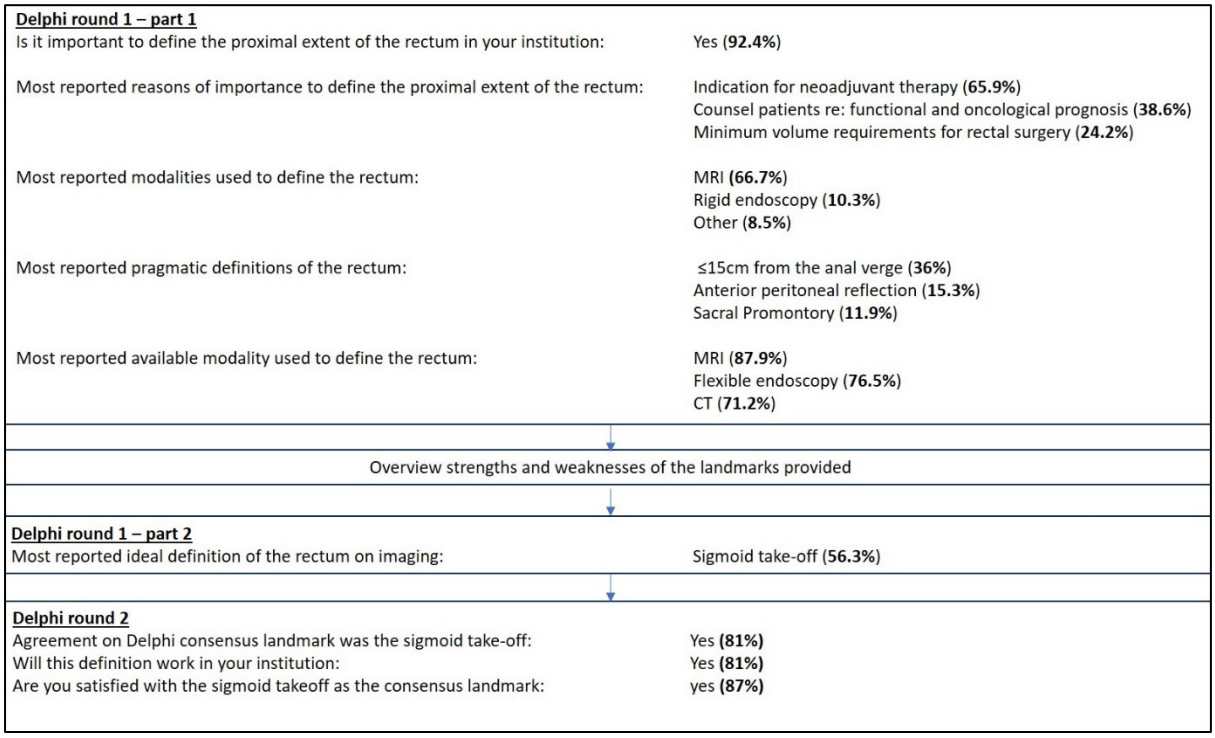


Figure 7-4: Summary of results from Delphi Consensus

Discussion

From a plethora of definitions for the rectum used globally, the sigmoid take-off, an anatomically based definition identifying the junction of the mesorectum and mesocolon, emerged as the consensus of international experts.

Pre-operative definitions of the rectum have been based on the traditional assessment modalities and treatment available. The digital rectal examination complemented by rigid endoscopy were the traditional methods of choice, as imaging was not available. A distance of 15cm from the anal verge by rigid endoscopy remains the most commonly used definition of the rectum in our initial survey (Nielsen and Wille-Jorgensen, 2014). While metric measurements at endoscopy are straightforward to perform, they bear no relationship to patient anatomy due to variation in rectal length as demonstrated in anatomical studies (Yun et al, 2008, Wasserman et al, 2016, Memon et al, 2009, D'Souza et al, 2018). In a series of 100 patients, the sigmoid colon began below 15cm in 84% of patients (D'Souza et al, 2018) confirming that metric measurements may incorrectly localise tumours to either the rectum or sigmoid. A metric definition is probably still preferred because it is easy to use in daily practice and enables a pre-operative decision about treatment or further diagnostic options. With the general adoption of MRI in staging rectal cancer, all disciplines moved towards the same language to describe tumour characteristics outside the bowel, but tumour localisation remains based on historical definitions employing luminal palpation and endoscopic visualisation. Consequently, the term “rectosigmoid” was introduced to take into account the difficulty distinguishing between the rectum and the sigmoid. Unfortunately, “rectosigmoid” tumours remain undefined, with differences of interpretation and management around the world.

The diversity in the number of definitions of the rectum was confirmed in round 1. While experts overwhelmingly (>90%) agree it is important to define the rectum, over 11 different definitions are employed in their daily practice. No single landmark was used by 40% of participants. These

different measurements are used by different guidelines, associations, and trials as seen above in table 1, reflecting the methods used in the past when the trials were designed. Colorectal clinical practice is therefore based on rectal cancer trials that had different definitions of the rectum, and will have included varying numbers of patients with sigmoid cancer, particularly if metric measurements were used to define the rectum. Trials on neoadjuvant therapy for rectal cancer will have reported on patients with tumours in the sigmoid colon. Consequently, we do not know which patients benefit from neoadjuvant therapy. Inclusion of these patients in these studies may dilute the benefits of pre-operative radiotherapy in rectal cancer, but it is also possible that the benefits of radiotherapy may also extend beyond extra-peritoneal rectal cancer to intra-peritoneal tumours in the distal sigmoid colon.

An imaging-based anatomic definition of the lower rectum has shown its benefits in cancer research, clinical management and outcomes (Battersby et al, 2016). A similar approach to the definition of upper rectal and sigmoid tumours will help improve the basis of treatment decisions and future research in this area. Despite metric measurements being the most commonly employed definitions, MRI was the most common modality used in clinical practice to define the rectum and available in 98% of participant institutions. The need for an anatomical based definition of the rectum was evident in the Delphi process as the sigmoid take off, emerged conclusively as the consensus landmark.

An anatomic definition such as the sigmoid take-off could in future be used to identify whether tumours in the intra-peritoneal rectum or sigmoid also benefit from radiotherapy. Consistent classification of distal sigmoid and upper rectal tumours will standardise future research from trials of neoadjuvant therapy, as well as local or national registries, and for MDT clinical management. The documentation of an anatomical location of the tumour could be used in the audit and accreditation of colorectal units, and reduce further inconsistencies in the use of chemoradiotherapy, or failure to adhere to treatment guidelines more generally for rectal or colon cancer.

Limitations of the sigmoid take-off and future research

The online Delphi technique enabled a global consensus to be achieved, with representation from all continents and from all members of the colorectal MDT. There was some over-representation from colorectal surgeons, and from the United Kingdom and the Netherlands, but the consensus remained consistent in participants in all countries and across different MDT specialties on logistic regression analysis.

An attrition rate is expected with a Delphi consensus, particularly with the larger sample size needed to sufficiently represent experts, in all specialties of the MDT, from all parts of the world. Our attrition rate of 36% to reach consensus was notably lower than other Delphi studies with smaller numbers of participants.

It was surprising that MRI is more available (98%) than flexible endoscopy (86%) and CT (80%). This may be because some participants only selected modalities they used to define the rectum, rather than all modalities available in their practice.

Implementation of this definition should occur on a routine basis for every patient during their evaluation in the colorectal MDT. Classification of tumours would be based on their anatomical location:

1. Distal sigmoid tumours that arise just above the take-off.
2. Tumours that commence in the rectum but straddle the take-off.
3. High rectal tumours which are located below the take-off.

This will enable a more consistent and accurate classification of the rectal versus sigmoid cancers and therefore a clearer understanding of the optimal clinical management of these tumours that were previously classified as “rectosigmoid”, or as rectal or sigmoid without consistency. Outcomes of these tumours could then be compared, particularly with regards to neoadjuvant therapy, but

also other strategies such as partial mesorectal excision. The sigmoid take-off offers a definition with an anatomical basis to harmonise efforts to investigate and improve outcomes.

Conclusion

An international panel of experts agreed that the sigmoid take-off as seen on CT or MRI defined the rectum. Colorectal practitioners are urged to use this intuitive, anatomical definition within their MDT to correctly localise tumours.

What does this study add to the literature?

Over 11 definitions for the rectum are employed in clinical practice across the world.

Through a Delphi process, an international group of expert colorectal MDT clinicians reached the first consensus definition of the rectum; the sigmoid take-off.

Chapter 8
The Rectosigmoid Waist

D'Souza N, Lord A, Shaw A, Patel A, Balyasnikova S, Tudyka V, Abulafi M, Moran B, Rasheed S, Tekkis P, Coffey JC, Terlizzo M, West NP, Quirke P, Brown G. **Ex-vivo specimen MRI and pathology confirm a recto-sigmoid mesenteric waist at the junction of the mesorectum and mesocolon.** *Colorectal Dis. 2020 Feb;22(2):212-8.*

Aim

This study aimed to characterise the anatomy of the mesentery at the colorectal junction by investigating whether a sigmoid mesenteric narrowing exists.

Methods

Patient selection, inclusion and exclusion criteria, ethical approval and generic MRI and histopathology techniques were described in chapter 3.

Endpoints

The primary endpoint was to determine if a mesenteric narrowing occurs in the sigmoid mesentery.

MRI/Histopathology Technique

During MRI scan of the specimen prior to cut-up, axial slices were taken at 3mm intervals, in addition to coronal and sagittal views (Figure 8-1).

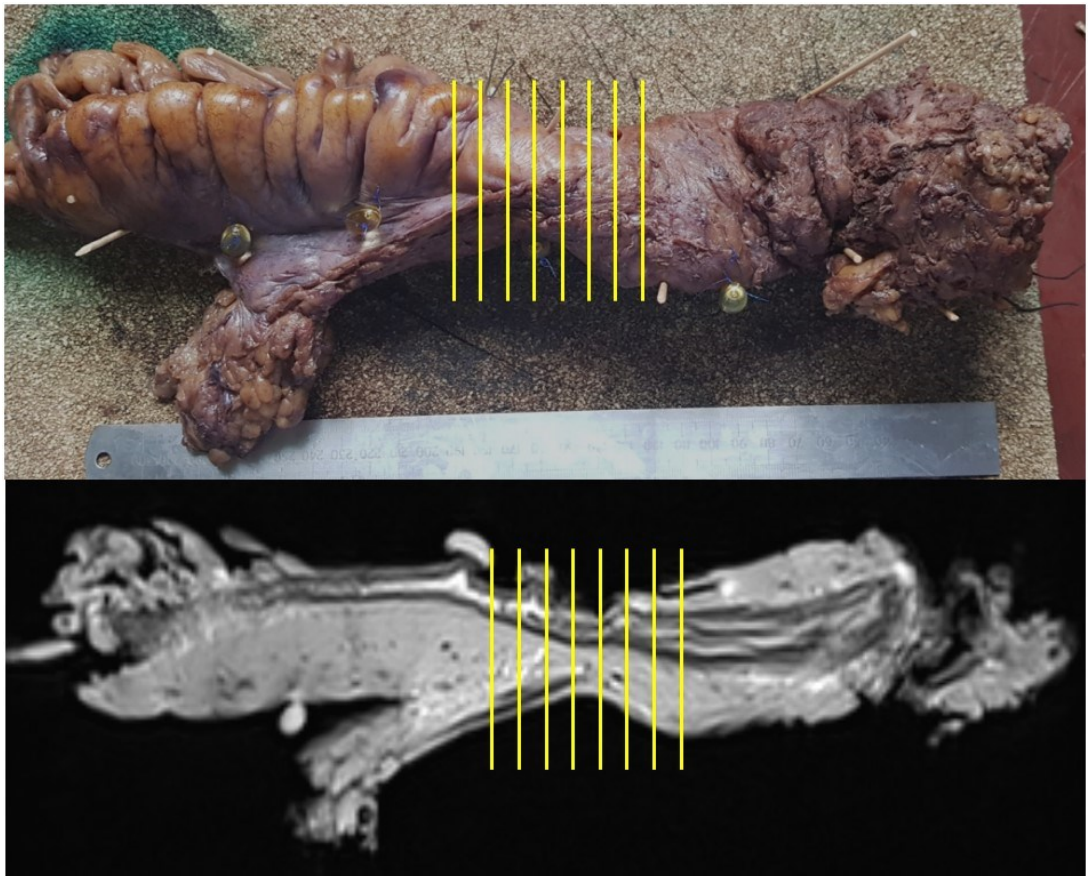


Figure 8-1: *Bowel specimen on photography and MRI*
Note. Specimen photograph (top) prior to MRI scan (bottom, coronal view). Blue lines represent transverse/axial slices taken during pathology and MRI processing.

During pathology cut-up, the specimen was sliced at 5mm intervals as per Royal College of Pathologists guidelines (Loughrey et al, 2014). Photographs were taken of these cross sectional slices using a high definition camera mounted on a tripod with a ruler for calibration (Figure 8-2).



Figure 8-2: Cross sectional specimen slices demonstrating mesenteric dimensions
Note. Serial slices through the formalin-fixed pathology specimen taken at 5 mm intervals, from top right. Posterior mesenteric distances (marked with black arrows and P) become greater from distal to proximal as the mesorectum becomes the sigmoid mesocolon. Waist in mesenteric surface area (marked with W) hypothesised to occur between sigmoid mesocolon and level of anterior peritoneal reflection (marked with star).

Mesenteric surface area and quadrant linear distances (posterior, left and right) above the anterior peritoneal reflection were measured per slice on MRI in the axial plane using Sectra PACS (Sectra Workstation IDS7, Sectra AB, Linköping, Sweden) and on pathology photographs using Digimizer (version 6.6.1, copyright MedCalc Software, Ostend, Belgium) software (Figure 8-3)

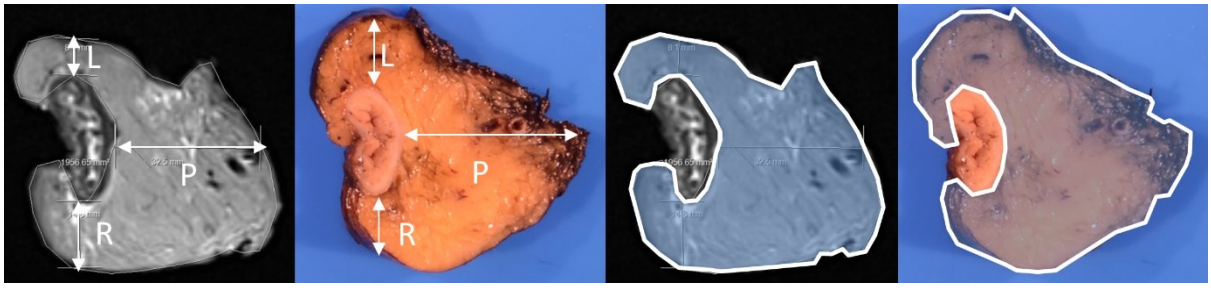


Figure 8-3: Measurements of mesenteric surface area and linear distances on MRI and pathology
Note. Labelled posterior (P), left (L) and right (R) mesenteric distances.

The area measurements were calculated by annotating the region between the outermost portion of the muscularis propria and the external border of the mesentery on both specimen cross sectional slice photos and MRI images (Figure 8-3). Linear distances were calculated by annotating the distance between the outer border of the muscularis propria and the left lateral, right lateral and posterior external border of the mesentery. Slice thickness on MRI (3mm) and pathology (5mm) was used to calculate the height from the anterior peritoneal reflection. All measurements were performed by the study investigator (ND'S) and reviewed by academic supervisors in pathology (NPW) and radiology (GB).

Statistical Analysis

For each patient, the minimum surface area and posterior mesenteric distance was plotted against height from the anterior peritoneal reflection for specimen pathology and MRI on two-way plots with quadratric best fit lines. Waist height was compared using descriptive statistics. Independent samples t-tests or one-way analysis of variance (ANOVA) were used to investigate continuous dependent variables for independent groups, and linear regression was used to investigate relationships between continuous variables.

Results

Recruitment was undertaken between April 2017 and April 2018 during which time 20 patients were consented to participate in the study (demographics in Table 8-1).

Patient Variable	
Mean Age (std. dev.)	58.5 years (12.5)
Mean Patient Height (std. dev.)	173.0cm (8.4)
Mean Patient Weight (std. dev.)	77.1kg (16.6)
Mean BMI (std. dev.)	25.6 kg/m^2 (4.5)
Gender	
Male	15 (75%)
Female	5 (25%)

Ethnicity	
White	17 (85%)
Indian	2 (10%)
Arabic	1 (5%)
Pre-operative radiotherapy	
Yes	18 (90%)
No	2 (10%)
Operation	
Exenteration	5 (25%)
Extra-levator abdomino-perineal excision	6 (30%)
Conventional abdomino-perineal excision	2 (10%)
Anterior Resection	7 (35%)

Table 8-1: Patient demographics

All 20 patients underwent MRI scanning of their specimens. Mesenteric distances on MRI in one specimen could not be measured due to distortion by tumour. Specimen cross sectional slice photographs were adequate for analysis in 17 out of 20 specimens. The remaining three patients either did not undergo specimen photography or the photographs taken did not include slices of the sigmoid mesentery.

Mesenteric surface area (as measured in the axial plane) was measured from distal (starting at the anterior peritoneal reflection) to the proximal extent of the specimen, or 10cm above the peritoneal reflection. Mesenteric surface area above the anterior peritoneal reflection gradually decreased before increasing (Figure 8-4) in the majority of specimens on MRI (18/20) and pathology (13/17), confirming the presence of a waist.

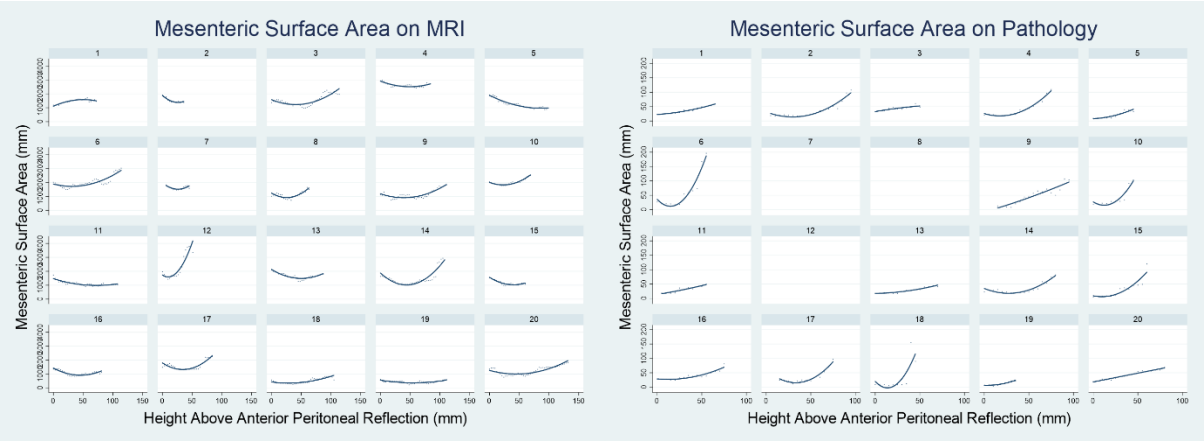


Figure 8-4: Mesenteric surface area vs distance from anterior peritoneal reflection
Note. Overall mesenteric surface area on MRI (left) and pathology (right) per specimen, commencing at the anterior peritoneal reflection. Line of best fit (quadratic) imposed over scatterplot of observed measurements. In most specimens, the mesenteric surface area of the upper rectum initially decreases to a minimum value (the waist) before increasing proximally as the sigmoid mesentery.

The area of mesenteric waisting included a reduction in the amount of posterior tissue (Figure 8-2) with the posterior mesenteric distance of the upper rectum initially reducing above the anterior peritoneal reflection, before elongating as the sigmoid mesocolon. This was evident on MRI (17/19) scans and pathology (15/17) specimens. The overall mesenteric waist occurred uniformly before the posterior mesenteric distance increased as the sigmoid colon (Figure 8-5). The lateral mesentery typically decreased between the peritoneal reflection and the overall mesenteric waist, and continued to diminish while the sigmoid mesocolon elongated (Figure 8-5).

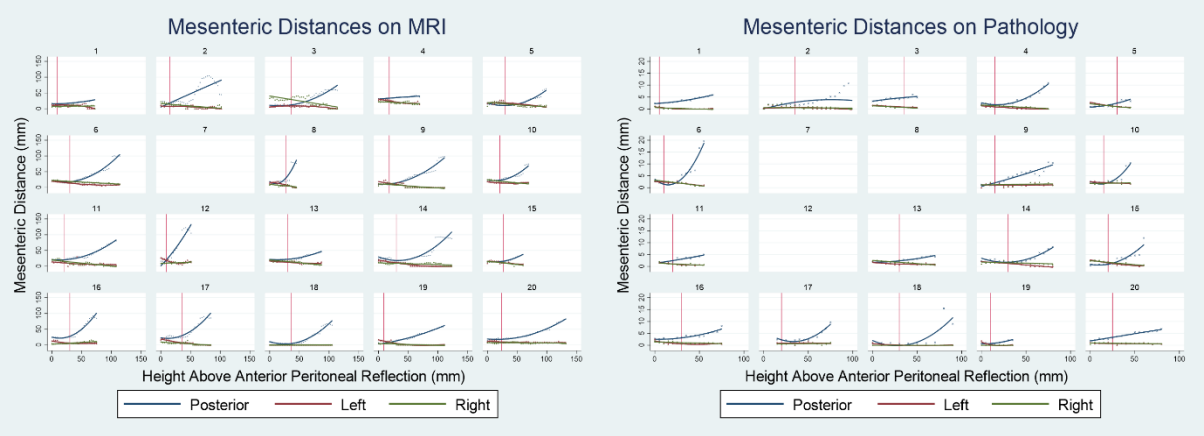


Figure 8-5: Mesenteric distances vs distance from anterior peritoneal reflection
Note. Posterior and lateral mesenteric distances on MRI (left) and pathology (right) per specimen, commencing at level of anterior peritoneal reflection. Red vertical reference line marking the level of the maximal point of overall mesenteric waisting.

Above the level of the waist, the posterior mesenteric distance increased as the sigmoid mesentery lengthened to its apex. The mesenteric waist occurred near/at the minimum posterior mesenteric distance, and before the sigmoid mesocolon began in all cases, suggesting it could be a mesenteric landmark for the rectum. The lateral mesenteric distances had diminished/were diminishing at the point of the mesenteric waist.

The mesenteric surface area decreased to a minimum at a mean distance of 23.6mm above the anterior peritoneal reflection on MRI, and 21.7mm on pathology (Table 8-2). The posterior mesenteric distance also reduced to a minimum at a mean distance above the anterior peritoneal reflection of 22.3mm on MRI, and 20.9mm on pathology. On MRI, the posterior waist occurred within 6mm (2 MRI slices) of the circumferential waist in 18/19 cases. On pathology, the posterior waist was within 10mm (2 pathology slices) of the circumferential waist in 17/17 cases. There was no significant difference in the distance to the circumferential and posterior waist on MRI (p=0.234) or pathology (p=0.92).

Landmark	*n*	Mean	St. Dev.	Min	Max	95% Confidence Interval
MRI mesenteric area waist	20	23.6	8.7	9	36	20.6 – 31.3
Pathology overall area waist	17	21.7	9.2	5	35	16.5 – 25.3
MRI posterior waist	19	22.3	9.4	9	42	17.6 – 26.3
Pathology posterior waist	17	20.9	8.1	5	35	16.6 – 24.6

Table 8-2: Distance from the anterior peritoneal reflection to waist on MRI or pathology
Note. All distances measured in millimetres.

There was no significant relationship between mesenteric surface area (on pathology) at the level of the waist and age (p=0.33), ethnicity (p=0.15) pre-operative radiotherapy (p=0.77), height (p=0.07) or BMI (p=0.10). Mesenteric area at the waist was significantly higher in men (p=0.04), and with increasing weight (p=0.04). Distance to the circumferential waist from the anterior peritoneal

reflection (on pathology) did not vary by any variable, including age, (p=0.99), sex (p=0.57), ethnicity (p=0.49), weight (p=0.42), height (p=0.64), BMI (p=0.25) or pre-operative radiotherapy (p=0.25).

Discussion

In this paired imaging and specimen anatomical assessment of the rectosigmoid region, a mesenteric narrowing was identified at the junction of the mesosigmoid and mesorectum. The narrowing created an appearance of a mesenteric waist, which may be an area of potential high risk for circumferential resection margin involvement in cancer surgery, particularly if the posterior margin is threatened. The waist was consistently identified approximately 20mm proximal to the anterior peritoneal reflection, and did not vary by age, sex, height, weight, body mass index, or use of pre-operative radiotherapy. Above this point, the mesorectum transitioned to the sigmoid mesocolon; this anatomical transition was reflected by an increase in the posterior mesenteric distance as the sigmoid mesentery elongates to the apex of the sigmoid loop (Figure 8-2). It follows that the recto-sigmoid mesenteric narrowing or “waist” could serve as a landmark to define the anatomical rectum and sigmoid.

Local recurrence after sigmoid cancer resection has been under-reported and hence its incidence under-estimated. A narrowing of the mesentery into a waist-like region, between the rectum and sigmoid, could increase the risk of margin involvement by tumours at this level. As with low rectal cancer the relative paucity of mesenteric tissue at this level renders oncological resection more challenging. Surgery outside the mesocolic plane or the presence of involved margins may adversely affect survival (West et al, 2009). However, while low rectal tumours may be managed using an extra-levator approach when the margin is threatened, posterior tumours may encroach on S1 and hence be deemed inoperable. Ensuring an adequate resection margin with wide excision requires planning and careful dissection and where this is not possible preoperative therapy may be beneficial. Such an approach requires review of each sigmoid cancer in a multidisciplinary team

(MDT) meeting, where each specialty will be contributing and sharing their expertise to optimize patient management. When this MDT process was implemented at the Royal Marsden, 3-year cancer specific survival for predicted poor prognosis tumours of the sigmoid, rectosigmoid and upper rectum improved from 62% to 81% (Burton et al, 2006a).

Our data supports descriptions by Coffey's group who recently found that the sigmoid mesocolon tapers to a "point of maximal convergence" before widening to continue as the mesorectum (Culligan et al, 2012). A pilot study of pathological specimens at the University of Leeds confirmed the presence of a waist in the sigmoid mesentery, but without reference to specific anatomical landmarks. In this study, the presence of a waist was confirmed—but as hypothesised by Coffey's group, this occurred at the junction of the mesorectum and mesocolon.

Limitations

As an exploratory study, this study was designed to generate a hypothesis rather than definitively confirm or refute the presence of a waist. Nonetheless, a waist was found in nearly all patients, despite the heterogeneity that would be expected from anatomy and surgery in a small sample size. The omission of usable specimen photographs for three patients was unfortunate and was due to urgent service pressures to report the histopathology of patients with cancer, and the requisite immersion time in formalin was not possible in these cases.

The slight discrepancy of specimen measurements and waist position between MRI and pathology may be due to several factors. This includes slices off the longitudinal axis on MRI or variable thickness of slices made on pathology. The consistently smaller measurements on pathology could be explained by formalin immersion in the interval between specimen MRI and pathology, which is associated with specimen shrinkage (Goldstein et al, 1999, Horn and Naugler, 2014). Thinner slices on MRI (3mm) compared with pathology (approximately 5mm) may have also contributed to a discrepancy in measurements. To pre-empt these problems, we performed measurements using both modalities (imaging and tissue analysis). There was some variation in mesenteric surface area

by weight and sex, but none in distance from the anterior peritoneal reflection to the waist by any other variable. Nonetheless, there may be undetected variation due to lack of power in this exploratory study, certainly with regards to pre-operative radiotherapy, when only 2/20 patients were not pre-operatively irradiated. To ensure that radiological and pathology findings do correlate, a larger sample size would be required, ideally with a large enough subgroup of non-irradiated patients to account for the effect of pre-operative radiotherapy. In only one case was the tumour high enough to distort the mesentery and peritoneum above the anterior peritoneal reflection, and in retrospect, high rectal tumours should have been a trial criterion for exclusion.

The rectosigmoid junction in this study was found to be only approximately 20mm (and maximum 32mm) above the anterior peritoneal reflection. This is consistent with estimates of upper rectal length from the National Cancer Institute (National Cancer Institute, 2019). The peritoneal reflection could therefore be a surrogate landmark for the rectum, as previously suggested (Massalou et al, 2018, Kenig and Richter, 2013, Culligan et al, 2014, Culligan et al, 2012). The short distance from the distal sigmoid to the upper rectum suggests that that tumour extension will commonly lead to rectosigmoid cancers, and that mesorectal excision may be necessary to achieve a clear distal margin for rectosigmoid or even distal sigmoid cancers.

Conclusion

Above the anterior peritoneal reflection, a mesenteric waist exists that marks the junction of the mesorectum and mesocolon. This rectosigmoid waist can be identified on both radiology and pathology, and may serve as a landmark for the rectum.

What does this study add to the literature?

A narrowing of the sigmoid mesentery has been described but not formally investigated. This study identified a mesenteric waist at the rectosigmoid junction. This is a landmark for the rectum found on both pathology and radiology, less than 30mm above the anterior peritoneal reflection. Tumours in the rectosigmoid may be prone to local recurrence due to the paucity of surrounding mesenteric tissue.

Chapter 9
A Radiological Definition of the Rectum

D'Souza N, Lord A, Shaw A, Patel A, Balyasnikova S, Tudyka V, Abulafi M, Moran B, Rasheed S, Tekkis P, Terlizzo M, West NP, Quirke P, Brown G. **The Sigmoid Take-Off: An Anatomical Imaging Definition of the Rectum Validated on Specimen Analysis.** *Eur J Surg Oncol.* 2020 Jan pii: S0748-7983(20)30008-1.

Aim

The aim of this study was to investigate whether the pre-operative radiological landmark of the sigmoid take-off was validated by measurements on specimen analysis to define the rectum.

Methods

Endpoints

The primary endpoint was to investigate whether the sigmoid take-off on imaging correlated to the mesorectal-mesocolic transition on specimen analysis. The study was conducted according to methods described in Chapter 3.

MRI/Histopathology Technique

The sigmoid take-off was identified on pre-operative MRI. The distance was then measured from the corresponding point of the anterior colon to the anterior peritoneal reflection using PACS (picture archiving and communication system, Figure 9-1). On pathology, measurements of the posterior mesenteric distance were performed on each slice: the slice with the shortest distance before it elongated corresponded to the mesorectal-mesocolic transition and hence the rectosigmoid junction. The distance to the anterior peritoneal reflection was measured by the number of slices and their thickness (5mm). To ensure the reliability of the MRI measurements, they were performed by 2 paired observers: a specialist gastrointestinal radiologist (Reader 1) and a surgical colorectal research fellow (Reader 2).

On pathology, the mesorectal-mesocolic transition was identified when the posterior diameter of the mesentery began to increase above the peritoneal reflection, reflecting the transition from the mesorectum into the U-shaped sigmoid mesocolon.

MRI and pathology measurements were reviewed by an academic gastrointestinal radiologist and pathologist respectively.

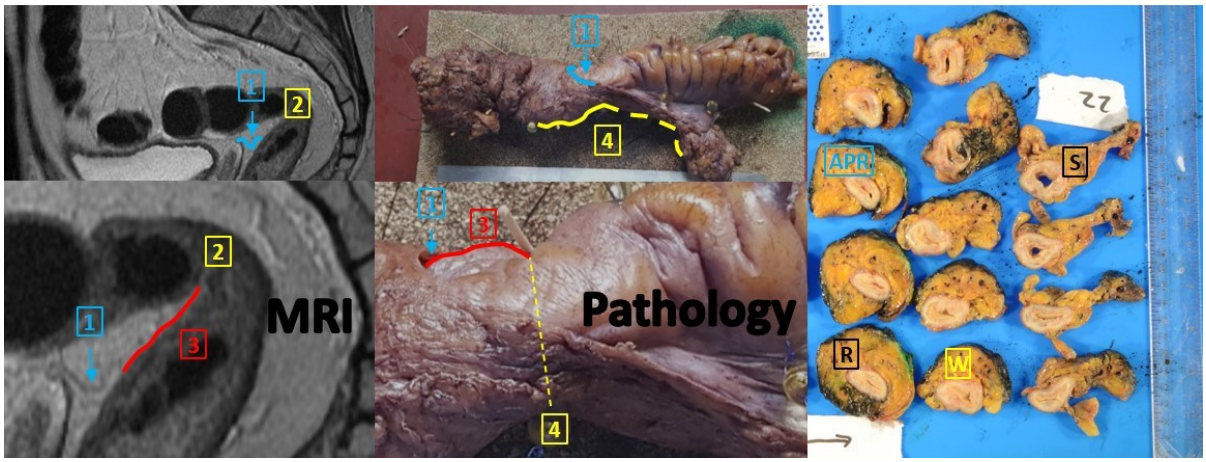


Figure 9-1: Measurements from the anterior peritoneal reflection to the sigmoid take off and mesorectal-mesocolic transition
Note.
Left*:* MRI image demonstrating distance from the anterior peritoneal reflection (APR) to the sigmoid take-off. Middle: pathology specimen image demonstrating distance from the anterior peritoneal reflection (APR) to the beginning of the sigmoid mesocolon. Right: Pathology cut-up specimen, demonstrating posterior mesenteric elongation from the mesorectum to mesocolon.
Labels: 1 = Anterior peritoneal reflection (MRI and pathology), 2 = Sigmoid Take-Off on MRI 3 = Distance (anterior) from APR to sigmoid take-off (MRI), and from APR to mesorectal-mesocolic transition (pathology). 4 = Mesorectal (solid line) - Mesocolic (dashed line) transition on pathology
Cut-up: R = Mesorectum, APR = Anterior Peritoneal Reflection, W = Mesenteric waist (transition from mesorectum to mesocolon), S = Sigmoid mesocolon

Statistical Analysis

Endpoints were summarised using graphical methods and descriptive statistics including Pearson's Correlation Coefficient. Bland-Altman methods were used to illustrate differences in paired MRI-pathology measurements from the anterior peritoneal reflection to the rectosigmoid junction. A mean difference between paired measurements of greater than 10mm was defined as being clinically significant.

Results

Twenty patients were recruited to the study (Table 8-1) between April 2017 to April 2018. MRI measurements were not feasible in one patient due to distortion by a locally advanced tumour, but were available for the remaining 19 patients. In 3 patients, the specimens were not dissected according to the study protocol, but measurements were available for the remaining 17 patients. The mean patient age was 58.5 years (range 32-78), and 25% of patients were female. Pre-operative radiotherapy had been given in 90% of patients.

On imaging, the mean distance from the anterior peritoneal reflection to the sigmoid take-off was 21.7mm for both readers (Table 9-1). On pathology, the mean distance from the anterior peritoneal reflection to the mesorectal-mesocolic transition was 20.6mm.

	MRI: APR → sigmoid take-off (mm)		**Pathology: APR → mesocolon (mm)**
	Reader 1	Reader 2	
Mean	20.3	23.1	20.6
St Dev	5.61	9.4	7.7
Median	19.5	20	20
25%	16	13.9	15
75%	25	31.7	30
Pearson's rank correlation	0.77	0.81	
Mean Difference (95% confidence interval)	-0.31mm (-2.83 to 2.20mm)	2.51mm (-0.31 to 5.33mm)	
Limits of Agreement	-9.89 to 9.27mm	-13.3 to 8.24mm	

Table 9-1: Rectal measurements on MRI vs pathology
Note. APR= Anterior Peritoneal Reflection

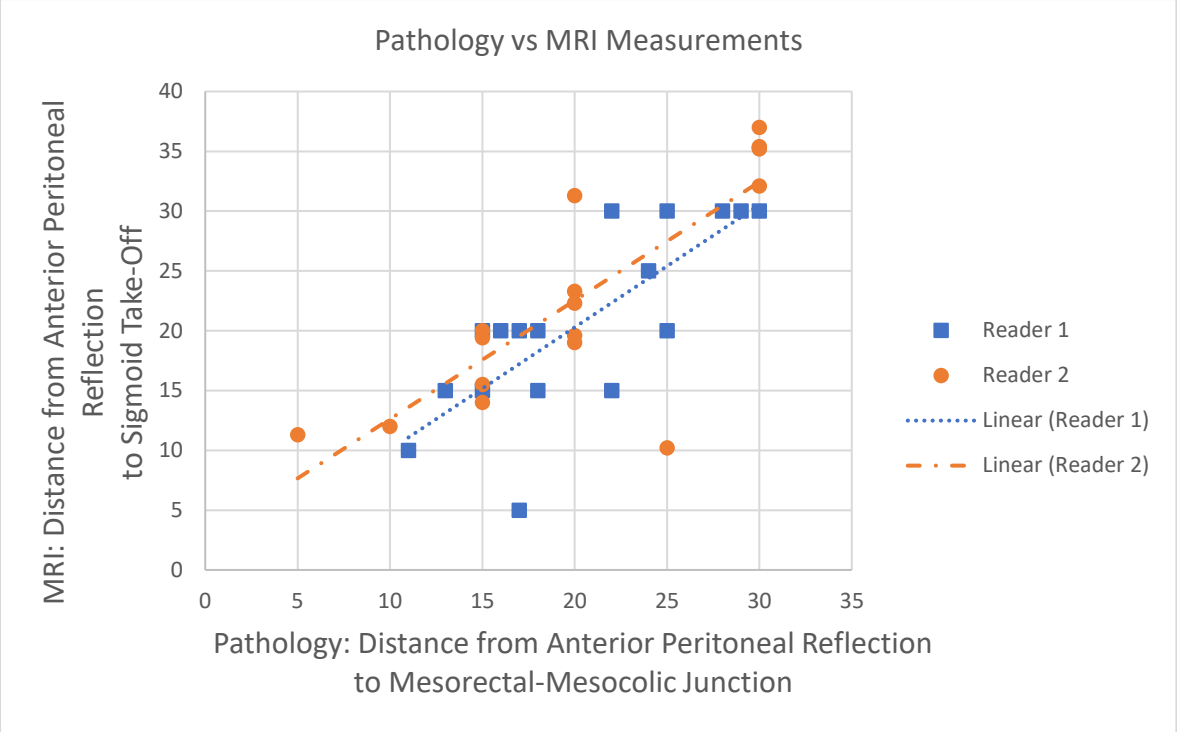


Figure 9-2: Measurements from the anterior peritoneal reflection to the rectosigmoid junction on MRI vs pathology

Increasing distance from the anterior peritoneal reflection to the rectosigmoid junction was matched on both imaging and specimen landmarks (Figure 9-2), demonstrated by Pearson's correlation coefficient (r) was 0.77 and 0.81 for each reader. The mean difference between imaging and specimen landmarks for the rectosigmoid junction to the anterior peritoneal reflection was -0.31 and 2.51mm for each reader, as illustrated by Bland-Altman plots (Figure 9-3). There was less than 10mm difference in 31/34 (91%) paired MRI-pathology measurements.

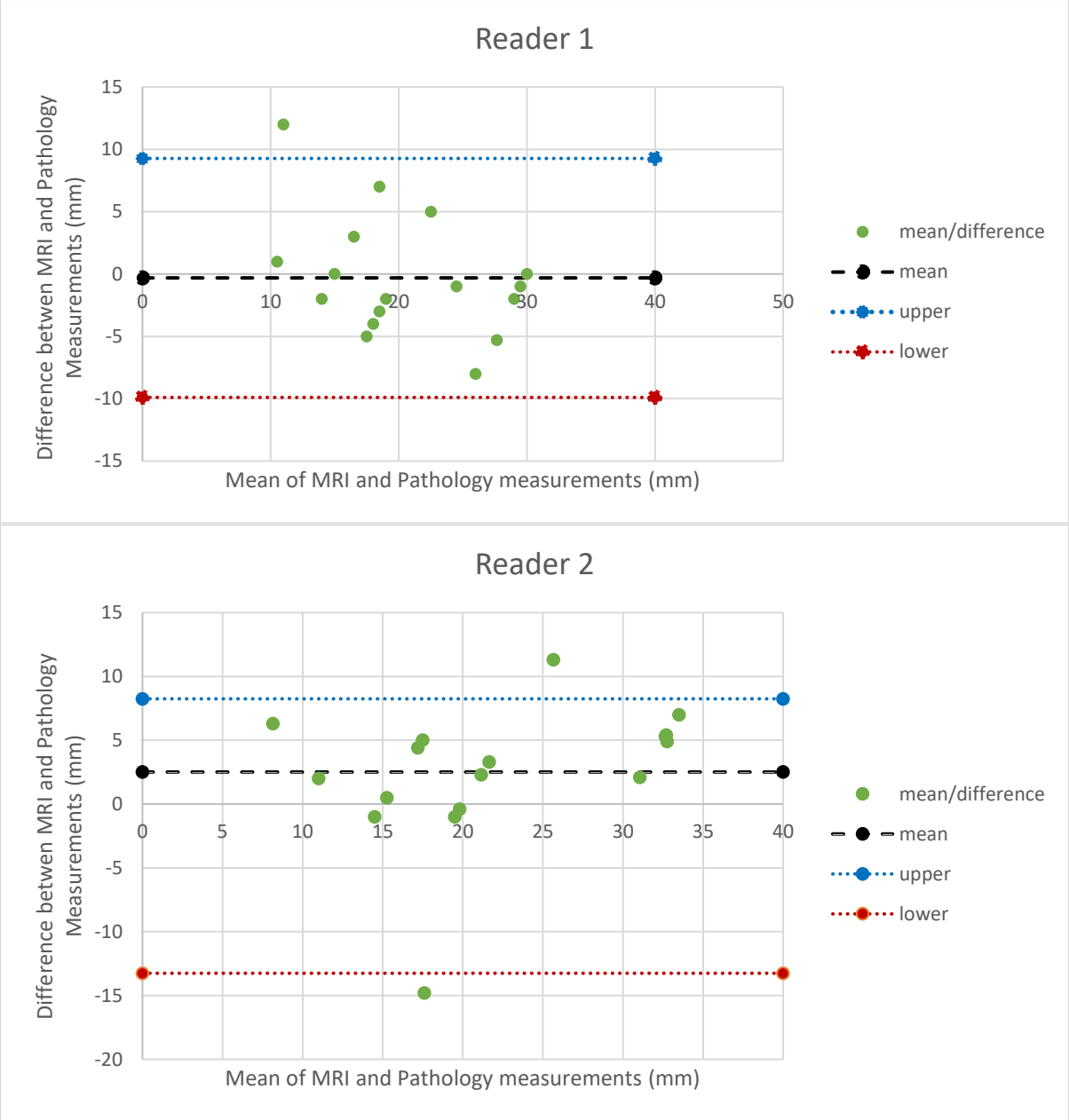


Figure 9-3: Bland-Altman plot of paired measured MRI and pathology distances
Note. Bland-Altman plots the differences between paired measured MRI and pathology distances (y axis) against the mean of the two values (x axis), for Readers 1 (top) and 2 (bottom). Positive measurements on y axis = greater distance on MRI than pathology.

Discussion

The sigmoid take-off was found to identify the rectosigmoid junction on pre-operative imaging, with mean differences from a specimen-based definition of less than 10mm (-0.31 and 2.51mm) and a strong correlation of 0.77 and 0.81 with two readers. The pre-operative definition was within 10mm

of the beginning of the rectum in 91% of measurements. This is an exploratory study to investigate the validity of this definition with a limited number of cases and only two readers. Yet this would appear to be a clinically significant correlation and agreement that may serve to validate the sigmoid take-off as an imaging definition of the rectum based on specimen anatomy.

Cross-sectional imaging enables identification of anatomical features that differentiate the rectum from the sigmoid. Using the sigmoid take-off, the mesocolon can be differentiated from the mesorectum, and the cascade of spidery sigmoid vessels can be distinguished from the larger calibre superior rectal artery that usually continues from the inferior mesenteric artery (Figure 5-2, page 110).

Two readers of pre-operative imaging were involved in this study, and further research into the inter-rater reliability of this definition is required, ideally in a larger sample. Nonetheless this is the first study to validate a pre-operative definition of the rectum using specimen anatomy. We highlighted variation in the length of the rectum and its position against bony landmarks both from the literature (Chapter 5) and in our own in-vivo study (Chapter 6). By using these arbitrary landmarks, tumours will be erroneously localised to the sigmoid or rectum. This may lead to radically different management for patients. It will inevitably have meant that rectal cancer trials that used metric measurements, including laparoscopic surgery (Stevenson et al, 2015) or neoadjuvant therapy (Sauer et al, 2004), will have included patients with sigmoid cancer, and been confounded. It also remains unclear whether distal sigmoid cancers, or rectosigmoid cancers, are best managed using a rectal cancer treatment strategy.

Limitations

The sigmoid take-off is usually intuitive and can be seen on any form of cross-sectional imaging on 2 views. While the results show good correlation and agreement, on a patient-by-patient basis there may be some discrepancies. We inspected the outlying results in our study with a discrepancy between their pathological-imaging distances. In these cases, we found the rectum was tortuous on

coronal imaging. Viewing images in this third plane may be required. We described possible explanations for discrepancy between anatomical measurement on pathology and radiology in Chapter 8 (page 140).

We have correlated radiology with pathology, but it is possible that pathology may not be the optimal gold standard for distinguishing between the rectum and sigmoid. The vascular supply and drainage may be more oncologically relevant, but this cannot be routinely assessed on pathology specimens. Further investigations regarding the vascular drainage of the rectum vs. the sigmoid may provide more appropriate distinction between the two bowel segments.

While tumours can now be localised to the rectum or sigmoid using the sigmoid take-off, it remains unclear how best to classify and manage tumours that straddle the take-off. These tumours are true rectosigmoid tumours; further research can be directed to investigate whether these tumours are best managed according to rectal cancer protocols.

Specimen analysis has confirmed that the sigmoid take-off can be identified on pre-operative imaging. This same landmark has been agreed to define the rectum by a Delphi consensus of international experts. Investigation of its inter-observer reliability may be required before adoption by trials and guidelines for rectal cancer treatment. In the interim, we would suggest that tumour position is checked routinely against the sigmoid take-off, for every patient with sigmoid or rectal cancer in the MDT.

Conclusion

The sigmoid take-off has been validated on specimen analysis to be an imaging landmark that defines the rectum. If used routinely in the MDT, rectal or sigmoid tumours will be correctly localised so that patients embark on the correct treatment strategy. The sigmoid take-off should be employed in future rectal cancer trials as a standardised definition of the rectum.

What does this study add to the literature?

The sigmoid take-off is an anatomical, imaging landmark that defines the rectum. This is the first study to validate a radiological definition of the rectum by specimen analysis.

Chapter 10

Predicting Local Recurrence of Sigmoid Colon Cancer

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Introduction

Aim

The aim of this study was to investigate the contemporary rates and patterns of local recurrence after surgery for sigmoid cancer, and which disease biomarkers on pre-operative imaging or post-operative pathology best predicted local recurrence.

Methods

Endpoints

The primary endpoints were the local recurrence rates and sites of sigmoid cancer.

The secondary endpoint was to investigate which variables, either pre-operative or post-operative, were associated with local recurrence.

Local Recurrence Classification

Data on subsequent local recurrence at follow up was recorded and analysed, including the anatomical location of the recurrence with regards to the primary tumour and the surrounding tissues, the time to local recurrence and the use of neo-adjuvant and adjuvant therapy. Local recurrence was classified as any intra-abdominal tumour regrowth outside of the liver as confirmed by biopsy or clinical suspicion on imaging.

Local recurrence has been classified into several sites (Elferink et al, 2012, Brown and Koh, 2020, Liska et al, 2016), which include:

6) Peri-anastomotic: In the immediate vicinity of the primary anastomosis
7) Peritoneal: Away from the primary tumour site but within the peritoneum
8) Retro-peritoneal: Posterior to the peritoneal cavity extending up to the pre-aortic region
9) Pre-sacral: Anterior to the Sacrum
10) Mesenteric: Within the sigmoid mesentery along draining venous vasculature

Statistical Analysis

The statistical analysis was described in chapter 3. Proportional Hazard models were created using backwards stepwise selection ($p<0.2$). Non-significant predictor variables were eliminated sequentially ($p>0.05$) and likelihood ratios were used to test inclusion/exclusion decisions.

Results

A total of 414 patients were included (Figure 3-1, page 79) in the analysis. The mean age was 66 years (12.7 years standard deviation) and 60% of patients were male. Neoadjuvant and adjuvant therapy was administered in 10% and 49% of patients respectively. The local recurrence rate was 52/414 (12.6%). The pathologically involved margin rate (R1 or R2) was of 2.4%. The median duration of follow up was 61 months (interquartile range 40-87 months). Overall, 399/414 (96.4%) had follow up for a minimum of 36 months or until death. Pre and post-op variables for all patients can be seen in Table 10-1. Genetic mutation analysis was performed in 26% of patients (106/414).

		n	%	% with LR	*p* value
Total		414	100	12.6	-
Age, mean (st dev)		66.1 (12.7)		66.7 (12.2)	
Female (%)		166	40.1	13.3	0.73
Emergency		49	12.0	18.4	0.19
Neoadjuvant therapy		42	10.1	11.9	0.89
CT T	**1**	**20**	**4.8**	**0**	**0.003**
	2	**66**	**15.9**	**12.1**	
	3a	**76**	**18.4**	**7.9**	
	3b	**97**	**23.4**	**8.3**	
	3c	**58**	**14.0**	**10.3**	
	3d	**24**	**5.8**	**25.0**	
	4a	**59**	**14.3**	**22.0**	
	4b	**14**	**3.4**	**35.7**	
CT N	**0**	**220**	**53.1**	**10.0**	**0.001**
	1	**92**	**22.2**	**6.5**	
	1c (TDs)	**81**	**19.6**	**25.9**	
	2	**21**	**5.1**	**14.3**	
CT EMVI		**170**	**41.1**	**19.4**	**<0.001**
CT local peritoneal infiltration		**31**	**7.5**	**38.7**	**<0.001**
pT	**1**	**24**	**5.8**	**8.3**	**<0.001**
	2	**62**	**15.0**	**4.8**	
	3	**120**	**29.0**	**10.0**	

	3a	**30**	**7.3**	**13.3**	
	3b	**61**	**14.7**	**1.6**	
	3c	**17**	**4.1**	**17.7**	
	3d	**4**	**1.0**	**0.0**	
	4a	**80**	**19.3**	**27.5**	
	4b	**16**	**3.9**	**31.3**	
pN	0	251	60.6	10.0	0.07
	1	101	24.4	12.9	
	1c (TDs)	9	2.2	22.2	
	2	53	12.8	22.6	
pEMVI		**142**	**34.3**	**18.3**	**0.01**
Lynch gene mutation		14/135	10.3	14.2	*0.98*
KRAS gene mutation		37/106	34.9	32.4	*0.60*
Grade	***Well – moderate***	**369**	**89.1**	**11.9**	**0.05**
	Poor	**30**	**7.3**	**16.7**	
	Fibrosis	**8**	**1.9**	**0**	
	Missing	**7**	**1.7**	**0**	
TNM Stage	*I*	60	14.4	6.7	0.18
	II	165	39.8	11.5	
	III	189	45.6	15.3	
R1		**10**	**2.4**	**40.0**	**0.008**
Anastomotic Leak		14	3.4	21.4	0.31
Adjuvant therapy		204	49.3	14.7	0.19

Table 10-1: patient demographics and staging data
Note. Pathology (p-prefix). EMVI = extramural venous invasion. TDs= tumour deposits.

Patterns of Local Recurrence

The most common site of local recurrence was peri-anastomotic (50%), followed by peritoneal recurrence (33%). The remainder of patients had local recurrence in the retroperitoneum (7.7%), mesentery (5.8%) or pre-sacral area (3.8%). Local recurrence was isolated without distant metastases in 42% of patients.

Predictors of Local Recurrence

On univariate cox regression analysis, the presence of advanced T stage, EMVI and tumour deposits was strongly predictive of recurrence (Table 10-2). These factors can commonly be identified on pre-operative imaging. EMVI and tumour deposits appear more important than advanced T stage. It has previously been suggested that lymph node positivity may be responsible for some cases of local recurrence but the current data highlights other factors that may be more important in identifying

patients at risk. Multivariate cox regression revealed that local recurrence was predicted by the presence of tumour deposits and local peritoneal infiltration on CT as well as tumour stage on pathology.

Variable	Univariate HR	*p* value	Multivariate HR	*p* value
Age	0.99 (0.99-1.01)	*0.90*		
Female Sex	1.10 (0.63-1.91)	*0.74*		
Emergency surgery	1.44 (0.99-2.06)	*0.05*		
Neoadjuvant therapy	0.90 (0.36-2.26)	*0.84*		
ctT (1, 2, 3, 4)	**1.18 (1.05-1.32)**	***0.004***		
ctN (0, 1, 1c, 2)	**1.48 (1.13-1.92)**	***0.004***		
ctTD (tumour deposits)	**3.24 (1.86-5.64)**	***<0.001***	**2.20 (1.22-3.97)**	**0.009**
ctEMVI	**2.75 (1.56-4.83)**	***<0.001***		
ctPeritoneal (local peritoneal infiltration)	**4.37 (2.29-8.33)**	***<0.001***	**2.42 (1.20-4.89)**	**0.014**
pT (1, 2, 3, 4)	**1.28 (1.14-1.43)**	***<0.001***	**1.19 (1.07-1.33)**	**0.001**
pN (0, 1, 1c, 2)	**1.18 (1.06-1.31)**	***0.002***		
pN < 12	1.29 (0.74-2.25)	*0.37*		
pTDs	1.18 (0.89-1.57)	*0.25*		
pEMVI	**2.08 (1.21-3.60)**	***0.008***		
Grade (fibrosis, well/mod, poor)	**1.36 (1.06-1.73)**	***0.02***		
Lynch gene mutation	1.02 (0.23-4.40)	0.98		
KRAS gene mutation	1.23 (0.59-2.52)	0.58		
TNM Stage (I, II, III)	**1.13 (0.99-1.28)**	***0.07***		
R1/R2	**4.82 (1.73-13.4)**	***0.003***		
Anastomotic Leak	2.01 (0.62-6.44)	*0.24*		
Adjuvant therapy	1.42 (0.82-2.46)	*0.21*		

Table 10-2: Cox univariate and multivariate proportional hazards analysis of variables impacting local recurrence
Note. CT imaging (ct-prefix) and pathology (p-prefix). HR = hazard ratio. EMVI = extramural venous invasion. TDs= tumour deposits.

Discussion

In this contemporary series, sigmoid cancer was associated with a local recurrence rate of 12.6%. This rate is higher than recent local recurrence rates for low rectal cancer (Deijen et al, 2017, Park et

al, 2017), and consistent with the 10.5% rate found on meta-analysis in Chapter 4. These results illustrate that pre-operative CT identifies high risk extra-nodal biomarkers of colon cancer. The importance of adverse features identified on pre-operative imaging opens up a range of potential neo-adjuvant treatments or more extensive surgical procedures, not applicable if post op histology alone is used for treatment planning. Since the majority of patients undergo CT staging prior to surgery, this offers an opportunity to target patients at high risk of local recurrence using neo-adjuvant therapy.

As described in Chapter 4, other contemporary local recurrence rates may be lower because most previous studies on sigmoid cancer outcomes did not publish R1 resection rates, and generally excluded outcomes in these patients. Most series also exclude patients deemed to undergo "palliative" resections, or patients undergoing emergency surgery, or patients with rectosigmoid or distal sigmoid tumours. In the current series we included all patients without metastases who underwent colonic resection for sigmoid cancer. Consequently, the number of patients with T4 (23%) or stage III disease (46%) on pathology was high. Nonetheless, the involved CRM (R1 and R2) rate of 2.4% was lower than the published literature of 4.5-20%. This may be attributable to better pre-operative planning with clinical assessment and imaging in the MDT.

Local recurrence occurred most commonly at sites in the peri-anastomotic region and peritoneum. Recurrence in the peri-anastomotic space is often attributed to technical failure, but only one (4%) of 26 patients with recurrence in this region had an involved margin. It is possible that poor quality surgery was present, but not measured in this study by endpoints such as specimen quality (Quirke et al, 2009) or assessment of intra-operative technique (Curtis et al, 2020). However, it is also possible the underlying cause of the high local recurrence incidence may be due to disease biology mechanisms that are not well understood. One possibility would be that residual mesenteric disease such as extramural venous invasion or tumour deposits (TDs) led to a recurrence, as has been shown

in previous studies (Bertelsen et al, 2015, Hohenberger et al, 2009). At present, ongoing trials are investigating whether prophylactic (Arjona-Sanchez et al, 2018) or adjuvant (Klaver et al, 2019a) intra-peritoneal chemotherapy can reduce the development of peritoneal metastases, but further research into recurrence in the peri-anastomotic area is warranted.

Traditionally many clinicians would agree that the accuracy of pre-operative local tumour staging with CT is poor. This is mainly due to the difficulties of predicting lymph node status with CT, with a specificity of 55-67% on meta-analysis (Nerad et al, 2016, Leufkens et al, 2011b, Rollvén et al, 2017), and consequent over-staging of lymph node status (Brouwer et al, 2018). The current results suggest that the majority of the patterns of recurrence in patients with sigmoid cancer cannot be explained by the lymphatic network; nodal disease was not prognostic on pathology or imaging on multivariate analysis. The strongest predictors of local recurrence were pre-operative imaging biomarkers on CT, including, peritoneal invasion, EMVI and TDs (currently categorised as N1c); these disease features suggest pathways of spread other than by the lymphatic system, and that a vascular mechanism of metastatic spread as being important in development of local recurrence. However, we would suggest that the focus should be predominantly on EMVI and TDs, in addition to T3 substage. These variables can be identified on CT and relevant findings should be used in treatment planning for sigmoid cancer patients.

Furthermore, CT may be superior to pathology at identifying these markers. TDs were more commonly reported on CT compared with the pathological reports and were prognostically significant for LR. CT detected TDs were associated with a worse prognosis than CT predicted N2 disease, whereas pathologically identified TD and pN2 disease had a similar risk of LR. This novel finding suggests that CT may be better in distinguishing TDs from N2 disease compared with pathology. This could be explained by the difficulties in distinguishing lymph node metastases from TDs on pathology, both due to limited sampling of the mesentery meaning that small TDs could be

missed, and due to changing definitions in TNM and high interobserver variation (Rock et al, 2013). N1c disease on pathology is only reported in the absence of lymph node metastases and furthermore we would hypothesise that pathologists are likely to call any indeterminate nodules within the mesentery lymph node metastases rather than TDs due to the historical importance of lymph nodes and greater clarity as to where they fit into colon cancer staging and determine treatment decisions. CT has the advantage of both visualising the entire mesentery and being able to assess the mesentery in three dimensions, such that the relationship between deposits and vessels is likely to be seen more clearly than on pathology. At present, TNM 8 classifies TDs found on pathology as N1c disease, with a proposed better prognosis to N2 disease (when over 4 lymph nodes are involved). In addition, TDs are only included in staging if no lymph node metastases are present. Our results confirm findings from previous studies that TDs confer a significantly worse prognosis (Lord et al, 2017) compared with TNM-classified nodal disease (N2), and suggest that TDs have more adverse prognostic impact compared with N2 disease and are currently underestimated in staging.

Local peritoneal infiltration on CT also significantly predicted local recurrence. Current pathology criteria for T4a disease (Compton and Greene, 2004) may include patients without true penetration of the peritoneum (Klaver et al, 2018); addition of these patients to the T4a category dilutes its prognostic impact and improves outcomes in this category. CT probably only identifies gross peritoneal infiltration and thus locally advanced disease but will not identify borderline peritoneal infiltration. Peritoneal infiltration was recognised on CT when tumour protruded more than 5mm beyond the muscularis propria.

There is an increasing interest in genetic aspects of colon cancer with potential for therapeutic interventions based on the findings. In this series genetic mutation data was not reported as standard. Genes coding microsatellite instability were recorded in 127 cases with 5 cases with mutation events. KRAS status was recorded in 106 cases with 37 mutation events. Neither were prognostically significant for local recurrence. Other genetic mutations were rarely recorded.

Limitations

This study has some limitations including the broad definition of local recurrence which included all peritoneal disease. While it may be argued that peritoneal disease could be classified as metastatic disease, we used similar definitions to other studies of colon cancer recurrence (Elferink et al, 2012, Brown and Koh, 2020, Liska et al, 2016) as well as the hypothesis of Paul Sugarbaker who proposes that local recurrence and peritoneal metastases have the same natural history (Sugarbaker, 2014).

A further limitation was that not all tumour recurrences were histologically proven in patients managed palliatively. In addition, pathology specimen data was extracted retrospectively, and did not consistently report variables such as T3 substage, TDs or plane of surgery, all of which are known to affect recurrence and survival (Lord et al, 2017, West et al, 2008, Merkel et al, 2001c). As pathology reports were based on TNM 5, other new prognostic features (e.g. perineural invasion or tumour regression grade) were not consistently reported and therefore not included (Edge and Compton, 2010). It is unfortunate that plane of surgery was not consistently graded, as this is a possible cause for local recurrence. Our study was underpowered to detect the prognostic impact of every variable; while an involved margin was predictive of local recurrence on univariate analysis, the low number of R1 resections meant that an involved margin was not prognostic on multivariate analysis.

It is possible that other centres may not be able to reproduce the level of accuracy in detection of adverse features such as advanced T3c substage, EMVI, or TDs. Specialist gastrointestinal radiologists can identify CT features that are not routinely reported (Yao et al, 2016, Rollven et al, 2013, Hunter et al, Dighe et al, 2010a). The prognostic importance of these features may make the case for greater specialist reporting of colon cancer. While workshop training can improve identification of high risk colonic tumours on CT (Foxtrot Collaborative Group, 2012), regular interface between specialist radiologists with the colorectal MDT may be more important to improve

an understanding of the disease and its outcomes. Further investigation into the reliability and prognostic impact of CT findings of TDs, EMVI and other disease features which are already included on standardised reporting proforma for colon cancer (Patel et al, 2018) is warranted.

Conclusion

In this study the local recurrence rate for sigmoid cancer was 12.6%. CT-imaging variables of local peritoneal infiltration and tumour deposits were associated with LR on multivariate analysis, enabling a selection criteria for more radical surgery and both neoadjuvant and adjuvant therapy.

What does this study add to the literature?

The local recurrence rate of sigmoid colon cancer in this contemporary, multi-centre study is high at 12.6%. The R1 rate was not high at 2.4%. This suggests that local recurrence still occurs following colonic resection with negative margin.

CT markers were prognostic for LR on multivariate analysis, suggesting that it may accurately capture relevant prognostic data not seen on pathology, and that it may be used pre-operatively to select patients with high risk of LR for neoadjuvant therapy.

Chapter 11

A Novel Staging System for Sigmoid Colon Cancer

D'Souza N, Shaw A, Lord A, Balyasnikova S, Abulafi M, Tekkis P, Brown G. **Analysis of a Novel Staging System for Sigmoid Colon Cancer Based on Tumour Deposits and Extramural Venous Invasion on Computed Tomography.** *JAMA Network Open. 2019 Dec 2;2(12):e1916987-.*

Aim

The primary aim of this study was to investigate whether T3 substaging was superior to TNM stage on CT at identifying a poor prognosis group of patients with colonic cancer at high risk of recurrence. The secondary aim was to investigate whether other pre-operative variables predicted recurrence.

Methods

The participants and process of data extraction of the study were described in chapter 3.

Endpoints

The primary endpoint was to investigate the relationship between known pre-operative prognostic factors on CT and recurrence: local recurrence (LR), distant recurrence (DR), or overall recurrence (LR or DR). The secondary endpoint was to compare the prognostic accuracy of different CT staging systems based on TNM, T3 substage, and a CT staging system based on significant risk factors for disease free survival on multivariate analysis.

CT Staging Systems

Two CT staging classifications for poor and good prognosis groups based on T stage (Table 11-1) have previously been described (Foxtrot Collaborative Group, 2012). The CT-TNM system uses conventional TNM staging and classifies all T3 and T4 tumours to a poor prognosis group, versus a good (T1-2) prognosis group. CT-TNM was used to select patients with T3-T4 colon cancer for pre-operative therapy by a prospective multi-centre trial (Foxtrot Collaborative Group, 2012). The CT-T3 substage system groups high risk T3 substage (T3c-d) and T4 tumours to create a poor prognosis group, versus while good prognosis T3 substage tumours (T3a-b) are grouped with T1-2 tumours. The CT-T3 substage system has been described in previous reports (Table 1-5, page 29) with high sensitivity and specificity for accurate substaging on meta-analysis (Nerad et al, 2016).

Staging System	Classification	Tumour stage on CT	Other CT criteria
CT-TNM	good	T1, T2	Any N
	poor	T3 (a-d), T4	Any N
CT-T3 substage	good	T1, T2, T3a-b	Any N
	poor	T3c-d, T4	Any N
CT- TDV	good	T1, T2, T3a-b	N0-2
	poor	T3c-d, T4	N0-2 (inc. N1c/TDs), EMVI

Table 11-1: CT prognostic systems for colon cancer

Statistical Analysis

Kaplan-Meier survival plots were calculated for recurrence free survival. Cox multi-regression analysis was used to derive univariate and multivariate hazard ratios for recurrence from pre-operative variables.

Results

Between 2006 and 2015, 780 patients with suspected sigmoid cancer on imaging were discussed in the MDT, of whom 414 patients met the inclusion criteria and had complete data (Figure 3-1, page 79). Median follow-up was 61 months.

		CT-TNM			CT-T3 Substage		
		good	**poor**	***p***	**good**	**poor**	***p***
		***N*=86**	***N*=328**		***N*=259**	***N*=155**	
Age, mean (st. dev.)		65.6 (11.6)	66.2 (13.0)	*0.70*	66.2 (12.2)	65.8 (13.5)	*0.80*
Female (%)		37 (45%)	129 (39%)	*0.54*	101 (39%)	65 (42%)	*0.61*
Emergency		**1 (1%)**	**48 (15%)**	***<0.01***	**20 (8%)**	**29 (19%)**	***<0.01***
Neoadjuvant		**2 (2%)**	**40 (12%)**	***<0.01***	**12 (5%)**	**30 (19%)**	***<0.01***
		CT variables					
CT T	1	**20 (23%)**	**0**	***<0.01***	**20 (8%)**	**0**	***<0.01***
	2	**66 (77%)**	**0**	***<0.01***	**66 (25%)**	**0**	***<0.01***
	3	**0**	**255 (78%)**	***<0.01***	**173 (67%)**	**82 (53%)**	***<0.01***
	4	**0**	**73 (22%)**	***<0.01***		**73 (47%)**	***<0.01***
CT N	0	**76 (89%)**	**144 (44%)**	***<0.01***	**182 (70%)**	**38 (25%)**	***<0.01***
	1	**6 (7%)**	**86 (26%)**	***<0.01***	54 (21%)	38 (25%)	*0.40*
	2	**1 (1%)**	**20 (6%)**	***0.09***	**4 (2%)**	**17 (11%)**	***<0.01***
	1c (TDs)	**3 (4%)**	**78 (24%)**	***<0.01***	**19 (7%)**	**62 (40%)**	***<0.01***
CT EMVI		**6 (6%)**	**164 (50%)**	***<0.01***	**42 (16%)**	**128 (83%)**	***<0.01***
CT localised peritoneal disease		**0**	**31 (9%)**	***<0.01***	**0**	**31 (20%)**	***<0.01***
		Post-operative variables					
pT	1	**19 (22%)**	**5 (2%)**	***<0.01***	**23 (9%)**	**1 (1%)**	***<0.01***
	2	**33 (38%)**	**29 (9%)**	***<0.01***	**58 (22%)**	**4 (3%)**	***<0.01***
	3	**30 (36%)**	**202 (61%)**	***<0.01***	148 (57%)	84 (54%)	*0.61*
	4	**4 (5%)**	**92 (28%)**	***<0.01***	**30 (12%)**	**66 (43%)**	***<0.01***
pN	0	58 (67%)	193 (59%)	*0.17*	**169 (65%)**	**82 (53%)**	***0.01***
	1	24 (29%)	77 (23%)	*0.40*	61 (24%)	40 (26%)	*0.65*
	2	**4 (5%)**	**49 (15%)**	***0.01***	**25 (10%)**	**28 (18%)**	***0.005***
	1c (TDs)	**0**	**9 (3%)**	***0.21***	4 (2%)	5 (3%)	*0.30*
pEMVI present		**15 (17%)**	**127 (39%)**	***<0.01***	**60 (23%)**	**82 (53%)**	***<0.01***
Grade	*Well/moderate*	75 (87%)	294 (90%)	*0.56*	232 (90%)	137 (88%)	*0.75*
	Poor	5 (6%)	25 (8%)	*0.81*	14 (5%)	16 (10%)	*0.08*
	No residual	**5 (6%)**	**3 (1%)**	***0.01***	7(3%)	1 (1%)	*0.27*
	Missing/other	1 (1%)	6 (2%)	*1.0*	6 (2%)	1 (1%)	*0.26*
R1/R2		0	10 (3%)	*0.13*	**3 (1%)**	**7 (5%)**	***0.045***
Leak		3 (3%)	11 (3%)	*1.0*	9 (4%)	5 (3%)	*1.0*
Adjuvant		**24 (28%)**	**180 (55%)**	***0.01***	**108 (42%)**	**94 (61%)**	***<0.01***
Median OS (months)		55.1	61	*0.61*	61	59	*0.13*
Mean RFS (months)		46	51.5	*0.84*	**52**	**48**	***0.03***
LR		8 (9%)	44 (13%)	*0.462*	**22 (8%)**	**30 (19%)**	***<0.01***
DR		13 (15%)	88 (27%)	*0.113*	**50 (19%)**	**51 (33%)**	***<0.01***

Table 11-2: Frequency of prognostic variables and outcomes
Note. CT-TNM good: T1-T2, any N. CT-TNM poor: T3-T4, any N. CT-T3 substage good: T1-T2, T3a-b any N. CT- T3 substage poor: T3c-d-T3, any N. T = tumour stage. N = nodal stage. EMVI = extramural venous invasion. TDs = tumour deposits. OS = overall survival. RFS = recurrence free survival. LR = local recurrence. DR = distant recurrence.

On univariate analysis, significant pre-operative CT variables for overall recurrence included T stage, nodal stage, EMVI, TDs, and peritoneal disease (Table 11-1).

CT variables of T stage, nodal stage, EMVI, TDs, and peritoneal disease were significantly associated with LR (Table 11-1). Emergency presentation, in addition to pre-operative CT variables of T stage, nodal stage, EMVI and TDs (Table 11-1) was significantly associated with DR.

Pre-Operative Variable	All recurrence			Local Recurrence			Distant Recurrence		
	HR	*p*	95% CI	HR	*p*	95% CI	HR	*p*	95% CI
Univariate analysis									
Hospital	0.97	*0.64*	0.84-1.16	0.82	*0.09*	0.65-1.03	1.04	*0.59*	0.89-1.22
Age	1.00	*0.82*	0.98-1.01	1.00	*0.59*	0.98-1.02	1.00	*0.61*	0.98-1.01
Sex	0.84	*0.33*	0.58-1.21	1.10	*0.75*	0.63-1.91	0.73	*0.14*	0.48-1.10
Neoadjuvant therapy	1.34	*0.27*	0.79-2.27	0.90	*0.83*	0.36-2.26	1.34	*0.33*	0.75-2.39
Emergency presentation	**1.44**	***<0.01***	**1.13-1.83**	1.44	*0.05*	0.99-2.06	**1.43**	***<0.01***	**1.10-1.86**
CT-T	**1.24**	***<0.01***	**1.12-1.39**	**1.18**	***<0.01***	**1.05-1.32**	**1.14**	***<0.01***	**1.05-1.24**
CT-N	**1.51**	***<0.01***	**1.27-1.80**	**1.48**	***<0.01***	**1.13-1.92**	**1.55**	***<0.01***	**1.28-1.87**
CT-EMVI	**2.69**	***<0.01***	**1.87-3.86**	**2.75**	***<0.01***	**1.56-4.83**	**2.89**	***<0.01***	**1.94-4.34**
CT-TDs	**2.95**	***<0.01***	**2.04-4.29**	**3.24**	***<0.01***	**1.86-5.64**	**2.90**	***<0.01***	**1.94-4.36**
CT-Peritoneal	**2.22**	***<0.01***	**1.31-3.76**	**4.37**	***<0.01***	**2.29-8.33**	1.32	*1.43*	0.67-2.62
CT-TNM poor prognosis	1.57	*0.10*	0.96-2.60	1.42	*0.36*	0.67-3.02	**1.83**	***0.04***	**1.02-3.28**
CT-T+ poor prognosis	**1.88**	***<0.01***	**1.32-2.68**	**2.43**	***<0.01***	**1.40-4.22**	**1.93**	***<0.01***	**1.31-2.86**
CT-TDV poor prognosis	**2.81**	***<0.01***	**1.95-4.05**	**2.67**	***<0.01***	**1.52-4.70**	**3.08**	***<0.01***	**2.05-4.64**
Multivariate analysis									
CT TDs	1.90	*0.01*	1.21-2.98	2.84	*<0.01*	1.62-5.01	1.73	*0.03*	1.06-2.984
CT EMVI	1.97	*<0.01*	1.26-.306				2.19	*<0.01*	1.50-3.58
CT Local peritoneal infiltration				3.63	*<0.01*	1.89-7.01			

Table 11-3: Univariate and multivariate analysis of pre-operative variables for disease recurrence
Note. HR = hazard ratio. T = tumour stage. N = nodal stage. EMVI = extramural venous invasion. TDs = tumour deposits.

On multivariate analysis, TDs and EMVI on CT scan were significant for overall recurrence (Table 11-1). TDs and peritoneal infiltration on CT scan were significantly associated with LR. TDs and EMVI on CT were significantly associated with DR. Lymph node disease on CT was not prognostic for overall, local or distant recurrence on multivariate analysis.

When comparing disease free survival in CT staging systems for good or poor prognosis groups, CT-TNM failed to show any significant difference between groups, while the CT-T3 substage classification was prognostic (HR 1.88, 95% Confidence Interval (1.32-2.68),). However, utilisation of the CT-**TDV** classification system based on CT-detected **TD**s and EM**V**I best identified a poor prognosis group (HR 2.81, 1.95-4.05,).

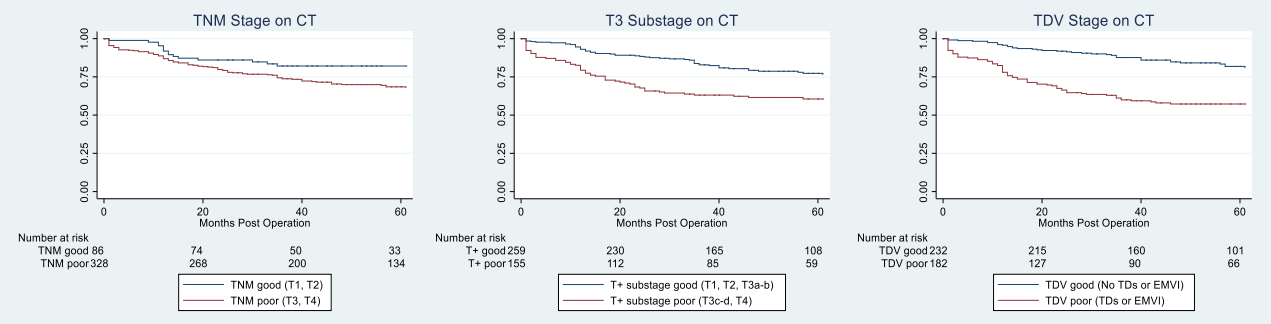


Figure 11-1: Kaplan-Meier curves comparing specific CT staging systems
Note. Left: TNM stage. Middle: T3 substage. Right: TDV system.

Further investigation confirmed that CT-TNM failed to achieve prognostic significance because CT-T3a/T3b tumours were not associated with worse disease free survival than CT-T1/T2 tumours when classified separately (HR 1.04, 0.87-1.25,). Similarly, CT-T4 tumours were not associated with worse disease free survival than CT-T3c/T3d tumours (HR 1.09, 0.85-1.40,). CT-N staging was not prognostic once patients with CT-TDs were separated (Figure 11-2).

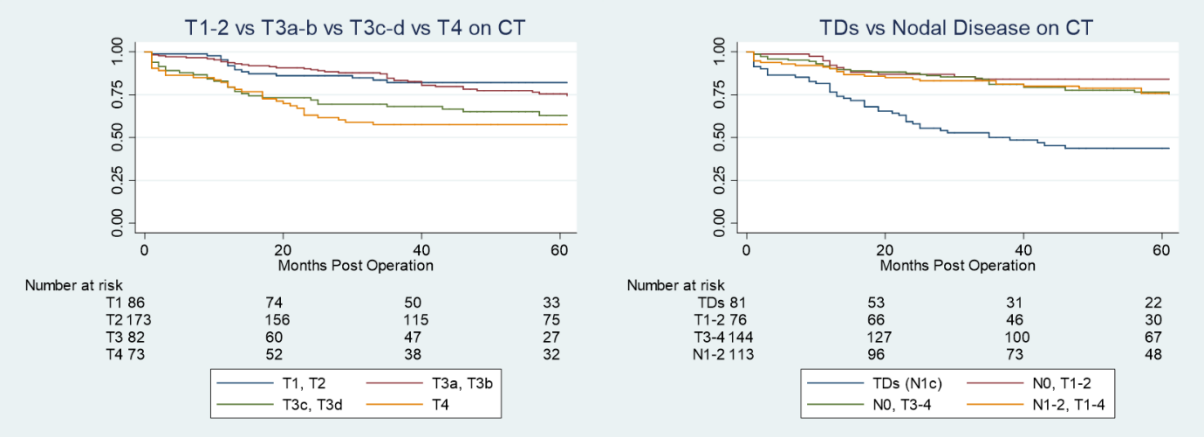


Figure 11-2: Kaplan-Meier curves comparing specific CT disease variables
Note. Left: CT detected T1-2, T3a-b, T3c-d, T4 disease comparison. Right: CT detected tumour deposits vs nodal disease.

Discussion

TNM stage as defined in pathology studies has been applied for CT staging of colon cancer, but our data confirms that it does not translate to CT staging and failed to provide prognostically accurate information prior to surgery. In contrast to the TNM system, CT-T3 substage enabled a poor prognosis group to be identified. On multivariate analysis, CT evaluation of lymph nodes was not of prognostic relevance. CT identified EMVI and TDs in 41% and 20% of patients respectively. Both EMVI and TDs were independent prognostic factors for recurrence free survival, and therefore provides a superior pre-operative staging system.

With the advent of selective pre-operative treatment for patients at risk of recurrence, identification of a poor prognosis group through a better CT staging system is now necessary to match the improvements seen in rectal cancer (Burton et al, 2006b, MERCURY Study Group, 2006, Glynne-Jones et al). Advanced T3 substage of colonic cancer on CT was associated for recurrence, consistent with previous studies (Yao et al, 2016, Smith et al, 2007, Hunter et al). Inclusion of all T3 sigmoid colon tumours into a poor prognosis group fails as a staging system because it does not stratify patients at risk of recurrence. This is explained by the equivalent recurrence rates of CT-staged T3a-b and T1-2 tumours, which has not been demonstrated previously. This may explain the results of the FOxTROT study (Seymour et al, 2019); pre-operative treatment for patients with cT3a-b staged disease would inevitably expose these patients to toxicity for negligible benefit as their risk of recurrence is already low. T3 substage of >5mm extramural spread should therefore be included on all CT reports for colon cancer. Given its high risk for recurrence, T3 substage poor disease should be investigated as an indication for neoadjuvant therapy.

We have shown that specialist gastrointestinal radiologists may identify other variables that were more closely associated with disease recurrence, particularly EMVI and TDs; advanced CT-T3 substage may act as a surrogate measure for adverse disease features Accurate identification of these markers individually will enable a more precise, personalized risk score for each patient.

Limitations of the study

Omission of relevant covariates (e.g. comorbidity, specimen plane, intra-operative technical performance) that were unavailable may have led to bias. There may also be undiscovered predictor data variables (e.g. molecular markers) that are confounders. Follow up data for patients that returned to their homes abroad or elsewhere in the United Kingdom was not present for 4% of patients.

Further research must be aimed at establishing the inter-reader reliability of radiologist for adverse CT prognostic features. One option is to test our T3 substage and TDV classifications against TNM in other test cohorts e.g. using CT scans for patients with colon cancer in the FOxTROT study, which is currently underway. This would also establish whether the adverse CT features for sigmoid colon cancer in this study carry the same prognostic weights for other sites of colon cancer. It may also be necessary to investigate whether further, specialist gastrointestinal training can improve accuracy and reduce variation in tumour staging (Table 1-5, page 29).

Conclusion

Advanced T3 substage disease in colon cancer can be identified on CT, and carried a significantly adverse prognosis for recurrence free survival. EMVI and TDs are both independent adverse prognostic features visible on CT imaging that are most strongly associated with worse disease free survival. Lymph node assessment of colon cancer on CT should not be relied upon as it has no prognostic value.

What does this study add to the literature?

Patients with colon cancer may benefit from neo-adjuvant therapy, but most clinicians agree the accuracy of pre-operative CT staging is poor. This study of 414 patients with sigmoid colon cancer identified novel imaging biomarkers (advanced T3 substage, extranodal tumour deposits, extramural venous invasion) that were associated with poor prognosis, enabling a pre-operative selection strategy.

Chapter 12

Discussion

Discussion

I performed an extensive literature review to inform the theoretical basis of this work. I wanted to know if sigmoid colon cancer outcomes were poor and whether imaging could play a role in improving them. My initial literature search, written up as my background (Chapter 1) led to several conclusions. Firstly, that published sigmoid colon cancer outcomes varied, and warranted further interrogation through a systematic review. Secondly, that the variation in sigmoid colon cancer outcomes was in part due to the number of definitions of the rectum in use. Finally, that pathology based TNM staging was an imperfect prognostic system that could potentially be improved with CT staging. I tackled each of these research questions simultaneously; this was necessary as each of these subjects was interlinked, and due to my finite dedicated time in research.

On meta-analysis (Chapter 4) the pooled local recurrence rate of sigmoid colon cancer was surprisingly high at 12.6%. But it was unclear how to interpret this data. Details on predictive variables or patterns of recurrence specifically for sigmoid cancer were usually not present in the source data, and higher risk patients such as “palliative” or R1 resections and emergency cases were often excluded. This analysis also demonstrated that research into sigmoid cancer outcomes was hampered by the inconsistent definition of the rectum. The criteria on which sigmoid tumours were classified were only documented in 7/17 studies, and were inconsistent; some studies excluded tumours within 18cm of the anal verge, others excluded rectosigmoid tumours. A comparison of sigmoid and rectal cancer outcomes on meta-analysis would have provided a higher quality of evidence, but at the start of my research, I did not have the statistical skills to perform this analysis.

To further investigate sigmoid cancer outcomes, a reliable definition of the rectum was needed to differentiate sigmoid from rectal tumours. I performed a literature review (Chapter 5) to investigate evidence for the reliability and validity of any definitions of the rectum. I found that metric measurements and bony landmarks did not have a sound anatomical basis. All studies demonstrated

significant variation in rectal length measurements in individuals. I published a description of the sigmoid take-off, the radiological definition of the rectum used at the Royal Marsden MDT, and related it to two previous definitions that were conceptually identical; the mesorectal-mesocolic junction (Culligan et al, 2012), which was consistent with the point of "mobility of the colon away from the vertebral column" described by (Memon et al, 2009).

After reporting the range of definitions of the rectum, I assessed the accuracy of these landmarks in-vivo to localise tumours to the sigmoid or rectum, against the sigmoid take-off (Chapter 6). I confirmed that existing pre-operative definitions of the rectum do not account for variation in patient anatomy and will mislocalise tumours to the rectum or sigmoid. The mean length of the rectum on MRI was 12.6cm; metric measurements of 12, 15 and 16 cm correspond to the sigmoid in 35%, 84% and 96% of patients respectively. This suggests that many distal sigmoid tumours may be incorrectly classified as rectal tumours.

This work on the rectosigmoid problem confirmed the number of different definitions of the rectum and reported their limitations; both theoretical as described in the literature, and on analysis of in-vivo anatomy. Unreliable definitions of the rectum will prevent consistent classification of rectal and sigmoid cancer. This will hinder research into which treatment options are best for patients, and assessment of clinical outcomes such as leak, recurrence or functional status after surgical treatment for rectal or sigmoid cancer. For example, landmark rectal cancer trials used landmarks of 10-15cm to classify "upper rectal cancers"; local recurrence was reduced by radiotherapy in these studies (Table 1-10, page 54). However, given that our study reported that the mean rectal length is 12.6cm, it is possible that a significant number of these tumours will have been in the sigmoid. This may suggest a potential role for neoadjuvant radiotherapy in sigmoid tumours.

The limitations of different definitions of the rectum were summarised from the studies included in the literature search. No published definition of the rectum had been validated by any means; while the reliability of different landmarks was assessed in radiological or operative in-vivo studies, the

validity of the reference landmark (e.g. coalescence of taenia coli) in each of these studies was assumed. In our radiological study of rectal dimensions to assess the validity of difference definitions, we also made this assumption, by taking the sigmoid take-off as our reference. This further illustrated the need for a validated, reliable definition of the rectum.

Having established the range of definitions of the rectum in practice, and that mainstream definitions were inaccurate, I sought to establish a new international definition to harmonise research and treatment of patients with rectal and sigmoid cancer (Chapter 7).

Professor Brown and I coordinated with Professor Wiggers from University Centre Groningen to lead a consensus definition of the rectum using the Delphi Technique with 132 international colorectal cancer experts across the MDT, including radiologists, clinical and medical oncologists, pathologists, gastroenterologists as well as surgeons. While these experts employed over 11 different definitions for the rectum in their daily practice, after an evidence review for all definitions, the majority selected the sigmoid take-off as their definition of choice. After a further round of voting, over 80% of experts agreed that this imaging-based sigmoid take-off was the consensus definition, and could be feasibly implemented in their own institution.

This work led to the sigmoid take-off being recognised as the first international consensus definition of the rectum, and provides an opportunity to harmonise trials and clinical practice. Although there was participation by experts from across all colorectal MDT specialties, from all parts of the world, there was disproportionate representation by surgeons from the United Kingdom and the Netherlands. If the survey was to be repeated, I would have engaged social media to achieve more representation from other specialties, and other parts of the world. Nonetheless, it is striking that within 2 rounds, there was swift recognition of the limitations of current definitions that led to convergence on the sigmoid take-off as the consensus definition. Several experts and journal reviewers commented that while there was conceptual agreement on this definition, that validation

of the sigmoid take-off against specimen anatomy would be required before it could be embedded into guidelines and clinical practice.

Previous anatomical and pathology studies had suggested the presence of a sigmoid waist that could predispose to local recurrence. I investigated the presence and dimensions of a waist on both specimen analysis and imaging (Chapter 8). When planning this joint radiology-specimen study, I also took the opportunity to investigate the correlation of the sigmoid take-off as seen on pre-operative MRI scans, with the rectosigmoid junction on pathology specimens (Chapter 9).

Our results demonstrated a sigmoid mesenteric waist; but rather than being within the sigmoid, the waist existed at the rectosigmoid junction, as the sigmoid mesentery elongated above it. However, unlike the abrupt low mesorectal waist at the insertion of the levators, the rectosigmoid waist tapers more gently, and is less likely to be a site of recurrence. In nearly all cases, the sigmoid take-off on imaging accurately identified the rectosigmoid junction and therefore defined the rectum. The mean distance of the sigmoid take-off from the anterior peritoneal reflection was 20.3mm and 23.1mm for both readers with good correlation.

These results suggest the sigmoid take-off is a radiological definition of the rectum that is validated by specimen anatomy. The sigmoid take-off correlated to the rectosigmoid mesenteric waist, which was found at the junction of the mesorectum and mesocolon on specimen and radiological analysis.

An interesting implication of our results was that the upper rectum may be shorter than commonly perceived. The short distance of the sigmoid take-off above the anterior peritoneal reflection (less than 30mm) may result in tumours easily extending from the distal sigmoid into the upper or middle rectum, and vice versa. When tumours more than 15cm from the anal verge are classified as sigmoid, but are seen on CT/MRI to be close to the peritoneal reflection, I suspect many are re-classified as rectosigmoid tumours. The sigmoid take-off may serve as a definition that could more

consistently classify tumours above (distal sigmoid), straddling (rectosigmoid) and below (upper rectum) the take-off. If this definition were to be adopted by international guidelines and associations, it may harmonise research and treatment.

The logistical considerations of a prospective tissue-radiology study imposed some limitations to the study. Although it has been reported that formalin immersion does not significantly affect specimen dimensions, the most faithful study of in-vivo anatomy would be through immediate specimen dimension measurement by MRI and cut-up. However, this is impossible in the case of pathology cut-up, which requires prior formalin immersion. Immediate MRI scan is difficult as it demands both MRI and radiographer availability, which is almost impossible to schedule in a busy clinical service, when the exact time of the specimen availability cannot be predicted.

As expected, there was significant variation in the specimen dimensions. A more representative study would require at participation of at least 50 patients; this sample size enabled other studies to associate rectal length with variables such as sex (Gollub et al, 2013, Yiqun et al, 2016) and body mass index (Wasserman et al, 2016), while studies with 50 or less patients did not report this association (Memon et al, 2009) Yun et al, 2008). To investigate whether radiotherapy may lead to discrepancies in radiological-specimen dimensions, a group of non-irradiated patients should also be recruited. However, to recruit this number of patients would require significantly more funding to extend the recruitment period, number of centres, and number of investigators.

Finally, there was less than 10mm difference in 31/34 (91%) paired MRI-pathology measurements, with correlation measured at 0.77 and 0.81 for both readers. However, the limited number of readers is a crucial limitation of this study. Further research into the inter-observer reliability would ideally involve assessment of the accuracy of multiple blinded readers across the MDT, including radiologists, surgeons and clinical oncologists. I found it difficult to persuade busy clinicians to volunteer hours of their time to undergo training and then perform these measurements; either funding or co-authorship may be a solution to this in future studies.

Imaging and Sigmoid Outcomes

Having established the definition of the rectum, I could then proceed to investigate sigmoid cancer outcomes. Using the sigmoid take-off to identify patients with sigmoid tumours, I created a database of 414 patients with detailed information on patient, imaging, pathological, and treatment variables, to investigate predictors, patterns and outcomes of sigmoid cancer recurrence (Chapter 10). In this contemporary series of resections for sigmoid colon cancer, the R1 rate was low at 2.4%, but the local recurrence rate was high at 12.6%. This was unexpectedly high, even after including resections that may have been deemed "palliative" in other series and emergency resections. Using the sigmoid take-off, distal sigmoid tumours were also included that may have been classified as "rectal" in other studies if they were less than 15cm from the anal verge. On multivariate analysis, CT findings of local peritoneal infiltration and tumour deposits were associated with recurrence, in addition to pT stage to predict recurrence on multivariate analysis. Nodal involvement was no longer prognostic on multivariate analysis once differentiated from tumour deposits on imaging.

I then investigated feasibility of a pre-operative staging system for sigmoid colon cancer (Chapter 11). I found that CT-T3 substage, but not the CT-TNM system used in the FOxTROT study, was significantly associated with disease recurrence. The highest risk of recurrence was associated with the CT-TDV system. Patients with nodal disease on CT were not at elevated risk of recurrence once distinguished from TDs.

Local recurrence of sigmoid colon cancer was found to be a problem, and non-TNM CT imaging features were prognostic on multivariate analysis, even when including pathology data. While TDs are not consistently differentiated from lymph nodes on pathology, this study has demonstrated that CT can distinguish TDs, which were significantly associated with recurrence, from non-prognostic lymph nodes. Consequently, CT prognostic staging systems are optimised by detection of TDs or EMVI. Advanced T3 substage on CT was also significantly associated with cancer recurrence.

Using these imaging features, provisional CT staging systems based on TDs and EMVI, or advanced T3 substage were found to be prognostic, but cannot yet be used in clinical practice. While this staging system was based on a high quality database of 414 patients with complete radiological and pathology data and a high rate of follow up, ultimately this number is too small. National databases cannot solve this problem, as they lack data on these variables that are not routinely captured by radiologists. This study ideally needs to be replicated in multiple other centres that can provide similarly complete datasets, with CT evaluation by blinded radiologists. Firstly, to establish that the local recurrence rate is not skewed by local practice within the participating hospitals. Secondly, to provide a stable logistic regression analysis, for rarer outcomes such as local recurrence or R1 resection. And finally, to investigate the reliability of radiologist identification of these novel CT findings, and validate the prognostic value of the TDV system, as discussed further in the next section.

Next Steps

The accurate definition of the rectum became crucial due to the sheer inconsistency in classification of sigmoid tumours. My series of studies on the definition of the rectum highlighted this issue, and led to the sigmoid take-off being accepted as consensus definition of the rectum, that was validated on specimen analysis. The consistency of the sigmoid take-off has been studied on CT and MRI in a dataset of 200 patient from China (Li et al, 2020). Before this definition is ready for primetime, further investigation of its inter-rater reliability is warranted; the MRIs used in our original study could be used, as they have the specimen measurements for validation. If another tissue-radiology were planned, another feature to investigate would be the relationship of the rectum, sigmoid and its mesentery with the vasculature. This may establish whether there is a clear demarcation of the blood supply from the sigmoidal vessels to the superior rectal arteries corresponding to current

landmarks. Whether another study may receive sufficient funding for a prospective tissue-radiology study in greater numbers than the WISE study is unclear.

However, it is promising that the definition of the sigmoid take-off has already been cited in guidelines (Benson et al, 2020, You et al, 2020), and used to define the rectum in clinical studies (Slooter et al, 2020, van Workum et al, 2020). Use of this landmark will hopefully reduce the variation in the classification of rectal, sigmoid but especially rectosigmoid tumours which deserve further investigation.

Patients with rectosigmoid tumours are in no man's land, classified and managed inconsistently outside of any guidelines, with outcomes that are largely unknown and merit further investigation. National data from PHE could directly compare survival outcomes between tumours of the rectum, rectosigmoid and sigmoid. Use of the sigmoid take-off can be used to classify these tumours— for retrospective outcomes analysis, but also to determine whether rectosigmoid tumours are feasible targets for pre-operative radiotherapy. Future work should investigate whether pre-operative therapy is of benefit in these tumours which are surrounded by a paucity of mesenteric tissue, and which may extend into the rectum.

To decrease sigmoid colon cancer recurrence, we need to optimise treatment by surgical or non-surgical means. Patients with sigmoid cancer in our network seemed to have good quality surgery, with clear margins in 97.6%, but still had a high local recurrence rate of 12.6%. Nodal yield has traditionally been associated as a marker of quality of surgery. In this study, less than 12 nodes were harvested in 34% of patients, but this was not associated with higher recurrence rates. However, other quality variables that are central to complete mesocolic excision such as plane of surgery and bowel length from the tumour site were not routinely described in pathology reports. Finally, quality of intra-operative technical skills has been demonstrated to affect complication rates, specimen quality and possible local recurrence (Curtis et al, 2020, Stulberg et al, 2020). Surgeon subspecialisation may also be investigated; surgery for distal sigmoid or rectosigmoid tumours,

which frequently require partial mesorectal excision, but may be optimally performed by rectal cancer specialists. All of these factors should ideally be quantified and investigated prospectively as independent variables for the quality of surgery.

Accurate, pre-operative identification of locally advanced colon cancer will enable selection of higher-risk patients for pre-operative treatment with chemotherapy or radiotherapy. Nodal disease was not prognostic when distinguished from TDs on CT. This would suggest that dissemination via alternate pathways to the lymphatic system may be more likely to result in metastasis. At present studies of the prognostic significance of tumour are limited by inconsistent classification of TDs on pathology. However, pre-operative imaging with CT may be a better modality to identify TDs and distinguish them from lymph nodes on pathology. The negative results of the FOxTROT trial (Seymour et al, 2019) may possibly be explained by the inclusion of good prognosis patients (T3a-b, no EMVI, no TDs) in the treatment group that diluted the benefits of chemotherapy.

The growing body of evidence to suggest CT can accurately stage colon cancer has so far been limited to single-centre studies with one exception (Dighe et al, 2012a). Advanced T3 substage on CT was also associated with recurrence in our data; national data from PHE may also shed light about whether T3 substaging can be performed by a larger cohort of radiologists with prognostic accuracy. However, the TDV system, while novel and exploratory, best identified a poor prognosis group. An investigation into inter-reader reliability could be performed by re-classification of scans with the TDV score by multiple blinded radiologists. This could also validate the prognostic value TDV score if performed in another cohort with outcome data. For example, if scans were from the FOxTROT study were reclassified, it may also demonstrate whether neoadjuvant therapy significantly improved outcomes with TDV disease on CT. It is possible that TDV scoring may be prognostic in an academic setting because it is performed by specialist gastrointestinal radiologists; similarly, T3 substaging may be prognostic in national data, but because it is only being performed by specialist

radiologists. This may have significant implications for radiologist specialist training and audit; especially if it is demonstrated that patients with poor prognostic features on CT do benefit from pre-operative therapy. Finally, if further studies find that CT imaging cannot reliably stage advanced colonic cancer, the IMPRESS study will shed light about whether MRI is a better modality to assess these features in distal sigmoid cancers.

Conclusion

This work in this thesis has established that published sigmoid cancer outcomes are poor, with high rates of local recurrence. I confirmed this in a contemporary multi-institutional series, despite a low rate of margin involvement in a high risk population. Sigmoid outcomes can only be improved if we know what differentiates a sigmoid tumour from a rectal tumour. I illustrated the inaccuracy of the commonly used definitions of the rectum, and found the rectum is shorter than commonly assumed; 12.6 cm. Through the Delphi technique, I established a consensus definition that was based on anatomical principles. The sigmoid-take off was then validated by specimen analysis; investigation of inter-rater reliability may be necessary before its use becomes commonplace.

CT scans are performed for every patient with colon cancer, but mainly to exclude metastatic disease. Our results suggest that these routine scans have vast, untapped prognostic information that could be used to improve pre-operative staging. Identification of tumour deposits and EMVI was prognostic; and could identify high risk patients with sigmoid cancers. This could be the basis of a staging system to select patients that may benefit from pre-operative chemotherapy or possibly radiotherapy in future research studies.

Chapter 13

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Chapter 14

Appendices

Appendix 1

Pubmed search terms.

Any field contains: neoplasm recurrence
Or any field contains: disease free survival
Or any field contains: disease-free survival
Or any field contains: local recurrence
Or any field contains: locoregional recurrence
And any field contains: Colonic Neoplasms/surgery*

Appendix 2

Modified Newcastle-Ottawa Scale

Selection
1) Representativeness of patients with sigmoid cancer
a) resectable, non-metastatic disease with no exclusion factors*
b) somewhat representative of resectable, non-metastatic disease, but some acceptable exclusion factors*
c) significant, unacceptable exclusion factors or unexplained stage variation within the data
d) no description of the derivation of the cohort

2) Non-exposed cohort: do these contain some sigmoid cancers that have been classified as rectosigmoid?
a) no rectosigmoid category
b) rectosigmoid category
c) no description

3) Verification of sigmoid cancer
a) biopsy proven colorectal cancer*
b) imaging proven cancer
c) no description

4) Demonstration that outcome of interest (recurrence) was not present following surgery
a) R1 data given*
b) R1 resections excluded
c) R0

Comparability
1) Comparability of cohorts based on the design or analysis
a) study controls for disease stage using TNM classification *
b) study describes criteria for localising sigmoid cancer*

Outcome
1) Assessment of outcome
a) independent blind assessment by CT and colonoscopy*
b) record linkage*
c) questionnaire/interview
d) no description

2) Was follow-up long enough for outcomes to occur
a) yes (median follow up over 5 years)*
b) no
c) unclear

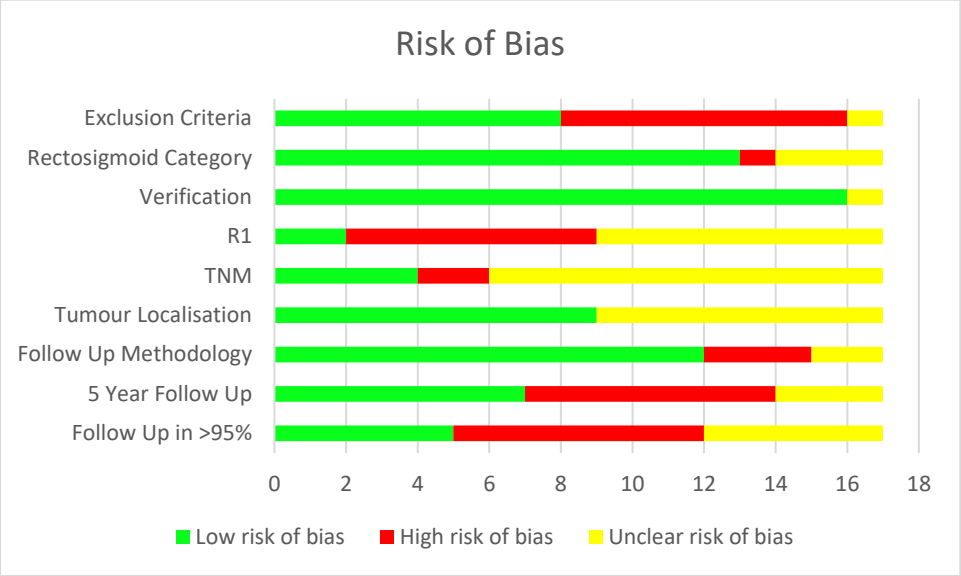
3) Adequacy of follow up of cohorts
a) complete follow up - all subjects accounted for*
b) subjects lost to follow up unlikely to introduce bias - small number lost - > 5% (select an adequate %) follow up, or description provided of those lost)*
c) follow up rate < 95% (select an adequate %) and no description of those lost
d) no statement

Newcastle-Ottawa Score by study

Author	Exclusion Criteria	Rectosigmoid Category	Verification	R1	TNM	Tumour Localisation	Follow Up Methodology	5 Year Follow Up	Follow Up in >95%	Total Score
Amri(Amri et al, 2015b)	0	0	1	0	1	0	0	0	0	2
Di Cataldo(Di Cataldo et al, 2007)	1	1	0	0	0	0	0	0	0	2
Harris(Harris et al, 2002)	0	1	1	0	0	1	0	1	1	5
Jagoditsch(Jagoditsch et al, 2000)	0	1	1	1	0	0	1	0	0	4
Kraemer(Kraemer et al, 2001)	1	1	1	0	0	0	1	0	0	4
Lautenbach(Lautenbach et al, 1994)	0	1	1	0	1	0	1	0	0	4
Leung(Leung et al, 2004)	1	1	1	0	1	0	1	0	1	6
Liska(Liska et al, 2016)	1	1	1	1	0	1	0	1	1	7
Manfredi(Manfredi et al, 2006)	0	1	1	1	0	0	1	1	1	6
Marinello(Marinello et al, 2015)	1	0	1	0	1	1	1	1	0	6
Michelassi(Michelassi et al, 1988)	0	1	1	0	0	0	1	0	0	3
Minsky(Minsky et al, 1988)	0	1	1	0	0	1	0	1	0	4
Olson(Olson et al, 1980)	0	0	1	0	0	0	1	0	1	3
Park(Park et al, 2016)	1	1	1	0	0	1	1	1	0	6
Radespiel Troger(Radespiel-Tröger et	0	0	1	0	0	0	1	0	0	2

al, 2004)										
Sjovall(Sjövall et al, 2007)	1	1	1	0	0	1	1	1	0	6
Willett(Willett et al, 1987)	1	1	1	0	0	1	1	0	0	5
	8	13	16	3	4	7	12	7	5	

Risk of bias overall



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23	Figure	Figure 1-1: Five-year relative survival for colorectal cancer patients (diagnosed 1996-2002) by stage at diagnosis	National Cancer Registration and Analysis Service, which is part of Public Health England (PHE).	Public Health England	12.05.2020	yes	Written permission*
23	Table	Number of cases (1996-2006) and five-year relative survival of colorectal cancer patients (diagnosed 1996-2002) by stage at diagnosis, England.	National Cancer Registration and Analysis Service, which is part of Public Health England (PHE).	Public Health England	12.05.2020	yes	Written permission
70	Figure	Figure 1-5: Sigmoid mesocolon in continuity with mesorectum (right)	Coffey JC, O'Leary DP. The mesentery: structure, function, and role in disease. The lancet Gastroenterology & hepatology. 2016 Nov 1;1(3):238-47.	Elsevier	22.02.2018	yes	Written permission (see below)
70	Figure	Figure 1-5: Sigmoid mesocolon in continuity with mesorectum (left)	Culligan K, Coffey JC, Kiran RP, Kalady M, Lavery IC, Remzi FH. The mesocolon: a prospective observational study. Colorectal Disease. 2012 Apr;14(4):421-8.	John Wiley and Sons	22.02.2018	yes	Written permission (see below)

Note. * Figures and tables under the terms of the Open Government Licence. This work uses data that has been provided by patients and collected by the NHS as part of their care and support. The data is collated, maintained and quality assured by the National Cancer Registration and Analysis Service, which is part of Public Health England (PHE)."

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Title:	The mesentery: structure, function, and role in disease
Author:	J Calvin Coffey,D Peter O'Leary
Publication:	The Lancet Gastroenterology & Hepatology
Publisher:	Elsevier
Date:	November 2016

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