

Establishing the Impact, Detection and Prevention of Colorectal Surgical Complications

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Thesis Abstract

This dissertation examines postoperative complications in colorectal surgery with an emphasis on anastomotic complications. Firstly, it investigates the impacts of anastomotic leakage and its subsequent treatment, on overall survival, disease-free survival and timing of adjuvant chemotherapy. Secondly it assesses intraoperative anastomotic testing utilities and alternative intraoperative surgical techniques such as the ileo-distal sigmoid anastomosis in prophylactic colectomy for polyposis patients, and the tube ileostomy, a variant of the loop ileostomy that negates the need for a subsequent reversal. Thirdly it interrogates the feasibility of remote patient self-monitoring using tablet computers and blue-tooth enabled technology to measure physiological parameters after elective surgery.

This thesis has demonstrated that anastomotic leakage and reoperation to manage it, adversely impacts overall survival following cancer surgery and also shows an association reaching significance ($p=0.058$) with increased recurrence rates in patients who suffered a leakage compared to those that did not. It has also shown that delay in adjuvant chemotherapy reduces overall survival and that patients who receive adjuvant chemotherapy early within eight weeks are conferred a survival benefit, compared to those who received chemotherapy after eight weeks, regardless of reoperative status.

Subsequently it has systematically reviewed intraoperative testing methods and has shown that basic mechanical patency tests reduce postoperative anastomotic leakage in non-randomised studies. It has also shown that intraoperative Near Infrared-Indocyanine Green autofluorescence anastomotic perfusion assessment is safe and feasible. It has also described the initial experience with the IDSA technique in Polyposis patients in a tertiary institution. A further systematic review of tube ileostomy reported no significant differences in anastomotic leakage when compared to the established loop ileostomy. Lastly, postoperative patient self-monitoring has been found to be feasible and comparable to nurse-acquired physiological measurements. Both this and the initial experience of IDSA will allow extrapolation into future studies in our local institution.

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Dedication

To my beautiful wife and confidante Sitaa, for understanding me, putting up with me and supporting me throughout. I love you.

எனக்காக விண்ணைத்தாண்டி வந்தாயே!
என் தங்கமே, என் காதலே, நான் என்றும் உன் ரௌடிதான்.

To our daughter, Keerthana, the apple of my eye.

உனக்கென்ன வேணும் சொல்லு, உலகத்தை காட்ட சொல்லு,
புது இடம் புது மேகம் தேடி போவோமே, என் கண்மணியே!

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Declaration

I hereby declare that the work presented in this thesis is original and I confirm that I have performed this research myself. The findings in the research are from studies undertaken by me, except where it is referenced or carried out in collaboration with others who are appropriately credited. This thesis is a record of work, which has not been previously submitted for a higher degree.

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List of Abbreviations

ACPGBI	Association of Coloproctology of Great Britain and Ireland
ALD	Alcoholic Liver Disease
ASA	American Society of Anaesthesiologists
ASGBI	Association of Surgeons of Great Britain and Ireland
BMI	Body Mass Index
CAA	Colo-anal Anastomosis
CCI	Charlson Comorbidity Index
CDC	American Centres for Disease Control and Prevention
CLASICC	Conventional vs Laparoscopic-Assisted Surgery in Colorectal Cancer
CLS	Colon Leakage Score
COLOR	Colorectal Cancer Laparoscopic or Open Resection
COPD	Chronic Obstructive Pulmonary Disease
COREAN	Comparison of Open vs laparoscopic surgery for mid or low Rectal cancer After Neoadjuvant chemoradiotherapy
COST	Clinical Outcomes of Surgical Therapy
CRA	Colorectal Anastomosis
CS	Clinical Score
CT	Computed Tomography
DFS	Disease Free Survival
DM	Diabetes
DRE	Digital Rectal Examination
ETE	End-to-End
ETS	End-to-Side
FAP	Familial Adenomatous Polyposis
FS	Fluorescence Score
HDU	High Dependency Unit
HES	Hospital Episodes Statistics
HTN	Hypertension
IBD	Inflammatory Bowel Disease
ICD-10	International Classification of Diseases, 10 th revision
ICU/ITU	Intensive Care Unit
ICV	Ileocaecal Valve
IDSA	Ileo-Distal Sigmoid Anastomosis
IMA	Inferior Mesenteric Artery
IMD	Index of Multiple Deprivation
IOT	Intraoperative Test
IPAA	Ileal Pouch-Anal Anastomosis
IQR	Inter-Quartile Range
ISREC	International Study Group of Rectal Cancer
MAP	MutYh Associated Polyposis

MBP	Mechanical Bowel Preparation
MeSH	Medical Search Headings
MOSAIC	Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer
MRC	Medical Research Council
NEWS	National Early Warning Score
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NIR-ICG	Near Infrared & Indocyanine Green
NOS	Newcastle-Ottawa Scale
NOTES	Natural Orific Transluminal Endoscopic Surgery
NSAID	Non-Steroidal Anti-Inflammatory Drug
ONS	Office of National Statistics
OPCS-4	Office of Population Censuses and Survey Classification of Surgical Operations and Procedures, 4 th Edition
OS	Overall Survival
PMH	Past Medical History
POD	Postoperative Day
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUASAR	QUick and Simple And Reliable
RCT	Randomised Controlled Trial
RPC	Restorative Proctocolectomy
RSI	Remote Site Infection
SBO	Small Bowel Obstruction
SC	Sigmoid Colectomy
SDD	Selective Decontamination of Digestive tract
SILS	Single Incision Laparoscopic Surgery
SLE	Systemic Lupus Erythematosus
SSI	Surgical Site Infection
STC	Subtotal Colectomy
STE	Side-to-End
STROBE	Strengthening the Reporting of Observational studies in Epidemiology
STS	Side-to-Side
TAH	Total Abdominal Hysterectomy
TC	Total Colectomy
TME	Total Mesorectal Excision
UC	Ulcerative Colitis
UICC	Union for International Cancer Control
VEGF	Vascular Endothelial Growth Factor
WCC	White Cell Count

Publications & Oral presentations abstracts

Publications

1. Nachiappan S, Askari A, Malietzis G, Giacometti M, White I, Jenkins JT, Kennedy RH, Faiz O. The impact of anastomotic leak and its treatment on cancer recurrence and survival following elective colorectal cancer resection. *World J Surg.* 2015 Apr;39(4):1052-8.
2. Nachiappan S, Askari A, Mamidanna R, Munasinghe A, Currie A, Stebbing J, Faiz O. Initiation of adjuvant chemotherapy within 8 weeks of elective colorectal resection improves overall survival regardless of reoperation. *Colorectal Dis.* 2016 Nov;18(11):1041-1049.
3. Nachiappan S, Askari A, Mamidanna R, Munasinghe A, Currie A, Stebbing J, Faiz O. The impact of adjuvant chemotherapy timing on overall survival following colorectal cancer resection. *Eur J Surg Oncol.* 2015 Dec;41(12):1636-44.
4. Nachiappan S, Askari A, Currie A, Kennedy RH, Faiz O. Intraoperative assessment of colorectal anastomotic integrity: a systematic review. *Surg Endosc.* 2014 Sep;28(9):2513-30.
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1. Nachiappan S, Askari A, Mamidanna R, Stebbing J, Faiz O. (2015) The impact of adjuvant chemotherapy timing on overall survival following colorectal cancer resection. *B J Surg.* 102 Suppl 7:25.
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3. Nachiappan S, Datta U, Askari A, Faiz O. (2015) Tube ileostomy as a faecal diversion for elective distal colorectal anastomoses - a systematic review and pooled analysis. *B J Surg.* 102 Suppl 7:75.
4. Nachiappan S, Askari A, Mamidanna R, Munasinghe A, Currie A, Stebbing J, Faiz O. (2014) Adjuvant chemotherapy following colorectal cancer resection – What timeframe constitutes a delay and how does this impact overall survival? *United European Gastroenterology Journal* 2:1:A1-A131.
5. Nachiappan S, Askari A, Malietzis G, Giacometti M, White I, Jenkins J, Kennedy R, Faiz O. (2014) The impact of colorectal anastomotic leak and its treatment on cancer recurrence and survival following elective colorectal cancer resection. *British Journal of Surgery* 101 Suppl 4:10.
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7. Nachiappan S, Askari A, Malietzis G, Giacometti M, White I, Jenkins J, Kennedy R, Faiz O. (2014) The impact of anastomotic leak on survival and transition to adjuvant chemotherapy in patients undergoing elective colorectal cancer surgery. *Colorectal Disease* 16 Suppl 3:31-32.

Chapter 1

Introduction

1.1 Why predict, prevent & detect complications?

The overarching ethos in medicine is to *'first do no harm'*. In surgery, there is an old saying that goes, *'a good surgeon knows how to operate, a better surgeon knows when to operate and the best surgeon knows when not to operate'*.

When a decision is taken to operate, there are several aspects, which come into play. A surgeon's surgical technique and skill, ability to proactively plan and execute the surgical steps, and ability to adequately react to emerging problems during the surgery, will all be tested acutely. Through surgery, a surgeon is able to provide the benefits of surgical intervention to the patient. However the greater skill and acumen will be that of ensuring that no harm befalls the patient as a result of the surgery. Postoperatively, the surgeon needs to be aware of possible deviations from standard post-surgical recovery, and be able to institute measures to resolve these deviations in a prompt manner too.

The aim is to ensure that as surgeons, we do no harm to the patient and prevent any harm that may occur as a result of our intervention as the benefits

of surgery come together with possible complications. Therefore the best surgeon one may opine, is the one who can live by the adage above and go further to ensure that if surgery is necessary, the surgical intervention results in maximal benefit and no or minimal harm. Being aware of what can go wrong and actively attending to and mitigating issues that can result in a complication is of utmost importance.

This continuous process begins from the moment a surgeon meets the patient, through actual surgery and postoperative care, and discharge back home and beyond. The importance of being aware of possible complications, of stratifying preoperative risk, and of actively looking out for, preventing, and detecting them promptly if they do occur, cannot be overstated. Furthermore, the detection of any complications must be followed by timely treatment to prevent long-lasting sequelae.

Colorectal surgery entails risk of complications, some of which are general to all forms of surgery and others that are more specific. Colorectal surgical complications include wound infection, anastomotic leakage, intra-abdominal collection and abscess, postoperative ileus, intra-abdominal bleeding, injury to intra-abdominal structures, and more general medical complications like venous thrombosis, myocardial infarction, and chest and urinary infection amongst others.

The risk of acquiring a complication in colorectal surgery depends on several factors. Furthermore, the impact of a given complication differs depending on the patient and on his or her individual circumstances. Often, a complication results in transient delay in complete recovery, which nevertheless is achieved. On other occasions, the complication may delay important subsequent necessary treatment such as adjuvant chemotherapy, may cause permanent lasting effect on the patient, or even result in death.

With this principle in mind, this thesis sets out to discuss and investigate various aspects of colorectal surgical complications and how surgeons can improve patient outcomes by being aware of complications and their impact, by preventing them and if they do occur, by detecting and managing them promptly and effectively. It also investigates novel intraoperative strategies that may reduce postoperative complication rates in specific subgroups of colorectal surgical patients. A major complication in colorectal surgery is anastomotic leakage and accordingly, a significant proportion of the thesis concentrates on this dreaded complication, its impact and implications, and utilities, which can prevent, detect and manage it.

First and foremost, this thesis will proceed to briefly lay out the types of complications encountered in colorectal surgical practice.

1.2 Colorectal surgery & its complications

Colorectal surgery has gone through a myriad of changes in the last three decades¹. The advent and increased uptake of minimal access techniques^{2,3}, multi-disciplinary team management⁴⁻⁶, and more thorough preoperative assessment and optimisation⁷ has led to improved outcomes in colorectal surgery. Furthermore, cancer screening and earlier detection of pathology^{8,9}, enhanced recovery programmes^{10,11}, alterations to the surgical training and subspecialisation¹², and more consultant-led service provision¹³, have had varying impacts on colorectal patients' management and eventual outcomes too. Regardless of these changes and improvements over time, there is always a potential risk of complications.

In this setting, post surgical complications have nevertheless vastly remained similar in characteristics, albeit with variations in type and frequency of complications, depending on factors such as operative access (open versus minimal access), premorbid/pre-existing conditions and Body Mass Index (BMI), amongst others.

The type and specific complication may be dependent on patient or disease factors, surgery-related factors or system level issues. Regardless of its root cause, a complication may have a profound effect on the patient. This is especially true in colorectal patients in whom complications such as anastomotic leakage have significant effects on patient morbidity and mortality¹⁴⁻¹⁶.

Low complication rates are important to strive for. However, once a complication occurs, it is the prompt and efficient management of the complication which has to be a cornerstone in a competent surgeon's skill set and on a larger scale, within a surgical unit or establishment^{17,18}. It is therefore the early recognition and amelioration of complications, which will impact upon surgical outcome^{19–21}.

Dindo and colleagues²² have broadly defined postoperative complications as 'deviations from the normal postoperative course'. There are various other classification methods employed in the surgical literature to categorise postoperative complications, in terms of type of complication (infective versus non-infective), site of complication (surgical site versus remote site) and timing of complication in the postoperative period (early versus late).

Clavien, Dindo and colleagues further established the Clavien-Dindo scale which has been taken up by the vast majority in surgical practice, which classifies complications into five grades and subgrades (Figure 1.1), and it has been cross-validated in different surgical subspecialties as well^{22,23}. The above authors have described complications in surgical practice generally in terms of the complications' sequelae and management strategies required/undertaken to ameliorate or treat them. The Clavien-Dindo scale's strength is in its ability to be utilised in almost all surgical subspecialties across different healthcare systems worldwide²³. It however does not directly deal with the intricacies of specific complications in any one particular subspecialty. It is nevertheless a

useful tool in standardising assessment and collation of complications, which help in comparing and contrasting complications and their managements described by different studies in different patient cohorts.

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge (see examples in Table 2), the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

*Brain hemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding transient ischemic attacks.
CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

Figure 1.1: Clavien-Dindo classification of surgical complications²³

1.3 Classification of complications

Complications in colorectal surgery may be divided into specific groupings, which allow the surgeon and the broader multi-disciplinary team to manage and treat them effectively. This thesis broadly divides colorectal complications into three groupings, namely infective, non-infective abdominal, and other medical complications. Table 1.1 lists the variety of postoperative complications that may occur in a colorectal surgical patient and the following sections elaborate on them further.

Table 1.1 Types of complication in colorectal surgery (Adapted from McSorley, 2015²⁴)

Type	Location	Complication
Infective	Surgical Site	Wound infection (superficial & deep incisional) Anastomotic leakage Intra-abdominal collection/abscess/fistula
	Remote Site	Pneumonia Urinary tract infection Septicaemia
Non-infective	Wound	Dehiscence Seroma Incisional herniation
	Surgical site	Anastomotic bleeding Anastomotic stricturing
	Gastrointestinal	Ileus Mechanical bowel obstruction Stoma-related
	Iatrogenic injury	Splenic Ureteric Bowel and other abdominal viscus Vascular
Medical complications	Cardiac	Myocardial infarction/ischaemia Arrhythmia
	VTE	Deep vein thrombosis Pulmonary embolism
	Urinary	Renal failure Urinary retention

1.4 Infective complications

Infective complications in colorectal surgery are broadly divided into surgical site infections (SSIs) and remote site infections (RSIs). The former includes incisional SSIs (superficial and deep), and organ-space SSIs (anastomotic leakage, intra-abdominal collection and abscess formation). The latter comprises of other infections not related to the abdomen, the most common being pneumoniae, urinary tract infections and septicaemia.

1.4.1 Surgical Site Infections (SSIs)

SSIs are a major source of morbidity after colorectal surgery^{25,26}. The American Centres for Disease Control and Prevention (CDC) has previously defined and categorised SSIs²⁷, which is detailed in Table 1.2. It also recently updated its guidelines for prevention of SSIs²⁸, with regards to specific steps to undertake prior to, during and after surgery.

In the United Kingdom, the National Institute of Health and Care Excellence (NICE) emphasises the importance of surgical site infection prevention and treatment and have recently updated their guidelines as well²⁹. There is also a national surveillance service in England, run by Public Health England to allow hospitals to record incidents of infection after surgery, track patient results and review or change practice to avoid further infections³⁰. This programme is mandatory for orthopaedic procedures such as hip and knee replacements, neck of femur fracture procedures and long bone fracture repairs. It is however

only voluntary for several other categories, of which colorectal (large bowel and small bowel) surgery is one. Although the rate of uptake of this service amongst colorectal units in the country is not published and likely to be variable, the availability of such a programme underlines the importance of surgical site infection prevention.

Specifically in colorectal surgery, several authors have reported on patient level, surgeon level and hospital/unit level factors which impact SSI rates to differing extents^{31–33}. Zywtot and colleagues, in their systematic review and meta-analysis noted that colorectal surgery reports one of the highest rates of surgical site infections amongst surgical specialties with rates upwards of 30% in some studies. Their review and analysis of 35 studies reporting on SSI prevention strategies, noted that ‘bundles of care’ incorporating evidence-based procedures and perioperative interventions to reduce SSIs, mitigated the risk of acquiring a SSI, by up to 44% in superficial/deep wound infections and by up to 34% in organ-space infections³⁴.

Anastomotic leakage is a complication that constitutes a large part of organ-space SSIs in colorectal surgery. In the literature, organ-space and incisional SSIs have often been discussed together. The two groups are interlinked in that they are both infective/inflammatory processes. However organ-space SSIs in colorectal surgery are often primarily due to anastomotic mechanical integrity loss or perfusion insufficiency (amongst other reasons described in later

chapters), resulting in anastomotic leakage and subsequent collections, abscess formation and/or peritonitis.

It is therefore important and imperative that they are assessed separately as they and their sequelae have significant differences on patient outcomes, compared to incisional SSIs. Several authors including How and colleagues²⁵ in their assessment of risk factors for incisional and organ-space SSIs, have noted this distinction and difference, and this thesis will discuss these two broad entities separately as well.

Table 1.2 Surgical Site Infections (CDC classification)²⁷

Superficial Incisional SSI

Infection within 30 days after the operation and only involves skin and subcutaneous tissue of the incision and at least one of the following:

1. Purulent drainage with or without laboratory confirmation, from the superficial incision.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.
3. At least one of the following signs or symptoms of infection: pain or tenderness, localised swelling, redness, or heat and superficial incision is deliberately opened by surgeon, unless incision is culture-negative.
4. Diagnosis of superficial incisional SSI made by a surgeon or attending physician.

Deep Incisional SSI

Infection occurs within 30 days after the operation if no implant is left in place or within one year if implant is in place and the infection appears to be related to the operation and infection involves deep soft tissue (e.g. fascia, muscle) of the incision and at least one of the following:

1. Purulent drainage from the deep incision but not from the organ/space component of the surgical site.
2. A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever ($>38^{\circ}\text{C}$), localised pain or tenderness, unless incision is culture-negative.
3. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
4. Diagnosis of deep incisional SSI made by a surgeon or attending physician.

Organ/Space SSI

Infection occurs within 30 days after the operation if no implant is left in place or within one year if implant is in place and the infection appears to be related to the operation and infection involves any part of the anatomy (e.g., organs and spaces) other than the incision which was opened or manipulated during an operation and at least one of the following:

1. Purulent drainage from a drain that is placed through a stab wound into the organ/space.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space
3. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
4. Diagnosis of organ/space SSI made by a surgeon or attending physician.

1.4.1.1 Incisional SSIs

Superficial or deep incisional SSIs are a significant issue in colorectal surgery^{35,36}. Colorectal procedures are most commonly classed as clean-contaminated procedures and not infrequently, the wound is contaminated by faeculent matter or intraluminal contents during surgery. This results in the risk of surgical wound infection being relatively higher compared to procedures in other surgical subspecialties. Furthermore, there are several other factors that increase the risk of incisional wound infections or SSIs.

Miki and colleagues noted in their single centre study³⁷ that perioperative risk factors for incisional SSIs in colorectal surgery include male sex, increased operative duration and concomitant medical comorbidities such as diabetes and Chronic Obstructive Pulmonary Disease (COPD). Several other studies have also noted to varying extents, increased rates of incisional SSIs in colorectal surgical patients who had risk factors such as chronic steroid use³⁸, high BMI^{38,39}, advanced age⁴⁰, positive smoking status⁴¹, poor nutritional status and immunity⁴², background of inflammatory bowel disease⁴³ and higher American Society of Anaesthesiologist (ASA) grading^{32,44}. Emergent surgery³⁸, prolonged operative time⁴⁵, open surgery (laparotomy as opposed to minimally invasive or laparoscopic surgery)^{39,46}, formation or closure of ileostomy or colostomy⁴⁷, and colorectal pathology (rectal versus left or right colonic)⁴⁸ were also risk factors described in the literature.

It is of interest to note that there appear to be possible differences in risk factors for incisional SSIs between colon and rectal surgery. Konishi and colleagues⁴⁹ in 2006 reported different statistically significant risk factors for incisional SSIs amongst patients undergoing colonic surgery as opposed to rectal surgery. They noted significantly increased risk of incisional SSIs on multivariate analysis in colonic surgical patients, when stoma closures were undertaken and when supplemental postoperative oral antibiotics were not used. In rectal surgery, the independent risk factors included use of preoperative steroids, preoperative radiotherapy and formation of ileostomy or colostomy. Murray and colleagues noted in their retrospective observational study in 2016⁴⁸ that rectal cancer resectional surgery entailed the greatest risk of both incisional SSIs and organ-space SSIs. This reflects the greater risk of contamination due to the location of incision, for example in abdominoperineal resection and the greater risk of contamination in rectal surgery, of both the laparotomic or laparoscopic incision in the anterior abdomen and in the perineal wound, and during formation of diversion stomata.

It is evident that the risk factors and reasons for incisional SSIs or wound infections in colorectal surgery are multifactorial. Furthermore, these risk factors and others in the perioperative setting can impact on both incisional SSIs and organ-space SSIs. For instance, Koullouros and colleagues⁵⁰ meta-analysed 23 randomised controlled studies and eight cohort studies and found that a combination usage of oral and systemic/intravenous antibiotic prophylaxis showed a statistically significant reduction in both incisional and organ-space

SSIs. Novel perioperative approaches such as wound edge protection devices have also been utilised and appear to be effective in reducing both incisional and organ-space SSI in abdominal surgery⁵¹. Organ-space SSIs will be discussed in detail in the next section, including anastomotic complications.

Specifically for incisional SSI, it is an entity with multifactorial risk factors and causation. Accordingly, the treatment of this problem is multi-faceted as well. Depending on severity, incisional SSIs are managed conservatively with oral or intravenous antibiotics, or with wound opening on the surgical ward. At times, the infection itself will cause wound dehiscence resulting in an open wound and a prolonged healing process via secondary intention. In less common situations, a return to theatre to surgically debride and lavage of the wound may be necessary. Regardless of its causation and management incisional SSI impacts negatively on the patient in terms of recovery and sequelae, and the broader healthcare in terms of utilisation of resources and economic burden⁵².

1.4.1.2 Organ-space SSIs

Organ-space SSIs, similar to incisional SSIs, are a major source of morbidity after colorectal surgery²⁵. However, as briefly described in the previous section, they differ in terms of specific risk factors and subsequent sequelae. For instance, although there is a wide overlap in terms of individual patient and surgery related risk factors, incisional SSIs are more associated with high BMI and procedures involving stoma closure, whilst organ-space SSI are more

frequently associated with blood transfusion, previous abdominal surgery and poor nutritional status^{47,53,54}.

Consequences of organ-space SSIs are more severe compared to incisional SSIs. Organ-space SSIs are more likely to require invasive procedures like radiologically guided drainage and reoperation and often have an increased risk of long-lasting or permanent postoperative morbidity, such as non-reversal of diverting ileostomy which was formed to ameliorate the effects of anastomotic leakage⁵⁵. Furthermore, some studies have shown that minimally invasive surgery has reduced incisional SSIs, but have had a less substantial effect on organ-space SSI rates^{46,56}. De Lissovoy and colleagues in their administrative hospital data analysis of over 700,000 surgical admissions, and Eagye and Nicolau in their retrospective analysis of 1127 elective colorectal surgical procedures, reported that patients who suffered an organ-space SSI had a longer length of postoperative hospitalisation and increased treatment costs^{57,58}. These issues make organ-space SSIs a significant and important aspect in colorectal surgical complications.

Organ-space SSIs in colorectal surgery include anastomotic leakage, intra-abdominal collection and abscess formation. The disruption of anastomotic integrity can lead to a collection of intra-luminal fluid in the peritoneum or extra peritoneal pelvis, constituting an intra-abdominal collection and subsequently can develop into an abscess. The three in essence are a continuum, although an intra-abdominal collection and abscess can occur without a leakage.

Residual fluid in the abdomen after surgery (after washouts for example), may not be completely absorbed by the body and if exposed to microbiota of the bowel or superficial skin, may lead to an infected collection and a walled off abscess.

1.4.2 Anastomotic leakage

Anastomosis construction is an integral part of colorectal surgery. Gastrointestinal luminal continuity after a colorectal resection is desired by both the patient and the operating surgeon. Establishing a patent and secure anastomosis is however fraught with risks and complications. Patients are exposed to possible anastomotic leakage, anastomotic bleeding and anastomotic stricture due to ischaemia, when two bowel ends are joined together. Furthermore, iatrogenic injury to the bowel wall can result in a direct communication between the gastrointestinal lumen and the abdominal cavity, and both this and anastomotic leakage can lead to gastrointestinal fistulae that connect the bowel to other hollow organs or to the exterior through the cutaneous layer.

The definition of colorectal anastomotic leakage is extremely variable in the surgical literature. Bruce and colleagues have reported 29 separate definitions for a colorectal anastomotic leakage in the literature in their 2001 systematic review of 97 studies which investigated upper and lower gastrointestinal anastomotic leakages⁵⁹. Furthermore, others have reported variability amongst what surgeons consider an anastomotic leakage, how they describe it⁶⁰ and

how accurate they were in predicting its occurrence through clinical assessment⁶¹. This lack of a precise definition of, and variability in what constitutes, a colorectal anastomotic leakage may have contributed to variable leakage rates in the literature. For example, amongst selected studies which assessed colorectal and coloanal anastomoses, there were leakage rates ranging from 5% up to 20%^{62–66}.

The underlying risk factors contributing to the occurrence of a colorectal anastomotic leakage are varied. They can be broadly divided into preoperative and intraoperative risk factors. There are multiple single centre and single surgeon studies in the literature over the years reporting on anastomotic leaks and their risk factors that may assist in predicting an anastomotic leakage.

Dekker and colleagues for example, specifically proposed a Colon Leakage Score (CLS) for left sided colorectal surgery, utilising a systematic review of 64 studies and a Delphi expert opinion and consensus methodology. The authors intended this to be utilised by the surgeon during or at the end of an operation, to ascertain the need for faecal diversion and also to predict anastomotic leakage. The CLS consists of a 43-point scoring system with differential weighting for perioperative risk factors (age, gender, ASA grading, BMI, alcohol intake, smoking status, steroid use, neoadjuvant radiotherapy or chemotherapy, volume of blood loss, presence of bowel obstruction or perforation, distance of anastomosis from anal verge and operative duration). The authors internally validated the scoring system and reported a score of 11/43 to be a

discriminator between a low-risk and a high-risk anastomosis, the latter of which would necessitate proximal defunctioning. In their series of patients, the above score was associated with a 3% risk of leakage.

There have also been several systematic reviews and meta-analyses which have collated evidence from different studies and presented risk factors which contribute to occurrence of anastomotic leakage in colorectal surgery, with the latest two having been published in 2014 and 2015. Pommergaard and colleagues⁶⁷ reviewed 23 prospective cohort studies with a total of 110272 patients in 2014 and McDermott and colleagues⁶⁸ reported on 451 studies including 71 systematic reviews and 12 Cochrane reviews in 2015. The former focussed on preoperative risk factors, whilst the latter was more extensive and included preoperative, intraoperative and postoperative aspects of colorectal surgery that may lead to postoperative anastomotic leakage.

With regards to anastomotic leakage, this thesis focuses on its impact on the patient and how it can be prevented in the intraoperative phase. It investigates impact of leakage on specific issues such as overall survival and disease-free survival. It also investigates its impact on timing of adjuvant chemotherapy and subsequent impact on overall and disease-free survival due to combined effects of a leakage, its subsequent management and delay in adjuvant chemotherapy. In this setting, appreciation and understanding of risk factors for anastomotic leakage are essential. The multitude of risk factors for anastomotic leakage have been extensively investigated in the surgical literature and has

been laid out in the reviews above and in several others in the surgical literature^{67–70}. These are listed in Table 1.3 and discussed in the following paragraphs.

Table 1.3 Risk factors for anastomotic leakage

Preoperative	Intraoperative
<u>Patient factors</u> - Male gender - Advanced age - Comorbidities - Obesity & BMI - Nutritional status - Smoking status - Alcohol consumption - Previous chemoradiotherapy - Medications -Corticosteroids -Immunosuppressants -Chemotherapeutic/Biologics -*NSAIDs - ASA grade <u>Disease factors</u> - Tumour location - Tumour size, stage & metastatic spread <u>Other factors</u> - Emergent surgery - Mechanical bowel preparation - Antibiotics & SDD	<u>Anaesthetic & Physiological factors</u> - Glycaemic control - Temperature - Tissue perfusion -Anaemia -Blood loss -Blood transfusion -Tissue oxygenation -Inotropes -Blood pressure -Fluid management -Epidural analgesia <u>Surgical factors</u> - Open vs. minimal access - Location of anastomosis - Type of anastomosis - Faecal diversion & Drains - Anastomotic testing

1.4.2.1 Preoperative risk factors

1.4.2.1.1 Male gender

Several studies have noted increased risk of anastomotic leakage in both colonic and colorectal anastomoses^{21,71–75} amongst male patients. This disparity between genders has been attributed to the male pelvis being narrower^{74,76} and the differential influence of sex hormones on the intestinal mucosal blood circulation⁷⁷.

1.4.2.1.2 Advanced age

Age as a single stand-alone factor has been found to be linked to anastomotic leakage in some studies^{73,78,79}. However there are several others which did not observe a significant link^{72,80–83}. Pommergaard and colleagues, in their subgroup meta-analysis of seven observational studies comprising more than 17000 patients did not identify any statistically significant increase in anastomotic leakage in older patients⁶⁷. The concept of attributing advanced age as an independent risk factor for leakage has been questioned and strong statistical evidence to prove a direct independent link is lacking^{67,68}. Advanced age alone is becoming less of a concern or a contraindication to major colorectal surgery. However comorbid conditions are more prevalent in older patients and physiological reserve is lower too, and these may contribute to increased risk of anastomotic leakage and the ability to withstand its sequelae

and associated treatment (i.e. reoperation in severe cases) and recover from one⁸⁴.

1.4.2.1.3 Comorbidities

The presence of diabetes mellitus^{85–87}, respiratory disease^{88–90}, vascular disease⁹¹ and renal disease or impairment⁹² have been implicated as risk factors for anastomotic leakage. However data on individual comorbid conditions are varied. For instance, Ziegler and colleagues reported that the presence of diabetes alone did not increase risk of leakage, however, they noted that diabetic patients who did suffer a leak had a four-fold increase in mortality rates⁹³. Similarly, a Danish retrospective administrative database analysis noted that there were no differences in leak rates between renal transplant patients who underwent colorectal surgery, compared to the general population. However it noted that the former were more likely to develop colorectal cancer at an earlier age and had higher wound complication and acute renal failure rates post surgically compared to the normal population⁹⁴. Currie and colleagues also noted that postoperative surgical complications were similar between patients who suffered chronic renal function impairment and those who did not, with only cardiovascular complications being significantly higher in the chronic renal impairment group⁹⁵.

Comorbidities have often been described in studies utilising scoring systems such as the Charlson Comorbidity Index (CCI)⁹⁶, which gives a composite score of severity by collating weighted scores of a patient's comorbid conditions. This

has been utilised by multiple studies across different surgical subspecialties in the literature, and specifically in some studies that assess risk factors for colorectal postoperative complications including anastomotic leakage. Some of these studies noted a significant association between CCI score and anastomotic leak risk⁹⁷ and others reporting no significant link^{98,99}. Interestingly Bakker and colleagues⁹⁷ reported that ASA grading was independently and more significantly associated with risk of anastomotic leakage compared to CCI, and Tan and colleagues actually reported that higher ASA grade was an independent predictor of anastomotic leakage but not CCI score⁹⁹.

1.4.2.1.4 Obesity

Obesity increases the risk of anastomotic leakage in colorectal surgery. This has been shown by several studies in the literature^{100–102}. However, a review of 13 observational studies⁶⁷ only noted one study¹⁰³ to report a link between BMI and anastomotic leakage, and a subgroup meta-analysis of three of these studies did not show any statistical association, albeit the studies showed significant heterogeneity and bias. A 2017 pooled analysis of 43 studies, including some from the previous review, showed significant association between higher BMI and risk of anastomotic leakage ($p < 0.02$)¹⁰⁴. Interestingly, Kartheuser and colleagues have shown that increased waist/hip ratio and waist circumference independently increase the risk of anastomotic leakage¹⁰⁵, whereas BMI was only a risk factor for occurrence of abdominal wall complications (incisional SSIs). It appears measurement methods other than BMI may be more sensitive in appraising anastomotic leakage in colorectal

surgery. This is an area for further research together with other aspects such as comorbid conditions like diabetes, metabolic syndrome and high blood pressure that may play interlinking roles in anastomotic leakage and other postoperative complications.

1.4.2.1.5 Nutritional status

Poor nutrition, preoperative weight loss and hypoalbuminaemia are independent risk factors for anastomotic leakage. A retrospective analysis of more than 72000 patients who underwent anterior resection for rectal cancer, noted that malnutrition and weight loss were associated with increased anastomotic leakage¹⁰⁶. Yamano and colleagues studied the effects of malnutrition after neoadjuvant chemotherapy in rectal cancer patients and noted that malnutrition was an independent predictor of anastomotic leakage¹⁰⁷. Several studies including a multicentre study by Hennessey and colleagues have shown low serum albumin levels to be a further predictor of anastomotic leakage as well¹⁰⁸.

1.4.2.1.6 Smoking status

Tobacco smoking is strongly linked to anastomotic leakage. Several studies report current smoking status^{75,109–111} and previous smoking history¹¹² to be independently linked to occurrence of anastomotic leaks.

1.4.2.1.7 Alcohol consumption

Excess alcohol intake is linked to increased risk of anastomotic leakage^{75,111,113}. Jannasch and colleagues for example noted an increased odds ratio of 1.63 (95%CI 1.23-2.15) on multivariate regression analysis when comparing anastomotic leakage risk between patients who leaked and those who did not, in their analysis of more than 17000 patients who underwent resection and primary anastomosis for rectal cancer in a German multicentre study⁷⁵.

1.4.2.1.8 Previous chemoradiotherapy

Some retrospective studies assessing rectal cancer resectional surgery noted preoperative radiotherapy with and without chemotherapy to be a risk factor for anastomotic leakage^{71,81,91,114,115}. However others have found no statistically significant link^{110,116,117}. Nisar and colleagues for instance noted that neoadjuvant radiotherapy was not independently associated with anastomotic leakage after restorative rectal cancer resection. The authors also opined that their findings support proximal faecal diversion in such patients, taking into account tumour location, size, patient characteristics and intra-operative findings¹¹⁷. Two randomised controlled trials, the Medical Research Council (MRC) CR07 trial¹¹⁸ and the Dutch Total Mesorectal Excision (TME) trial¹¹⁹, also did not show any statistical difference in anastomotic leakage rates between patients who received preoperative chemoradiotherapy and those who did not.

1.4.2.1.9 Medications

1.4.2.1.9.1 Corticosteroids

Prolonged corticosteroid use has been found to be an independent predictor of anastomotic leakage by several studies. Eriksen and colleagues in their systematic review of corticosteroid usage and lower gastrointestinal anastomotic leakage, noted a significantly increased leakage rate in patients who were treated with varying doses and duration of corticosteroids compared to those who did not receive any¹²⁰. Further studies also reported increased incidence of anastomotic leakage with corticosteroid use^{90,121}. A recent meta-analysis by Haddad and colleagues noted increased risk of anastomotic leakage in emergency general surgery, when corticosteroids were used¹²²

1.4.2.1.9.2 Immunosuppressants

Inflammatory bowel disease (IBD) patients are often on corticosteroid and immunomodulator therapies such as infliximab, cyclosporin, mycophenolate mofetil and tacrolimus amongst others. These immunotherapy drugs, individually and in combination with corticosteroid therapy may contribute to poor healing and consequently anastomotic dehiscence and leakage. Experimental studies assessing these immunomodulator drugs have shown possible mechanisms for poor healing^{123–125} but clinical studies have not shown immunomodulators such as infliximab to independently increase leak rate in Crohn's patients, although there may be an effect when used in combination

with corticosteroids. Canedo and colleagues¹²⁶ analysed 225 Crohn's disease patients who underwent surgery and noted no significant differences in anastomotic leakage rates between those who have received infliximab compared to those who received other immunosuppressant's/corticosteroids or no medication at all. Krane and colleagues¹²⁷ reported similar findings in their patient cohort which included both Ulcerative Colitis (UC) and Crohn's sufferers who underwent elective laparoscopic surgery.

Patients who are on immunosuppressive medication for other indications, such as previous transplantation (e.g. renal), were however noted to have an increased risk of postoperative colorectal surgical complications including anastomotic leakage⁹². This may in part be due to additive effects of underlying renal disease, other comorbidities and emergent surgery.

1.4.2.1.9.3 Chemotherapeutic & biologic agents

With neoadjuvant chemotherapy being more commonplace in colorectal surgical practice, several authors have reported adverse events linked with them. There have been several reports in the literature of anastomotic breakdown, stricturing and gastrointestinal fistulae formation, both in the early and late postoperative period due to neoadjuvant bevacizumab therapy ['Avastin', a vascular endothelial growth factor (VEGF) inhibitor] used in metastatic colorectal cancer^{128,129}. Yoshioka and colleagues¹³⁰ reported on bevacizumab utilisation as part of neoadjuvant chemotherapy regimes in 78 patients with metastatic but resectable rectal cancer with 24 receiving an

anastomosis. The median time between last dosing of bevacizumab and surgery was nine weeks. The authors noted that 6/24 in total and five out of ten patients who had a low anterior resection without faecal diversion, suffered an anastomotic leakage. Furthermore, four of them had a delayed leakage after two weeks. The authors noted that the time interval between the last dose and surgery did not appear to ameliorate the risk of leakage and that the effects of bevacizumab may last longer than initially thought¹³¹. The drug manufacturer recommend that it should not be used in patients the month preceding and the month after surgery, however some suggest a longer period of 60 days without treatment¹³².

1.4.2.1.9.4 NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) are important and useful analgesic agents. Although patients may be on regular NSAIDS for pain relief for other conditions preoperatively, its use perioperatively and postoperatively has been discouraged. This is due to concerns that non-selective NSAIDs such as celecoxib may be associated with increased anastomotic leakage in colorectal resections¹³³. A six RCT meta-analysis¹³⁴ comprising 480 patients did not find any significant impact on leakage due to NSAID use, however, it was noted that some of the included studies may lack statistical power. More recent meta-analyses however noted increased incidence of anastomotic leakage with NSAID use. A meta-analysis of NSAID use in emergency general surgery recommended cautious usage of perioperative NSAIDS when colonic or rectal anastomoses are performed, due to statistically increased rates of

anastomotic leakage in this subgroup¹²². Peng and colleagues¹³⁵ in their 2016 meta-analysis of 12 RCTs with 3829 patients reported that nonselective NSAIDS significantly increased anastomotic leakage in intestinal surgery as well.

1.4.2.1.10 Location of tumour or benign pathology

The site of a colorectal cancer, or of a benign pathology, and by extension, the subsequent location of the anastomosis, impacts on the risk of postoperative anastomotic leakage. Data in the surgical literature widely confirms that the more distal the anastomosis, or closer to the anal verge, the higher the associated risk of leakage. Several studies and meta-analyses have confirmed this, especially so in the case of sigmoid or rectal cancer resections which entail a colorectal or coloanal anastomosis^{67,68}. Pommergaard and colleagues noted, in 13 of 19 observational studies evaluating the location of anastomosis in resectional colorectal surgery, a more distal or low anastomosis to be an independent risk factor for leakage. Subgroup analysis of only rectal anastomoses in this meta-analysis, noted a higher leak rate in anastomosis which were considered low rectal compared to those higher in the rectum⁶⁷.

1.4.2.1.11 Tumour size, stage & metastatic spread

Size of a colorectal malignancy is seldom assessed as a risk factor in isolation and data is sporadic. Two studies nevertheless, by Eberl and colleagues and Nisar and colleagues, have noted that tumour size, especially those greater

than 3 cm, were significantly associated with increase anastomotic leak risk^{117,136}.

There is relatively more evidence with respect to tumour stage and leak risk. Some studies noted an independent association with increased tumour stage and leakage^{75,91,114,137,138}. However Pommergaard and colleagues noted that only one study¹³⁷ in their analysis of 15 studies interrogating cancer stage and leakage risk, reported a statistically significant association between higher disease stage and anastomotic leakage. On further subgroup meta-analysis of eight of these studies comprising of 18084 patients, a pooled odds ratio of 0.86 (95% CI: 0.67-1.10) was noted, signifying no definite association between higher tumour stage and occurrence of postoperative anastomotic leakage⁶⁷.

Data on impact of distant metastatic disease on anastomotic leakage is also limited. Most patients with metastatic disease are often treated with neoadjuvant chemoradiotherapy, at times with palliative intent. Some do proceed to resection and others often only have defunctioning procedures for symptomatic relief. Nevertheless, some studies have assessed this, including a single institution study which reported that presence of metastatic disease was a major risk factor for leakage¹⁰⁹. Kiser and colleagues, in 2016, also noted a similar independent association amongst patients who had stage IV colorectal cancer¹³⁸.

The impact of preoperative tumour characteristics on colorectal cancer patients' anastomotic leak risk is often investigated as part of a group of risk factors and has been described above. However the impact of anastomotic leakage on subsequent tumour recurrence, delay to adjuvant treatment such as chemotherapy and overall survival is an area of previous and on-going research. This thesis will investigate this further utilising local patient series ([Chapter 2](#)) and national level administrative datasets ([Chapter 3](#) & [Chapter 4](#)).

1.4.2.1.12 ASA grading

American Society of Anaesthesiologists (ASA) grading of II or more has been significantly associated with sequentially increased risk of anastomotic leakage in different single institution studies⁶⁸. Subgroup analysis of seven of 14 observational studies in Pommergaard and colleagues' review, reported a pooled odds ratio of 1.71 (95% CI: 1.09-2.67) in terms of anastomotic leak risk, albeit with a significant level of heterogeneity⁶⁷.

1.4.2.1.13 Emergent surgery

Numerous studies, including single centre and multicentre studies, administrative database analyses, cohort studies and trials have reported increased leak rates in restorative emergency colorectal resections. Some of the more recent studies on emergent, unplanned colorectal resection for both benign^{139,140} and malignant indications¹⁴¹ confirm that it is an independent risk factor for anastomotic leakage.

1.4.2.1.14 Bowel Preparation & SDD

1.4.2.1.14.1 Mechanical bowel preparation

Mechanical bowel preparation (MBP) has been a contentious subject in colorectal surgery. MBP became popular and remained normal practice ever since Nichols and Condon published landmark articles on preoperative preparation of the colon in 1971¹⁴² and 1973¹⁴³. However support and use of MBP has been waned due to uncertainty in its ability to reduce the risk of SSIs and anastomotic leakage in particular, together with reported side effects of dehydration and renal impairment. In 2011, a meta-analysis¹⁴⁴ of 18 RCTs comprising 5805 patients (both colonic and rectal surgery), reported no significant differences in anastomotic leakage rates between patients who received mechanical bowel preparation (including enemas) and those who did not. However, the above meta-analysis included some studies which did not use concomitant oral antibiotics, (which Nichols and Condon did) which in essence is a form of Selective Decontamination of the Digestive tract (SDD) and has the effect of reducing intraluminal bacterial concentration¹⁴⁵.

1.4.2.1.14.2 Selective Decontamination of Digestive tract (SDD)

SDD is proven to prevent severe infections and reduce mortality in critically ill patients. A full protocol of SDD consists of parental and enteral antibiotics, high level of hygiene and surveillance cultures. However, there are several

variations and partial application of it in the literature and in practice. In UK colorectal surgical practice, patients are often treated preoperatively with intravenous systemic antibiotics (prior to start of surgery), and at times enteral antibiotics (rarely), together with hygiene measures and surveillance culture swabs when patients are seen in preoperative clinic or during admission for surgery. The aim is to clear oropharyngeal and gut carriage in overgrowth concentration of potentially pathogenic microorganisms, such as Gram-negative aerobic bacteria, methicillin-sensitive *Staphylococcus aureus* and yeasts¹⁴⁶.

Roos and colleagues¹⁴⁷ meta-analysed eight RCTs which compared systemic antibiotic therapy and SDD and only systemic antibiotic therapy in elective colorectal surgery, which found that combination of the two reduced the rates of postoperative infective complications including anastomotic leakage.

There have since been several studies that have investigated the impact of MBP with and without oral antibiotics on SSIs, including anastomotic leakage. Englesbe and colleagues¹⁴⁸ and Scarborough and colleagues¹⁴⁹ both reported incisional SSI and organ-space SSI rate reductions in those who received oral antibiotic therapy together with MBP, compared to those who received only MBP. Kiran and colleagues¹⁵⁰ compared three groups of patients who had no MBP (n=2296), had MBP only (n=3822) or had MBP with oral antibiotics (n=2324), and reported that on multivariate analysis, MBP with oral antibiotics, was independently associated with reduced rates of anastomotic leakage, other

SSIs and postoperative ileus. Morris and colleagues¹⁵¹, in a similar study, reported similar findings and further reported shorter length of stay and fewer readmissions in patients receiving MBP and oral antibiotics. A recent RCT in Japan¹⁵² comparing intravenous perioperative antibiotics alone and combined preoperative oral and intravenous perioperative antibiotics, reported that there were no significant differences in all types of SSI (incisional and organ-space) in patients undergoing elective laparoscopic colorectal cancer surgery. In Europe, there is an on-going randomised controlled trial which aims to ascertain the impact of SDD on specifically anastomotic leakage and infective complications in general^{153,154}.

In the United Kingdom colorectal surgical landscape currently, prophylactic intravenous antibiotics is administered in both elective and emergent colorectal surgery, ideally at least thirty minutes before start of surgery¹⁵⁵. However, MBP and oral antibiotic therapy (SDD) is not practiced in all centres. This is an area that has potential for further research and possibly may result in reductions in anastomotic leakage and other infective complications.

1.4.2.2 Intraoperative risk factors

There is abundant literature on preoperative risk factors, which contribute postoperative anastomotic leakage and other complications in colorectal surgery. However, there is comparatively lesser literature and data with regards to intraoperative factors and issues. The second section of this thesis will concentrate on intraoperative issues such as intraoperative assessment of

anastomotic perfusion and integrity (Chapter 5 & Chapter 6), and novel technologies and techniques (Chapter 7 & Chapter 8) being employed in surgery to prevent or reduce the risk of postoperative complications, such as anastomotic leakage. The following paragraphs will briefly elaborate important intraoperative factors that need to be taken into consideration with specific regard to anastomotic leak risk.

1.4.2.2.1 Anaesthetic & physiological factors

1.4.2.2.1.1 Glycaemic control

Diabetes is noted to be a preoperative risk factor for anastomotic leakage and indeed other postoperative colorectal surgical complications. Blood glucose level control in the intraoperative period is generally thought to be beneficial to the patient. Several studies have noted significant increased risk of anastomotic leakage with hyperglycaemia^{156,157}. Poor glycaemic control also adversely impacted patients in terms of other infective complications such as incisional SSIs and other postoperative complications such as myocardial infarction. Kotagel and colleagues¹⁵⁸ reported on adverse events in general surgical patients comparing those with and without diabetes mellitus. They found that non-diabetic patients who experienced hyperglycaemia intraoperatively were more at risk of adverse events compared to matched diabetic patients. Interestingly even though the non-diabetic patients experienced sequentially increasing risk of adverse events depending on the glucose level, there were no significant differences in diabetic patients with similar glucose levels. They

also noted that the non-diabetic patients were less likely to receive intra-operative insulin therapy. Although the higher glucose concentration in non-diabetics may represent a stress response, the authors opined that the lack of glucose control with insulin therapy at the patient's baseline range might contribute to this finding. Therefore, prevention of hyperglycaemia and good intraoperative and perioperative glucose control is likely to reduce the risk of adverse events. Some authors have recommend a blood glucose range of 80-120 mg/dl in the perioperative period, whilst avoiding hypoglycaemia^{85,157} to minimise postoperative complications in general and anastomotic leakage specifically.

1.4.2.2.1.2 Temperature

There is limited data on the impact of intraoperative body temperature on anastomotic leakage risk. However several have reported on SSIs as a grouping of complications or specifically on wound or incisional SSIs specifically. Kurz and colleagues¹⁵⁹ have note that active rewarming in the peri-operative period reduced the rate of postoperative wound infections, although this was in 1997 and in the era of open colectomies. Shaffer and colleagues¹⁶⁰ noted that greater than 60 minutes of low body temperature ($<36^{\circ}\text{C}$) was a risk factor for SSIs in general after colorectal resections. This was however not significant on multivariate analysis. An elegant study by Melton and colleagues¹⁶¹ assessed body temperature continuously to ascertain its impact on SSIs in 1008 colorectal procedures. Maximum, minimum, median and end-of-procedure temperatures were found to be similar in patients who suffered a

SSI and those who did not. Similar to the previous study, increased duration correlated to SSIs on univariate analysis only. A further study reported near exact findings as well¹⁶². Maintaining normothermia and perioperative rewarming strategies are part of the World Health Organisation's Guidelines for Safe Surgery¹⁶³. It must also be noted that extreme hypothermia is not an issue in this day and age in the operating theatre, at least in the elective setting, and hence the paucity of data to compare with normothermia¹⁶⁴. Rather than artificially stratifying and designating lower temperatures within the normal range to be hypothermia, the aim should be to maintain normothermic range in surgery, which is generally defined to be between 36°C and 37°C. Although no definite link is evident between hypothermia and anastomotic leakage risk, maintaining normothermia/rewarming appears beneficial in incisional SSI and other complication prevention and in keeping with recommended and good practice.

1.4.2.2.1.3 Operative blood loss

Haemorrhage is a dreaded problem in any surgery. In colorectal surgery, intraoperative blood loss is significantly associated with anastomotic leakage in multiple studies^{165–167}. This is due to the sequelae of blood loss, including hypovolaemia, shock and subsequent reduced tissue perfusion, oxygenation and impaired tissue healing at the anastomotic site. Similarly, preoperative anaemia is also a risk factor for anastomotic leakage. Several studies have shown association between low haemoglobin levels in the preoperative period and postoperative complications including anastomotic leakage^{168–170}.

Intraoperative and postoperative blood transfusion is often a surrogate marker of blood loss and also an independent predictor of anastomotic leakage, noted by several studies^{137,171,172} including a systematic review from 2015⁸⁸.

1.4.2.2.1.4 Blood pressure & Fluid management

Blood pressure is dependent on blood volume, cardiac function and vascular tone¹⁷³, and in turn blood pressure and microcirculation impact on tissue perfusion and oxygenation and by extension tissue healing¹⁷⁴. However technically sound and robust an anastomosis is, its viability has been shown to be at least partly dependent on the perianastomotic tissue perfusion and oxygenation^{175–178}.

In this setting, a high preoperative diastolic blood pressure and prolonged or significantly low hypotension has been noted to be linked to increased risk of anastomotic leakage^{179,180}. Control of perioperative hypertension is known to protect end-organ function and may also reduce overall complications in surgical procedures, including anastomotic leakage in colorectal surgery¹⁸¹.

Fluid replacement and management in the perioperative period has trended towards a goal-directed approach to maintain physiological parameters such as systolic/diastolic blood pressure, mean arterial pressure, blood gases and pH in their normal ranges. Fluid management is further guided by oesophageal Doppler for accurate quantification and two meta-analyses have noted reduced overall complications in abdominal surgery^{182,183}. With the increased utilisation

of enhanced recovery protocols in colorectal surgery, several studies have compared restrictive and liberal fluid management regimes and these did not detect significant differences in anastomotic leakage rates between the two regimes^{184,185}. One study noted reduced respiratory complications in the restrictive group, although other complications were more prevalent¹⁸⁶. Individualised goal-directed fluid therapy is in general promoted in colorectal surgery to reduce overall complications, but there is not definite direct link between restrictive versus liberal fluid therapy, and anastomotic leakage.

1.4.2.2.1.5 Tissue oxygenation

Reduced tissue oxygenation can contribute to both wound breakdown and anastomotic compromise. Some studies have reported perioperative supplemental oxygen delivery reduced the risk of anastomotic breakdown and leakage^{187–189}.

1.4.2.2.1.6 Inotropic support

Inotropic or vasopressor drugs utilised in the intraoperative period are associated with increased rates of anastomotic leakage^{180,190}. Some authors recommend formation of a protective ileostomy in such situation, especially if there were concomitant intraoperative complications, concerns regarding anastomosis viability and prolonged operative duration¹⁸⁰.

1.4.2.2.1.7 Epidural analgesia

The impact of epidural analgesia specifically on risk of anastomotic leakage is equivocal. Holte and colleagues¹⁹¹ in their 2001 meta-analysis of 12 studies noted no significant effect on anastomotic leakage rates, although the authors cautioned a high risk of type II error in their analysis. However several other studies since reported that epidural analgesia have no or little if any, independent impact on anastomotic leakage^{192–194}.

1.4.2.2.2 Surgical factors

1.4.2.2.2.1 Surgical approach

The first laparoscopic-assisted colectomy was reported by Jacobs and colleagues¹⁹⁵ in 1991 and subsequently colorectal surgeons have adopted more minimally invasive procedures ranging from fully laparoscopic surgery, single incision laparoscopic surgery (SILS), natural orifice transluminal endoscopic surgery (NOTES) and robot-assisted surgery. The assimilation of MIS techniques in colorectal surgery increased exponentially in the 2000s^{196,197} but not without initial scepticism and concerns over safety and high complication rates in both benign¹⁹⁸ and malignant surgery, especially over adequacy of oncological clearance and recurrences of malignant disease^{199,200}. Early randomised controlled trials and cohort studies comparing conventional open and laparoscopic surgery for colonic resection, indicated the latter to be superior in terms of short-term outcomes such as estimated intraoperative

blood loss, length of hospital stay, postoperative pain, return to normal bowel function and wound infection rates^{201,202}. Similar short term outcomes were noted in rectal cancer surgery²⁰³.

Initial worry over oncological outcomes for colonic cancer surgery were disproved by multicentre randomised studies such as the CLASICC²⁰⁴, COLOR^{205,206} and COST²⁰⁷ trials which showed no statistically significant differences in resection margins, lymph node yield, disease-free and overall survival, when appropriately trained laparoscopic surgeons performed the operations. Data from the COLOR II trial²⁰⁸ and COREAN trial²⁰⁹ indicate similar superior short-term outcomes for laparoscopic rectal cancer surgery and no significant differences in completeness of resection compared to open surgery. Rates of locoregional recurrence, disease-free survival and overall survival were also similar in long term data analysis of the COLOR II cohort²¹⁰.

In terms of differential impact on anastomotic leakage between open and minimally invasive surgery, the CLASICC trial reported similar rates in both colonic (3% vs. 4%) and rectal surgery (7% vs. 8%)²⁰⁴. Breukink and colleagues²¹¹ in their meta-analysis of open and laparoscopic TME surgery for rectal cancer, reported no significant differences in anastomotic leakage too. However laparoscopic surgery at times entails multiple firings of stapler guns to divide and anastomose bowel, compared to open surgery, especially in laparoscopic rectal surgery and some authors²¹² have reported increased anastomotic leakage rates due to this. Ito and colleagues reported that TME

and multiple stapler firings during distal rectal division were significantly associated with anastomotic leakage. More recently, Braunschmid and colleagues²¹³ in their retrospective single institution study, noted that usage of three or more stapler cartridges in laparoscopic rectal division was significantly associated with postoperative anastomotic leakage. However, some authors have opined that with advances in stapler technology and surgical experience this may improve^{114,212}.

1.4.2.2.2 Conversion to laparotomy

A decision to convert a laparoscopic operation is often taken due to locally advanced disease (in cancer surgery), technical difficulty, lack of sufficient progress of the procedure, intra-operative complications including emergent bleeding, bowel injury and iatrogenic damage, or patient compromise from an anaesthetic point of view²¹⁴. This may often be in the patient's best interest to prevent or minimise sequelae due to non-conversion that may occur otherwise. Both patient factors such as BMI, rectal cancer (opposed to colonic), height of tumour and male gender and surgeon factors such as inexperience, learning curve and operative volume have been implicated to be risk factors for conversion amongst many others²¹⁵.

The independent impact of conversion on postoperative anastomotic leakage is however less clear. The intraoperative difficulties entailed which led to conversion, are themselves predictors of postoperative morbidity such as intensive care admission, prolonged hospital stay, medical complications such

as chest infections, and poor wound healing²¹⁶. Furthermore, conversion to open surgery often results in longer operative times and higher blood loss, which could increase the stress response and reduce the patients' immunity response leading to a higher susceptibility to develop postoperative complications²¹⁷. These factors in themselves may contribute to increased anastomotic complications and leakage too. Yamamoto and colleagues²¹⁸ in their multi-centre retrospective analysis of 1073 laparoscopic rectal cancer surgeries, noted increased rate of anastomotic leakage (18% vs. 7.2%) and overall more postoperative complications of any kind (54% vs. 24%) in patients who underwent a conversion as opposed to those who had their surgery completed laparoscopically.

Other studies^{215,219} however reported no significant differences in anastomotic leakage rates between open, converted and fully laparoscopic procedures. Furthermore, Kim and colleagues²²⁰ have also shown that early decision to convert, within 60 minutes, does not increase risk of 30-day postoperative complications.

On balance, conversion increases the risk of postoperative complications due to several factors and conversion by itself has been shown to be directly increasing the risk of anastomotic leakage in some instances. Astute patient selection to laparoscopic surgery, early recognition of difficulty and early decision to convert, are likely to reduce postoperative complications, including

anastomotic leakage, in this specific subset of patients who require laparoscopic to open conversion.

1.4.2.2.2.3 Location of anastomosis

Colorectal anastomotic leakage is directly associated with the location of anastomosis in the bowel, with more distal anastomoses having a significantly higher leakage rate compared to more proximal ones. This has been shown to be the case in numerous studies over the decades^{121,221–223} and by several systematic reviews and meta-analyses^{67–69}. Specifically in rectal anastomoses, several further studies^{224,225} have shown that anastomotic leakage risk is higher in infra/extra-peritoneal anastomoses compared to supra/intraperitoneal anastomoses. In a review⁶⁷ of 19 observational studies which assessed the level or location of anastomoses, 13 noted a low anastomosis to be an independent risk factor for anastomotic leakage. Subgroup analysis of six studies that investigated rectal anastomoses found that a low rectal anastomosis had an increased risk compared to a high rectal anastomosis. Although the definition or cut-off for level of rectal anastomosis was not the same in these studies, most defined the cut-off to be five cm or less from the anal verge. This 2014 meta-analysis reported a mean anastomotic leak rate for low rectal anastomoses to be 11.6% vs. 9.2% compared to high rectal anastomosis.

1.4.2.2.2.4 Type of anastomosis

The impact of type of anastomosis technique on anastomotic leakage has also been extensively studied in the literature. Since the introduction of stapler technology, in part due to the advent of laparoscopic surgery, several authors have investigated the differences between stapled and hand-sewn anastomoses, in both emergency and elective surgery.

A 2012 Cochrane review update²²⁶ of stapled and hand-sewn anastomoses in elective colorectal surgery for all indications, identified nine RCTs comprising a total of 1233 patients. The authors noted anastomotic stricturing to be more frequent with stapled anastomoses and that hand-sewn anastomoses took longer to perform, but there were no significant differences in terms of anastomotic leakage, bleeding or reoperation rates. It was however noted that the recent study included was from 1995, with several more recent studies not meeting the inclusion criteria. Another Cochrane review²²⁷ assessing anastomotic type in elective ileocolic anastomoses only, reported reduced anastomotic leakage with stapled anastomoses in cancer resections but no differences in Crohn's disease resections.

A 2014 meta-analysis²²⁸ concentrating on emergency laparotomic surgery (both trauma and general surgical) reported that there were no significant differences between stapled and hand-sewn intestinal anastomoses in general. A recent 2017 multi-institutional prospective study²²⁹ on emergency general surgical patients specifically, noted that there were no significant differences in

anastomotic leakage rates between hand-sewn and stapled anastomoses. However, it noted that there was an apparent bias amongst emergency surgeons to perform handsewn anastomoses in higher risk patients despite this. In both these studies there were no subgroup analyses of colorectal anastomoses or other individual anastomoses depending on location in the gastrointestinal tract. With current evidence, it is not feasible to state which type of anastomosis is better in the emergency surgical setting, let alone in the specific subset of colorectal resection and anastomoses. There is however an opinion that in the emergency setting (different patient physiology and intraoperative issues such as contamination in contrast to elective setting), bowel wall oedema, ischaemia and viability may preclude the use of stapled techniques^{230–232}. Conversely, handsewn anastomoses are reported to take longer to perform and this excess duration under general anaesthesia may be critical to a patient who is in physiological extremis in emergency surgery²³³.

The substantial literature assessing the type of anastomosis in colorectal surgery and its impact on subsequent anastomotic leakage and other complications is varied in its conclusion with no clear difference in anastomotic leakage rates between hand-sewn and stapled anastomoses. With the available evidence, taking into account patient/disease characteristics and intraoperative findings, it is a surgeon's preference, training and experience, which will dictate the type an anastomotic technique.

Within the discussion of anastomosis types, there are several configurations and height/location of the anastomosis constructed, depending on the clinical indication and location of pathology. These could be colo-colonic, colo-rectal, ileo-rectal (IRA) or an ileal pouch anal anastomosis (IPAA) in terms of the afferent and efferent limbs. Furthermore, they may be configured in a several ways as well (end-to-end, side-to-end, end-to-side and side-to-side & in various pouch configurations).

Our local institution, which is a tertiary level referral centre for Polyposis patients, performs a significant number of prophylactic colectomies in such patients. It also has a substantial number of IBD patients who require colectomies as well. To this end, various anastomotic techniques, including IPAA and IRAs have been utilised to reconstitute intestinal continuity. IRAs have been shown to have a lower postoperative complication profile compared to IPAA and also better functional outcomes in a 2006 meta-analysis of 18 studies²³⁴. However the authors reported a significant 11.6% 30-day reoperation rate (a surrogate marker of anastomotic leakage) in IRA patients nevertheless.

With the broad aim of reducing this, specifically in the Polyposis cohort, we trialled an alternative/variant anastomosis, namely the ileo-distal sigmoid anastomosis (IDSA). This was on a background of ileorectal anastomosis being closer to the anal verge and being a risk factor for anastomotic leakage, and with a hypothesis that in a select group of Polyposis patients who have no or

minimal rectal polyp burden (therefore amenable to regular polyp surveillance flexible endoscopy), long term function and quality of life metrics in IDSA patients may be better compared to IRA patients. This thesis will present a short series of patients in Chapter 7, describing the technique and our early results.

1.4.2.2.2.5 Faecal diversion

The exteriorisation of proximal bowel as a form of faecal diversion to protect the bowel is well established. Some important factors previously described, such as male sex, left sided or rectal anastomoses (especially infraperitoneal or low), emergent surgery, intraoperative complications and inflammatory bowel disease amongst others, increase the risk of a leakage. There is general consensus that a diverting stoma does not prevent a leakage, but does blunt the consequent intra-abdominal sepsis, especially so in rectal anastomoses^{66,235}.

Most surgeons prophylactically create a faecal diversion with either a loop ileostomy or colostomy when performing anastomoses in these circumstances to dissipate the clinical effects of an anastomotic leakage if it does occur. However, the quality of life in patients with a stoma is reduced²³⁶, a significant proportion of patients do not get their stomas reversed and if they do, there is associated morbidity and even mortality associated with it²³⁷. As such patients being given a stoma after careful consideration to the above and risk stratified so that they gain the benefit of alleviating the consequences of a leak and also

not be exposed to the disadvantages of a stoma. Several studies have also compared ileostomy and colostomy, with a recent meta-analysis concluding that ileostomies were slightly preferred due to reduced stoma complications and incisional SSIs with the former²³⁸.

A novel diversion technique, the tube ileostomy, which has been previously used in the past, has seen a revival recently with several authors reporting on its utility. The main attraction of this technique is the avoidance of a reversal operation. However, its efficacy and safety has not been fully evaluated, and compared with the current established loop ileostomy. Chapter 8 of this thesis will interrogate this utility and compare it with the gold-standard loop ileostomy.

1.4.2.2.2.6 Prophylactic drainage

Several studies have previously reported no significant differences in anastomotic leakage with or without prophylactic drainage^{239–241}. A 2006 systematic review of six RCTs, concluded that there was insufficient evidence showing that routine drainage prevented anastomotic complications²⁴². However, Rondelli and colleagues noted specifically investigated the utility of routine drainage in extraperitoneal anastomoses in their meta-analysis of eight studies (2277 patients) and reported reduced leakage rates (OR 0.51 95%CI:0.36-0.73) and reduced need for reintervention (OR 0.29 95%CI: 0.18-0.46). The available data show that prophylactic drainage does not impact colonic anastomotic leak rates, but may impact in low/rectal anastomoses,

although this must be taken in the context of other variables such as faecal diversion and type of anastomosis (stapled/hand-sewn) as well.

1.4.2.2.2.7 Anastomotic testing

Anastomotic testing in the intraoperative period is a common if not standard practice in colorectal surgery, especially in pelvic/rectal anastomoses. The various types of anastomosis testing techniques, such as air-leak testing, have experienced different levels of acceptance and uptake in the surgical community. Some have shown benefit in reducing anastomotic leakage, whilst others are less conclusive. Newer technologies such as perianastomotic perfusion assessment have also gained traction. This area will be further discussed in section two of this thesis, by way of a systematic review ([Chapter 5](#)) of the available literature on this topic and a feasibility pilot study ([Chapter 6](#)) in our local institution of one of the newer techniques, near infrared and Indocyanine green autofluorescence (NIR-ICG) perfusion analysis.

1.4.2.3 Detection of anastomotic leakage in the postoperative setting

Notwithstanding the variability of risk factors and their ability to definitively predict an anastomotic leakage, knowledge and understanding of each risk factor and their cumulative effects will assist a surgeon in appropriately stratifying a patient's risk of leakage and in perioperative decision-making. However, once an anastomotic leakage occurs, its presentation as a clinical

entity needs to be recognised by the surgeon as soon as possible²⁴³. In the postoperative period, clinical examination, physiological and biochemical parameters, endoscopy and imaging adjuncts such as computed tomography and fluoroscopy all help in diagnosing an anastomotic leakage²⁴⁴.

Clinical signs of systemic inflammatory response syndrome, sepsis, fever, ileus and pain are often noted, however when observed separately, are not highly predictive of leakage occurrence²⁴⁵. Several biochemical assays have been proposed and investigated in the diagnosis of an anastomotic leakage. Inflammatory markers such as C-reactive protein (CRP) and White Cell Count (WCC) are the most investigated and used clinically at present, although other markers such as calcitonin, lactate and pH levels in the perianastomotic tissue have been interrogated in the past²⁴⁶. A meta-analysis by Singh and colleagues noted that CRP was useful as a negative predictive test, where a low CRP value between the third and fifth postoperative day can help to predict patients who do not suffer an anastomotic leakage²⁴⁷. Garcia-Granero and colleagues noted that CRP and calcitonin were useful in prediction anastomotic leakage which required relaparotomy²⁴⁸. Given that surgical stress may result in elevated inflammatory markers in the early postoperative period, markers such as CRP, calcitonin and WCC may not be very useful in the first few days. However persistent elevation of these markers beyond postoperative day three increase the risk and raise suspicion of an anastomotic leakage having occurred⁶⁸.

Previously, suspected anastomotic leakages were investigated with x-ray contrast enemas, rigid sigmoidoscopy or digital inspection in rectal anastomoses and at times when clinically indicated, a reoperation^{59,249,250}. The increased use of computed tomography imaging, the increased availability of diagnostic laparoscopy, flexible endoscopy and interventional radiology has firstly allowed more accurate and quicker detection of colorectal anastomotic leaks²⁵¹ and secondly given the surgeon more options in terms of managing them²⁵².

The risk of an anastomotic leakage occurring is not dependent on biochemical markers or radiological investigations. However the timing of these investigations and subsequent interpretation, together with other aspects such as clinical examination, may allow early identification and prompt commencement of appropriate therapy. In this sense, these postoperative investigations, when used judiciously and in tandem with clinical acumen, may prevent anastomotic leakage and more specifically its sequelae, due to delayed recognition.

1.4.2.4 Classification & management of anastomotic leakage

With respect to classification of leakage and management strategies, there have been groups that have aimed to standardise the definition, and improve the overall management of colorectal anastomotic leakage. Several authors, including den Dulk and colleagues²⁵³, have proposed postoperative standardised surveillance protocols to improve diagnosis of leakage and also

minimise the delay in its diagnosis, so as to ensure prompt treatment and minimisation of its impact on the patient. The Dutch Leakage Score proposed by den Dulk in 2009 allowed quantitative scoring of symptoms in the postoperative period on a daily basis in a systematic manner, with patients who get higher scores being stratified to closer monitoring and radiological investigations. They reported reduced delay in diagnosis of anastomotic leakage from four days to less than two days.

In 2010, the International Study Group of Rectal Cancer (ISREC), proposed a definition for anastomotic leakage in anterior resection and a severity grading scale²⁵⁴. The group defined an anastomotic leakage as,

‘a defect of the intestinal wall integrity at the colorectal or colo-anal anastomotic site (including suture and staple lines of neorectal reservoirs) leading to a communication between the intra- and extraluminal compartments. A pelvic abscess close to the anastomosis is also considered an anastomotic leakage’.

The group’s authors also specifically proposed a severity grading scale according to the type of intervention undertaken to treat the anastomotic leakage: a conservative approach with no active intervention; a non-surgical interventional approach (antibiotics or radiological drainage) without the need for reoperation; or a surgical reoperative approach. In 2013, the same working group validated their definition and severity classification by testing it on a prospectively collated patient database of 746 rectal cancer patients (with 56

leakages), and noted that the definition and severity grading scale provided a simple and easily applicable model for classification and opined that the use of this system may facilitate comparison of results from different studies investigating anastomotic leakage in rectal surgery²⁵⁵.

In 2016, in the United Kingdom, the ‘Anastomotic Leakage Working Group’ comprising expert members from The Association of Surgeons of Great Britain and Ireland (ASGBI) and the Association of Coloproctology of Great Britain and Ireland (ACPGBI) jointly published a guidance document on prevention, diagnosis and management of anastomotic leakage²⁵⁶. This guidance employed a Delphi process to reach consensus on important aspects of colorectal anastomotic leakage and associated issues such as preoperative and intraoperative risk factors, considerations for defunctioning of an anastomosis, intraoperative anastomosis testing and postoperative assessment and surveillance for anastomotic leakage.

Compartmentalisation and classification of colorectal surgical complications dictates that anastomotic leakage is considered under the broad grouping of surgical site infections. However it does form a substantial part of colorectal surgical complications as a whole and has a wide-ranging list of risk factors attributable to it. Furthermore, its sequelae can also severely impact patients and even result in death. As such, it has been constantly researched and investigated by the surgical community to minimise it as much as possible. This

thesis will also concentrate on it in subsequent chapters, with specific emphasis on intraoperative detection and prevention (Section II).

1.4.3 Intra-abdominal collection, abscess & fistula

In the postoperative setting, collections, abscesses and fistulae formation are often a progression or sequelae of anastomotic leakage. Fluid collections around the anastomosis with an anastomotic dehiscence apparent on cross-sectional imaging may be identified in patients who suffer an anastomotic leakage²⁵¹. However fluid retained after peritoneal lavage at the end of operations may result in fluid pooling in dependent areas of the abdomen and between loops of bowel and mesentery, and form collections. Miliaras and colleagues noted in their study of fluid collections detected by ultrasound following uncomplicated colorectal surgery, that the presence of a collection was not related to peritoneal lavage pre-operative closure, intraoperative blood loss or presence of drains²⁵⁷. However if there is contamination, the risk of an organised, walled collection or abscess formation is present and may result in the patient being symptomatic.

The management of symptomatic collections and abscesses are similar to anastomotic leakages. They may require conservative management with antibiotics, but at times require radiological drainage or reoperation, including resection and exteriorisation of bowel. Baig and colleagues reported that radiological (CT-guided) drainage is a treatment of choice in elective colorectal surgical patients with intra-abdominal abscesses without signs of generalised

peritonitis²⁵⁸. Similarly, in diverticulitis a 2016 meta-analysis²⁵⁹ noted that diverticular abscess less than 3 cm may be treated with antibiotics, whilst larger abscesses may need either radiological drainage or operative management. However, those who show signs and symptoms of generalised peritonitis need a reoperation.

Diverticular disease and diverticulitis, and IBD (especially Crohn's disease) can result in abscess and fistulous tract formation. Patients who suffer the above pathologies are at increased risk even without any surgical intervention and may also develop them post surgery, which at times is on an emergent basis. Fistulae may form a communication between the bowel lumen and adjacent structures in the abdomen and pelvis, with the abdominal wound or the abdominal skin and perineum²⁶⁰. IBD patients are inherently at risk of this complication due to the pathophysiology of the underlying disease²⁶¹. However, patients who undergo surgery for any indication is at risk too, especially if they suffer an anastomotic leakage and subsequent collection or abscess. Management of enterocutaneous fistulous disease is complex and involves bowel rest with total parenteral nutrition and further, often multiple operations^{262–264}.

Similar to anastomotic leakage, these associated complications impact the patient adversely, are difficult to manage and have cost implications too^{57,265}.

1.4.4 Remote site infections (RSIs)

Postoperative non-abdominal infective complications occur in colorectal surgery due to several factors. Firstly, factors that increase the risk of surgical site infections and anastomotic leakage are similarly implicated in this situation, albeit to different extents. These include patient factors such as ASA score, comorbidities such as diabetes, cardiovascular and respiratory disease, renal impairment and malnutrition⁴⁴. Surgery-related factors include operative duration, blood loss, blood transfusion, intraoperative surgical and anaesthetic complications amongst others⁴⁵. Furthermore, the surgical stress response lowers global immune responses in the postoperative period, making the patient more susceptible to infections²⁶⁶.

1.4.4.1 Pneumonia

Pulmonary atelectasis and subsequent development of pneumonia, is associated with previous smoking history, previous respiratory disease and in the postoperative period, poor pain control, reduced mobility, poor respiratory effort, and neurological impairment²⁶⁷. Postoperative ileus, nausea, vomiting and subsequent aspiration are also risk factors²⁶⁸. Pesseaux and colleagues²⁶⁹ also noted nasogastric tube placement to be an independent risk factor of postoperative pneumonia, although this was noted in hepatectomy patients, it is also noted that NGT placement is avoided in colorectal surgery unless there is evidence of non-resolving mechanical intestinal obstruction²⁷⁰.

1.4.4.2 Urinary tract infection

Similarly urinary tract infection may occur due to reduced mobility, traumatic urinary catheterisation, intestinal flora contamination and prolonged placement of catheter. Sheka and colleagues²⁷¹ noted over 4% of patients undergoing colorectal surgery in their clinical database analysis developed urinary tract infections. They reported that female gender, open procedure, rectal surgery, older age, higher ASA grading, longer operative time, reduced functional status and steroid usage to be independent predictors of urinary tract infection.

1.4.4.3 Septicaemia

If the sources of these infective complications are not treated promptly and effectively they may exacerbate the already developing systemic inflammatory response, progressing to septicaemia, severe sepsis and septic shock and end-organ damage²⁷².

1.5 Non-infective abdominal complications

Non-infective complications include complications such as wound seroma, dehiscence and herniation, haemorrhage, gastrointestinal complications such as ileus and small bowel obstruction, iatrogenic injuries and medical complications such as myocardial infarction, deep vein thrombosis and renal failure.

1.5.1 Wound-related complications

1.5.1.1 Wound dehiscence

Wound or incisional SSIs have been discussed previously and dehiscence or partial dehiscence of the wound often occurs secondary to this and very commonly, the wound is opened to release infective collections as a treatment⁴⁹. Wound dehiscence may however occur without underlying infection due to poor surgical technique or tension, and due to oedema or ascites.

1.5.1.2 Seroma

Seroma are mostly associated with repair of abdominal hernias with mesh products²⁷³. However, seroma can sometimes form in abdominal incisional wounds if 'dead space' is not adequately plicated and closed during laparotomy closure²⁷⁴. Most abdominal seroma can be managed conservatively and on occasion may require local ultrasound-guided drainage, although there is a risk of recurrence and need for multiple drainages before complete resolution.

1.5.1.3 Incisional herniation

An incisional hernia in colorectal surgery or following any abdominal surgery is a recognised complication which often occurs or is detected in the mid to long term²⁷⁵. In open colorectal surgery, the midline wound closure can result in subsequent herniation due to poor technique and other risk factors similar to

those that increase the risk of abdominal dehiscence and incisional SSIs, such as diabetes, obesity, smoking and steroid use amongst others^{276,277}. In fact, patients who suffer incisional SSIs or wound infections in the postoperative period after colorectal surgery are at increased risk of incisional herniation²⁷⁸. The incidence of incisional hernia have been reported by various studies to be between 8.6% to 33% in open colorectal surgery and between 4.7% to 24.3% in laparoscopic procedures^{279–281}. Patients may present with incarceration of bowel within incisional hernia and subsequent bowel obstruction, which may necessitate reoperation to rectify²⁸². In patients who receive an ileostomy or colostomy, there is risk of incisional herniation occurring after reversal of their stomas as well²⁸³. Incisional hernia in colorectal surgery is a considerable postoperative problem for the patient, causing significant morbidity, reduced quality of life metrics and financial cost²⁸⁴.

1.5.2 Anastomosis-related non-leakage complications

1.5.2.1 Anastomotic bleeding

Anastomotic bleeding and stricturing although related to anastomotic leakage, can be considered slightly different problems to the surgeon. Anastomosis construction is undertaken with the main aim of ensuring mechanical integrity and intraluminal patency postoperatively. This entails that there is good perfusion, adequate intra-luminal space and no tension across the joint, amongst other important aspects. Anastomotic bleeding at the anastomotic site in the perioperative period can result in a perianastomotic collection of blood,

which is a nidus for infection and abscess formation. Bleeding can therefore lead to a similar clinical picture to anastomotic leakage, collection and abscess formation. Active bleeding at the anastomosis can result in substantial blood loss which may require reintervention to treat, however bleeding after a colorectal or indeed any gastrointestinal anastomosis is usually minor and self-limiting²⁸⁵. Some authors recommend close inspection of anastomotic staple lines for pulsatile bleeding points to control with suture ligation and others advocate use of intraoperative endoscopy to visualise the anastomosis to ensure haemostasis at the anastomotic line, which can be achieved with over-the-scope hemoclips if required²⁸⁶.

1.5.2.2 Anastomotic stricture

Anastomotic stricture in colorectal surgery is a complication which is known to occur but which is poorly defined. It is only detected during routine follow-up with surveillance endoscopies in colorectal cancer management or if the patient is clinically symptomatic. Consequently it is difficult to ascertain actual incidence of this entity, although a rate of 8.2% was noted by Werre and colleagues in a cohort of 256 low anterior resection patients²⁸⁷, with a median time of presentation at 7.7 months. Bannura and colleagues²⁸⁸ defined the inability to pass a rigid endoscope through the anastomosis as a stricture and noted 21.1% of their cohort of 179 patients to have stricturing based on this definition. Strictures were also reported to be slightly more common in stapled anastomoses in a Cochrane review which primarily assessed anastomotic leakage differences between the two hand-sewn and stapled anastomoses²²⁶.

However, simple intervention with Hegar dilators, pneumatic balloon dilators, stenting, corticosteroid injection or radial incision of anastomotic stricture scar have been utilised and reported in the literature. Reoperation with excision of the stricture and re-anastomosis or exteriorisation with an end-colostomy have also been reported²⁸⁵. Although not a life-threatening perioperative complication, anastomotic stricture can impact quality of life in patients with normal defecation patterns not being regained.

Both the above-described anastomotic complications are amenable to detection within the intraoperative setting. This thesis will expand on this aspect further in Chapter 6, which reports on a feasibility study of anastomotic perfusion assessment utilising near infrared technology and Indocyanine Green autofluorescence.

1.5.3 Gastrointestinal tract complications

1.5.3.1 Ileus

Postoperative ileus is the reduced or impaired motility of the bowel without any mechanical obstruction, due to its intraoperative manipulation during colorectal surgery. It is characterised by nausea, vomiting, abdominal bloating and discomfort, absence of bowel movement or flatus and accumulation of gas and fluid in the bowel^{289,290}. The aetiology of postoperative ileus is multifactorial and is associated with delayed return to normal diet and function, and delayed prolonged hospital stay and financial cost. In colorectal surgery specifically,

postoperative ileus has been extensively investigated to prevent and mitigate it. Intra-abdominal sepsis, use of opioid drugs, prolonged operative duration and intraoperative complications are some reported risk factors²⁸⁹. Of note, laparoscopic surgery has been reported to have a lower incidence of ileus compared to open procedures in a meta-analysis of 54 studies comprising 18983 patients²⁹¹. There have been several approaches to minimising ileus. Some authors have suggested keeping intraoperative bowel manipulation to a minimum²⁹¹ and others have utilised postoperative measures such as early feeding, mobilisation, avoidance of opioid analgesia and other aspects as part of an enhanced or accelerated recovery programme in the immediate postoperative period to optimise the patient^{292–294}. Postoperative ileus is a significant issue in colorectal surgery. It delays patient recovery and increases the risk of other complications secondary to patient discomfort and reduced ambulation, such as respiratory infections and venous thrombosis. Its prevention and management forms an integral part of enhanced recovery programmes^{292,295,296}.

1.5.3.2 Mechanical small bowel obstruction

Small bowel obstruction after colorectal surgery most commonly occurs due to intra-abdominal adhesions but may also occur due to incarceration and/or strangulation of bowel in anatomical hernial orifices or internal herniation within unclosed mesenteric defects. It may also occur when bowel wall gets trapped within sutures or staples within the abdominal cavity, or within laparotomy or port-site wound closures. Small bowel obstruction is much more common

although large bowel obstruction can occur²⁹⁷. Anastomotic failure and stricturing at a colorectal anastomosis can result in large bowel obstruction beyond the immediate postoperative period.

Development of small bowel obstruction in the immediate postoperative period is at times due to non-adhesional causes, usually presenting with the patient being acutely unwell and with radiological evidence of the cause of obstruction, such as a loop of bowel incarcerated and strangulated within a hernia, necessitating a return to theatre²⁹⁸. Adhesional bowel obstruction can occur anytime after surgery, but usually after the immediate postoperative period due to the time interval taken for adhesions to develop in the peritoneum²⁹⁹. Several meta-analyses, in the two most recent in 2014 and 2016 have noted that laparoscopic surgery reduced the risk of small bowel obstruction^{300,301}. However, even with the increased utility of laparoscopic and other minimally invasive surgery in colorectal surgery, small bowel obstruction still remains a problematic postoperative complication. The incidence of small bowel obstruction after any abdominal surgery was reported to be 2.4% in a systematic review of 87 studies comprising more than 100,000 patients²⁹⁸ and is a common postoperative complication which accounts for 4% of all emergency admissions and 20% of emergency surgical operations in large population based study³⁰². Furthermore, the latter study reported that patients may suffer repeated bouts of small bowel obstruction subsequent to their primary index surgery and this has a significant patient morbidity and cost implications too.

Patients who present with signs and symptoms of adhesional bowel obstruction often get investigated with CT, which may show a 'transition point', with proximal small bowel dilatation and collapsed bowel distal to it³⁰³. Despite it being a fairly common complication of colorectal surgery, up to 80% of adhesional small bowel obstruction cases resolve with conservative management of nasogastric decompression and bowel rest³⁰⁴. However, in cases of non-resolution or evidence of bowel compromise, patients require surgical management that may be via an open or laparoscopic approach. Of note, amongst those that require reoperative intervention to treat this complication, Behman and colleagues³⁰⁵ noted that reintervention using a laparoscopic approach resulted in a slight higher risk of subsequent bowel injury compared to open laparotomy. Small bowel obstruction is therefore one of the more difficult complications to manage and has a significant impact on patient morbidity and cost implications in colorectal surgery.

1.5.3.3 Stoma-related complications

Stoma formation is undertaken within operations performed for malignant, benign, inflammatory, and trauma (including iatrogenic) indications. In elective colorectal cancer resection, an ileostomy or colostomy is created to 'protect' a distal, rectal, often infra-peritoneal anastomosis and more correctly to mitigate the consequences/sequelae of any subsequent anastomotic leakage. The relationship of stoma creation and its impact on anastomotic leakage has been discussed in depth previously. On occasion, end ileostomies or colostomies are

performed, when bowel continuity/anastomosis is not possible due to location of the lesion or other factors such as peritoneal faecal contamination and in management of gastrointestinal fistulae and inflammatory bowel disease³⁰⁶.

Stoma as a separate distinct entity is in itself associated with complications. Although a fairly straightforward procedure to perform, if done poorly, can result in a variety of complications for the patient. Multiple studies have reported stoma related complications to range between 21-70% of all stoma created and include peristomal leakage, ischaemia/necrosis, prolapse, stenosis, herniation and retraction^{307–309}. Even when done well, it can cause other issues such as high output, electrolyte loss and consequent dehydration^{310–312}. Furthermore surgery for reversal of stoma can also result in complications, associated with re-anastomosis of the bowel and incisional herniation³¹³, amongst others. Prevention, detection and management of its complications are therefore important and entail close monitoring, patient education and support, both in the perioperative period and after discharge, with specialist stoma therapist playing an important role³¹⁴. One specific entity explored in the surgical community is the usage of tube ileostomy instead of the established loop ileostomy. This thesis will systematically review this technique in Chapter 8 of this thesis.

1.5.4 Iatrogenic injury

Intra-abdominal iatrogenic injuries in colorectal surgery can occur to the solid organs, hollow viscus and to other parts of the bowel. With the advent and

increased use of laparoscopic techniques, iatrogenic injury profile and detection thereof has also changed slightly. Laparoscopy as a skillset, has been developed by surgeons over the last two to three decades and there are now established laparoscopy training programmes throughout the world and is a baseline requirement in the armamentarium of a newly qualified colorectal surgeon.

The following section will discuss the more common iatrogenic injuries, including the changing impact of laparoscopy as well.

1.5.4.1 Splenic injury

Iatrogenic splenic injury for example, can occur in 1-8% of left hemicolectomies and it has been reported that 40% of all splenectomies performed are due to iatrogenic injuries resulting in elective procedures such as colectomies, open anti-reflux procedures, left nephrectomy and proximal abdominal aortic surgery³¹⁵. The issue of splenic flexure mobilisation, in open and laparoscopic colorectal surgery, is controversial in the literature. Some operators have argued for routine mobilisation in rectal resectional cases, citing anastomotic vascularity as being the paramount reason and others have advocated selective splenic flexure mobilisation^{316,317}. The controversial topic has a spillover effect from the era of open surgery to laparoscopic surgery and as techniques are being developed and formalised in the laparoscopic setting, the need for routine splenic mobilisation is still being questioned. Chand and coworkers³¹⁸ opined that splenic flexure mobilisation should be selectively used

in laparoscopic anterior resection whereas Ludwig and colleagues³¹⁸ disagree and felt that it should be a routine part of the operation. The common discussion point is the anastomotic tension and by extension the vascularity of the perianastomotic tissue.

1.5.4.2 Ureteric Injury

Intra-abdominal surgical procedures account for 80% ureteric injuries compared to external trauma³¹⁹. Amongst iatrogenic intraoperative causes, more than half have been estimated to occur during gynaecological procedures. However up to a substantial 9% of all ureteric injuries occur during colorectal resectional procedures^{320–322}. Ureteric injury can be a very serious complication of surgery in the lower abdomen or pelvis³¹⁹ with iatrogenic damage occurring in elective or emergency operations, in both benign and malignant pathology.

The ureters are more commonly damaged at certain points in their course from the renal pelvis to the urinary bladder. In colorectal surgery specifically, ureteric injuries most often occur in reoperations, low anterior resections, abdominoperineal resections or Hartmann's reversals^{323,324}. The left ureter is more commonly damaged than the right as it may be elevated with the sigmoid mesentery and mistaken for a mesenteric vessel or the ascending inferior mesenteric vein³¹⁹ which are routinely divided as part of the resection. Both ureters are also injured more frequently during ligation of mesenteric vessels, dissection at the level of the sacral promontory where they cross the iliac arteries, division of the lateral rectal ligaments and the most cephalad portion of

perineal dissection^{319,322,323,325}. Palaniappa and coworkers also reported a significant increase (0.66% vs. 0.15%, $p=0.007$) in the incidence of ureteric injuries with laparoscopic colectomies compared to open procedures³²⁶.

50% to 70% of ureteric injuries are often not recognised intraoperatively^{327,328}. Minor injuries may heal without any intervention. However more substantial injuries to the ureter may result in the patient having fever, flank pain, ureteral fistulation, urinomas or hydronephrosis. The primary injury may often necessitate a further operation. As such, to avoid delay in diagnosis of iatrogenic ureteric injuries and their consequent complications, it is pertinent that the ureters are evaluated intraoperatively for any injuries and more importantly identified/localised and kept safe from inadvertent injury. To assist surgeons in identifying the ureters and more importantly improve outcomes for the patient, various manoeuvres were employed, such as insertion of metallic J-stents via cystoscopy prior to laparotomy³²¹ and intraoperative gamma probe localisation³²⁹. In open surgery, the surgeon has tactile feedback and a three dimensional views of the peritoneum and this guided him or her to an extent in identifying and preserving the ureters. In laparoscopic colectomies, these are not available, resulting in difficulty in identification of the ureters and consequently a higher complication rate³²⁶. To overcome the loss of tactile feedback and three dimensional vision, a further development in stent technology, lighted stents, as described by various authors^{330–333}, have been utilised too. In a recent review of prophylactic stent placement in colorectal surgery³²⁵, the authors opined that stent prophylaxis in laparoscopic surgery

may reduce the need for conversion to laparotomy because of failure to identify the ureter, which according to other reports account for up to 15.4% of conversions in their individual cohort of patients^{334,335}. Although ureteric stents reduce iatrogenic injury and possibly reduce need for conversions, they have their own risk profile, including transient haematuria, oliguria, anuria and infection and more severe complications like hydronephrosis, perforation, loss of kidney, artificial renal support and even death from uraemia^{322,336}.

1.5.4.3 Injuries to bowel & other viscus

Injury to bowel and other intra-abdominal organs may occur during both laparotomy and laparoscopy. Increasing use of laparoscopy exposes the patient to a different risk profile in terms of iatrogenic intra-abdominal injury. Laparotomy inherently allows easier and greater access and tactile feedback to the surgeon during surgery, compared to laparoscopy. It may also allow easier recognition and management of an intraoperative complication and in fact may in the first place, prevent it if the surgeon anticipates a complex operation and plans a conventional laparotomy rather than a laparoscopy due to preoperative factors such as multiple previous surgeries. Laparoscopy on the other hand, may mask intra-abdominal injuries, such as bowel injury. Injuries may be due to blunt trauma from trocars and laparoscopic instruments and thermal injuries that can both result in delayed bowel leaks³³⁷. Other laparoscopy-specific injuries include port-site herniation of bowel that has been previously discussed. Other organs, including the liver can be iatrogenically injured during trocar insertion. Trocar related injuries, especially when vascular in nature,

could have catastrophic consequences. Bowel injuries can occur in a similar fashion during trocar insertion and when excessive adhesiolysis is performed. It may also result from inappropriate use of grasping forceps, bowel retraction, insertion and reinsertion of instruments or sharp dissection. Such injury may be unrecognised or occur outside the operating field, leading to late presentation and delayed diagnosis.

1.5.4.4 Vascular injury

Intra-abdominal injuries include vascular injuries and postoperative bleeding. This is especially true for laparoscopic or minimally invasive surgery, where, initial injury to vessel walls may not be diagnosed and subsequently, postoperative bleeding occurs. Reported incidences of vascular injuries in laparoscopy range from 0.04% to 0.5% of all cases³³⁸ and some reports suggest that this may actually be underreported³³⁹. A large proportion of vascular injury and bleeding occurs during port insertion in laparoscopy. The epigastric vessels are at risk of injury and more importantly this injury very often only becomes apparent postoperatively due to the relative tamponade of the vessel by the trocar itself and to a certain extent by the high intraperitoneal pressure during surgery. The distal aorta, vena cava and their branches are at risk during peritoneal access manoeuvres during laparoscopy. Of note, vascular injuries have been reported in all methods of laparoscopic access methods, including the open Hasson technique and Veress needle technique and in both primary entry and reinsertion of trocars during the operation³⁴⁰. The timing of diagnosis is again an important aspect of managing such bleeding.

Very often, the signs of vascular injury may be clear as the patient decompensates but on other occasions an initial injury to a vessel may go unnoticed and subsequently present as a delayed bleed. Significant bleeding may also arise from injury to the superficial epigastric, superficial circumflex, inferior epigastric or deep circumflex vessels from insertion of secondary trocars³⁴¹.

The occurrence of any vascular injury intra-abdominally can be judiciously looked out for by stratifying the risk of such an injury occurring by analysing the patient's preoperative risks, such as previous multiple surgery, abnormal bleeding diatheses, medications such as warfarin, clopidogrel and steroid use. Intraoperatively, standard precautions should be taken to prevent injuries and the surgeon must also actively and constantly examine the abdominal contents and specifically in the case of laparoscopy, care must be taken to be fully aware of the position of the instruments' tips when they are in the abdomen, with constant visualisation on the laparoscopic camera.

Iatrogenic injuries in colorectal surgery, although can be minimised with good surgical technique and practice, may still occur, and awareness of possible complications and prompt recognition, detection and management are essential in good colorectal surgical practice.

1.6 Non-infective medical complications

Surgical patients often have comorbid conditions as described previously and can also suffer medical complications after surgical intervention. These complications must be sought after when there is deviation from normal, expected postoperative recovery. Riccardi and colleagues for instance have noted that patients who suffer major postoperative complications such as cardiac arrest, neurological strokes, myocardial infarction and renal failure are at the highest risk of death, following colorectal surgery³⁴². The same principles of recognition, detection and management in specific surgery-related complications should also apply in this regard. Some important medical sequelae are described in the following sections, which may occur in the postoperative period and impact the colorectal surgical patient.

1.6.1 Cardiac complications

Postoperative myocardial infarction is a rare but severe complication in colorectal surgery. Moghadamyeghaneh and colleagues reported a 1.5% incidence amongst more than 2.5 million patients undergoing colorectal resections in an American national database study over a 9-year period, but noted that it was associated with 28.5% of in-hospital mortality. The authors also noted that patients who suffered a myocardial infarction had a six fold increased risk of death compared to those who did not. Presence of congestive cardiac failure, valvular heart disease, renal failure or impairment, respiratory disease, preoperative anaemia and malignant or emergent indication for

surgery were also noted in the study to be significant risk factors³⁴³. Other cardiac problems such as arrhythmias and myocardial ischaemia were also reported after colorectal surgery, albeit transient in most occasions³⁴⁴.

1.6.2 Venous thromboembolic complications

Deep vein thrombosis and pulmonary embolisms are possible complications after any surgical intervention. They are known to be significant in lower limb orthopaedic procedures and it is routine practice in the trauma and orthopaedic specialty to actively prevent venous thrombotic events with postoperative prophylactic anticoagulation up to 30 days³⁴⁵. Colorectal surgery is also considered high-risk and peri-operative venous thromboembolic prophylaxis is recommended³⁴⁶. However, the duration of treatment is not standardised and several authors have reported on postoperative thromboembolic events. For instance, El-Dhuwaib and colleagues³⁴⁷, in their recent study utilising Hospital Episode Statistics data from England, noted that there was a 2.3% incidence of venous thrombotic events in colorectal patients and that they were more common in those who underwent elective surgery for malignancy, or emergency surgery for inflammatory bowel disease. They also noted that these patients had longer lengths of stay and that the thrombotic events occurred more commonly after discharge, than in the in-hospital postoperative period. Currently, colorectal patients receive postoperative venous thromboembolism prophylaxis in the perioperative period within hospital and are not routine discharged with any. There are several preoperative patient and disease factors, intraoperative factors such as length of procedure and postoperative

issues such as reduced ambulation that can impact its occurrence. Therefore venous thromboembolism risk is an area that may benefit from further research, especially with regards to length of postoperative prophylaxis³⁴⁷.

1.6.3 Urinary tract complications

Urinary tract infections and iatrogenic injury to the urinary tract, especially the ureters, have been discussed. However, urinary retention and subsequent renal impairment and failure can occur in the postoperative period. Urinary retention is a significant but potentially avoidable complication in colorectal surgery. In elective colorectal surgery, catheterisation is performed prior to surgery in the operating theatre and the catheter is usually removed within the first two to three days postoperatively, especially so in the context of enhanced recovery programmes^{11,310,348}. However, certain subgroups of patients are at increased risk of urinary retention, with surgery-related risk factors including prolonged operative time, type of anaesthesia and preoperative patient factors including age and presence of benign prostatic hyperplasia amongst others. Reduced postoperative ambulation is again an important postoperative issue, which may increase the risk of urinary retention. Retention is often easily identified due to patient discomfort and abdominal distension. However, in postoperative patients, clinicians should be alert to this complication occurring as it can result in proximal obstruction of the renal tract and cause renal impairment. Retention and renal impairment and failure increase the length of stay postoperatively and are also associated with patient readmissions. Renal failure can also result in patients with high stoma output, which has been previously discussed.

1.7 Impact of complications on cancer outcomes

Several studies have interrogated the impact of anastomotic leakage on cancer recurrence, DFS and OS. For instance, Mirnezami and colleagues, in their meta-analysis of 21 studies comprising 21902 patients, have noted a negative prognostic impact on local recurrence after rectal cancer resection and a statistically significant negative association between colorectal anastomotic leakage and cancer specific survival³⁴⁹. Law and colleagues reported postoperative complications in cancer resections to be independently associated with lower overall survival⁷⁴ (Hazard Ratio: 1.26; 95%CI: 1.03-1.52, $p=0.023$) and an increased recurrence rate (Hazard Ratio: 1.26; 95%CI: 1.01-1.57, $p=0.04$). To further assess this in our local institution, the first study in this thesis will assess the impact of anastomotic leakage on overall survival and disease free survival in our local institution.

Complications also impact patients with regards to adjuvant treatment and subsequently cancer survival as well. Previous studies evaluating timing of adjuvant chemotherapy, including a 2010 systematic review and two meta-analyses, noted chemotherapy initiation within six to eight weeks conferred a survival benefit, and also reported reduced survival the longer the delay to adjuvant chemotherapy initiation^{350,351}. Furthermore, Merkow and colleagues noted that postoperative complications resulted in 16.8% of their study cohort not receiving planned adjuvant chemotherapy and also reported a substantial increase in the time to chemotherapy in those who suffered an anastomotic leakage³⁵². However, some studies did not observe any differences in survival

between early and late initiation of adjuvant chemotherapy. To interrogate these further, the second and third studies in section I of this thesis will be assessing the impact of timing of adjuvant chemotherapy, and the interplay of anastomotic leakage and timing of chemotherapy initiation on DFS and OS.

1.8 Summary overview of complications

The role of a surgeon in colorectal surgery continues after the actual operation. The monitoring of patients in the postoperative period involves ensuring satisfactory progress and also looking out for complications arising directly due to the surgical intervention and also associated medical complications. The tendency to prioritise ‘surgical’ type complications over ‘medical’ complications can sometimes result in delay or non-detection of evolving complications. Some complications such as venous thromboembolisms may occur late in the postoperative recovery too. Also importantly, complications can occur after discharge from hospital as well. The first indication of a complication will be derangement of the patient’s physiological markers, such as heart rate and temperature. To this end, patient self-measurement of physiological markers, to detect complications early will also be investigated in this thesis. Chapter 9 will assess this utility further.

Regardless of the type, postoperative complications, both surgery related or otherwise, have a significant impact on postoperative morbidity, mortality and subsequent adjuvant treatment as well. As such the management of the colorectal surgical patient needs to be global in nature, to ensure that

deviations from normal physiological parameters, deranged biochemical investigations and overall recovery progression are taken into account, to actively look out for any type of complication which may arise.

This introduction has described postoperative complications in colorectal surgery with specific emphasis on anastomotic complications such as leakage, which are the most important complications colorectal surgeons are concerned about. It serves as a basis and background for the following studies and reviews undertaken in this thesis.

1.9 Thesis structure

1.9.1 Thesis hypotheses

The thesis sets out to test the following hypotheses:

1. Complications of colorectal surgery impact patient survival (overall and disease-free), to varying extents and also impact adjunct treatment delivery such as chemotherapy, thereby impacting its efficacy.
2. Intraoperative anastomotic integrity testing techniques improve patient outcome.
3. Novel techniques, such as tube ileostomy to 'protect' the anastomosis and variant anastomotic configurations such as the ileo-distal sigmoid anastomosis in polyposis patients, reduce anastomotic complication rates and subsequently improve patient outcome.
4. Postoperative physiological monitoring, performed independently by the patient, is similar in accuracy to nurse-performed monitoring in the hospital setting. This will allow extrapolation of the final study of this thesis to assess independent patient monitoring in the home-setting, post-discharge from hospital.

1.9.2 Thesis aims

1. Describe the types of complications sustained by the patient in colorectal surgery in general and describe anastomosis-related ones in detail.
2. Assess the impacts of anastomotic leakage, its sequelae and subsequent treatment options, on patient survival and disease-free survival in colorectal cancer.
3. Investigate the impact of anastomotic leakage and its subsequent treatment on timing of adjuvant chemotherapy receipt and overall survival.
4. Investigate intraoperative assessment methods and novel, or alternative, surgical techniques to detect and prevent potential anastomotic complications.
5. Investigate remote monitoring utility and processes in the postoperative colorectal surgical patient.

1.9.3 Thesis outline

This thesis is broadly divided into three sections. The first section comprising three chapters, concentrates on anastomotic leakage and its associated treatment options (conservative, radiological drainage and reoperation) and their subsequent implications on the patient outcome and adjuvant treatment. The first chapter investigates the impact of anastomotic leakage on cancer recurrence and overall survival in single institution, our colorectal surgical unit in St Mark's Hospital. The second and third chapters, which utilise the English health administrative database [Hospital Episode Statistics (HES)] over a fifteen-year period, assess how overall survival is impacted by adjuvant chemotherapy timing after surgery and by an added complication of reoperation, in elective colorectal cancer patients.

The second section comprising four chapters, concentrates on the intraoperative aspects of anastomotic complication prevention and detection, and novel intraoperative techniques that have been utilised in unique situations in colorectal surgery, to reduce the risk and/or mitigate the sequelae of anastomotic complications. This section includes a systematic literature review of available intraoperative techniques in colorectal surgical practice that have been utilised to assess colorectal anastomotic integrity. It also includes a clinical study that assesses a specific technique to assess peri-anastomotic perfusion intraoperatively, namely near-infrared angiography with Indocyanine Green dye autofluorescence. The latter two chapters in this section describe novel techniques utilised in colorectal surgery. The first lays out the technical

aspects of a novel utility of ileo-distal sigmoid anastomosis construction in a short series of hereditary polyposis patients who underwent prophylactic colectomy in our institution, and the second systematically reviews studies in the literature which describe a unique technique of faecal diversion, tube ileostomy, in elective planned colorectal surgical resection.

The last section comprises a further clinical study that examines the utility of patient-led physiological monitoring, using handheld computer devices with Bluetooth enabled adjuncts such as pulse oximeters and sphygmomanometers, and digital thermometers, in the immediate postoperative period. Such devices have been utilised in chronic conditions such as asthma and diabetes in the home setting on a long-term basis. However, its utility has not been thoroughly examined in the immediate postoperative setting. Given that complications post colorectal surgery may occur soon after discharge, this is an area that needs further evaluation and this study targets this lacuna in colorectal surgical practice.

In brief, this thesis sets out to describe and investigate specific facets of colorectal surgical complications, that is, their impact, prompt detection, prevention and briefly on its management as well. It also specifically concentrates on colorectal anastomosis complications that form a substantial proportion of complications in this subspecialty. The above form a continuum of management strategy that often overlap each other. In fact, manoeuvres undertaken to tackle complications, can be instituted in the preoperative period

to optimise the patient, in the intraoperative period to detect and therefore prevent postoperative complications, and in the postoperative period, where again, complications can be detected at the earliest possible occasion to prevent subsequent sequelae.

1.9.4 Methodologies

The thesis explores the various aspects laid out above using specific research methodologies and statistical techniques, using both local single institution patient cohorts and national level administrative datasets. Each study in this thesis elaborates on the specific methodology employed and details patient groups and characteristics thereof in each of the chapters. Methodologies employed in this thesis include, single institution retrospective analyses, national level retrospective administrative data analyses, three case series of patients within our institution in pilot level studies, a thorough systematic review of the literature (assessment of colorectal anastomotic integrity) and a further systematic review and meta-analysis of the literature (tube ileostomy).

Section I: Colorectal anastomotic complications & subsequent implications

This section investigates the impact of colorectal anastomotic complications on the patient, in terms of cancer recurrence and survival. It specifically looks at how treatment options available to the surgeon, be it conservative management with oral or intravenous antibiotics, radiological image-guided drainage or a reoperation, influence patient outcome. This is done utilizing a single hospital database of over 1000 patients spanning a nine-year period. Subsequently, a national level administrative database is interrogated to investigate the impact of adjuvant chemotherapy timing in elective colorectal resections, on overall patient survival. The third study specifically investigates the combined impact of both reoperation and timing of adjuvant chemotherapy receipt on overall patient survival, utilizing the same national level database.

In brief, the three chapters in this first section of the thesis study the impact of different management strategies of colorectal anastomotic complications, the impact of adjuvant chemotherapy timing and finally the combined impact of reoperation and adjuvant chemotherapy delay, on patient outcomes such as cancer recurrence and overall survival.

Chapter 2

The impact of anastomotic leak and its treatment, on cancer recurrence & survival following elective colorectal cancer resection

2.1 Study abstract

Aims: Anastomotic leakage is a serious complication in restorative colorectal surgery. Anastomotic leakage and its subsequent management may have long-term impact on survival. This study aims to assess the impact of colorectal anastomotic leak on overall (OS) and disease-free (DFS) survival.

Methods: A prospective database of 1048 patients undergoing restorative colorectal cancer resections at St Mark's hospital between October 2004 and October 2013 was examined.

Results: The overall leak rate was 99/1048 (9.4%). 43 ALs were managed conservatively with antibiotics or radiological drainage and 56 with reoperations. OS was significantly reduced in the AL group treated with a reoperation [HR: 2.74 (95% CI 1.67 – 4.52, $p < 0.001$]. Anastomotic leak was not significantly associated with worse DFS [conservatively managed AL's vs. no AL HR: 2.07 (95% CI 1.05 – 4.10); Reoperated AL's vs. no AL - HR: 1.56 (95% CI 0.81-2.99), overall p value =0.058].

Conclusion: Patients who suffer anastomotic leaks requiring reoperations have worse overall survival compared to patients who do not leak but there were no clearly significant differences in disease-free survival between patients who leaked and those who did not.

2.2 Introduction

Anastomotic leak (AL) is a serious complication occurring in a minority of patients following restorative colorectal cancer surgery. Leakage predisposes patients to increased risk of reintervention and at times, death within the perioperative period. In addition, some studies have identified a potential adverse impact of AL on long-term survival following colorectal cancer surgery.

A recent meta-analysis of 21,902 patients reported that AL had a significant negative prognostic effect on local recurrence rates in restorative rectal resections, and was associated with a significant reduction in long term survival³⁴⁹. Moreover, other investigators have observed a negative impact on both 'disease-free' and 'overall' survival in patients who suffered postoperative surgical complications when compared with those who did not³⁵³. Despite the above studies it remains unknown whether postoperative abdominal sepsis, or reoperation for its treatment, is definitively associated with poor oncological outcome.

Therefore the aim of this study is to investigate the impact of anastomotic leaks and their treatment on long-term 'overall' and 'disease-free survival' in patients undergoing restorative colorectal cancer surgery at our institution, St Mark's Hospital.

2.3 Methods

2.3.1 Variables & definitions

A prospectively collected institutional colorectal cancer database comprising 1475 patients who underwent surgical resections between October 2004 and October 2013 was analysed.

Patient demographic data including age, sex, Charlson comorbidity score⁹⁶ and disease specific data such as tumour site and tumour staging (Union for International Cancer Control Classification – UICC)³⁵⁴ were analysed. Operative access, procedure performed, formation of diverting stoma, administration of neoadjuvant chemoradiotherapy in all patients, and delivery of adjuvant chemotherapy specifically in stage III cancers, were also included in the analyses.

Occurrences of anastomotic leakage was recorded on the database and were retrospectively classified into three patient categories ('no leak', 'leak treated conservatively – antibiotics or radiological drainage', and 'leak managed with a reoperation') as per the validated proposal by the International Study Group of Rectal Cancer²⁵⁴.

Our institution follows a standardized surveillance protocol and follows up patients for 5 years with biannual clinical assessment intervals for the first 3 years, followed by annual surveillance at years 4 and 5. Computed tomography

is performed annually and annual colonoscopy or computed tomography-colonography is used for luminal surveillance. Cancer recurrence and mortality data were derived from both the local patient information computer system and through linkage to the Office of National Statistics³⁵⁵.

2.3.2 Database inclusions and variable categories

Age was categorised into three cohorts: 18-65 years, 66-85 years and greater than 85 years. Patients' Charlson Comorbidity Index scores were calculated and categorised into 0-2, and greater than 2 (excluding presence of current cancer). Tumour site was classified as: right colon, left colon, and rectum (<15 centimetres from the anal verge). UICC staging was categorised as stages I to IV. Anastomoses were grouped into ileo-colonic (right sided), colo-colonic (left sided), colo-rectal and others (colo-anal anastomosis, ileal pouch-anal anastomosis and ileorectal anastomosis).

For UICC stage III patients who received chemotherapy, initiation dates were categorised into within and beyond eight weeks of index surgery. Primary outcome measures comprised overall survival (OS) and disease-free survival (DFS). A patient was considered disease free if there was no evidence of recurrence clinically, endoluminally or radiologically during follow-up.

2.3.3 Statistical methodology

Statistical analyses were carried out using SPSS Version 20.0. All patients' survival data were checked as of 15th December 2013 using ONS-linked data that confirmed dates of death if a patient has died in OS analysis. The date of last documented clinical contact with patient was used as their censor date in DFS analysis. Variables with a significance of $p < 0.1$ on univariate analyses were entered into the multivariate model. The anastomotic leak variable was entered regardless of univariate significance as it was the main exposure variable. Survival functions were presented using Kaplan-Meier survival curves. Multivariate Cox proportional models were used to interrogate disease free survival and overall survival. A two-tailed p-value less than 0.05 was used to indicate statistical significance.

2.4 Results

2.4.1 Demographics

Of the 1475 patients identified as having undergone surgery, 1048 patients underwent elective restorative colorectal resections. The remaining 427 patients were excluded because their operations were done under emergency settings or an anastomosis was not constructed. There were 590(56.3%) males and the median age was 69 years (range 24-95). Detailed variables are described in

Table 2.1.

The overall AL rate was 9.4%(n=99), 43(4.1%) of which were managed conservatively (with antibiotic therapy or radiological drainage) and 56(5.3%) with reoperations (53 laparotomies and three examinations under anaesthesia and drainage of collection per anus).

The median patient follow-up was 40 months (interquartile range (IQR) 21-61 months). 232 patients (22.1% of 1048 patients) in this cohort were recorded as deceased and 125 patients [13.3% of 937 non-stage IV (metastatic) patients] suffered a recurrence.

Table 2.1 Patient and perioperative variables

Variable	Total	No leak	Leak + conservative management	Leak + reoperation	P Value
Number of patients	1048	949 (90.6)	43 (4.1)	56 (5.3)	
Age					0.508
18-65	420	374 (89.0)	22 (5.2)	24 (5.7)	
66-85	560	512 (91.4)	20 (3.6)	28 (5.0)	
>85	68	63 (92.6)	1 (1.5)	4 (5.9)	
Gender					<0.001
Male	590	512 (86.8)	35 (5.9)	43 (7.3)	
Female	458	437 (95.4)	8 (1.7)	13 (2.8)	
Charlson Score					0.660
0-2	390	349 (89.5)	18 (4.6)	23 (5.9)	
>2	658	600 (91.2)	25 (3.8)	33 (5.0)	
Tumour Site					<0.001
Right colon	377	365 (96.8)	5 (1.3)	7 (1.9)	
Left colon	305	276 (90.5)	6 (2.0)	23 (7.5)	
Rectum	366	308 (84.2)	32 (8.7)	26 (7.1)	
Stage					0.479
I	257	237 (92.2)	11 (4.3)	9 (3.5)	
II	344	309 (89.8)	11 (3.2)	24 (7.0)	
III	355	319 (89.9)	16 (4.5)	20 (5.6)	
IV	92	84 (91.3)	5 (5.4)	3 (3.3)	
Surgical Approach					0.792
Open	340	309 (90.9)	11 (3.2)	20 (5.9)	
Minimally Invasive	651	587 (90.2)	30 (4.6)	34 (5.2)	
Converted	57	53 (93.0)	2 (3.5)	2 (3.5)	
Anastomosis					<0.001
Ileo-colonic (right)	360	350 (97.2)	4 (1.1)	6 (1.7)	
Colo-colonic (left)	245	227 (92.7)	5 (2.0)	13 (5.3)	
Colo-rectal	371	314 (84.6)	29 (7.8)	28 (7.5)	
CAA, IPAA, IRA	72	58 (80.6)	5 (6.9)	9 (12.5)	
Diversion Stoma					<0.001
Yes	286	232 (81.1)	31 (10.8)	23 (8.0)	
No	762	717 (94.1)	12 (1.6)	33 (4.3)	
Neoadj Chemo					<0.001
Yes	54	37 (68.5)	12 (22.2)	5 (9.3)	
No	994	912 (91.8)	31 (3.1)	51 (5.1)	

2.4.2 Overall Survival

Overall survival was 40 [Interquartile range (IQR)] 21-61, 36 (IQR 25-53) and 37 (IQR 8-54) months respectively for patients that did not leak, leaked but were managed conservatively and leaked requiring reoperation. Figure 2.1 illustrates the poorer OS amongst patients who suffer leaks requiring re-operation.

Table 2.2 describes Cox regression analyses investigating the impact of leak on OS. A significant reduction in overall survival was identified in patients requiring a reoperation to treat anastomotic leakage [HR: 2.74 (95% CI 1.66-4.52), $p=0.001$], compared to patients who did not leak. However, patients who were conservatively managed did not significantly differ in OS when compared to those who did not leak. Together with AL and type of management ($p=0.001$), older age ($p<0.001$), Charlson score ($p=0.030$), higher tumour stage ($p<0.001$) and open surgical approach (laparotomy) ($p=0.001$) were indicators of poorer OS on multivariate regression analysis.

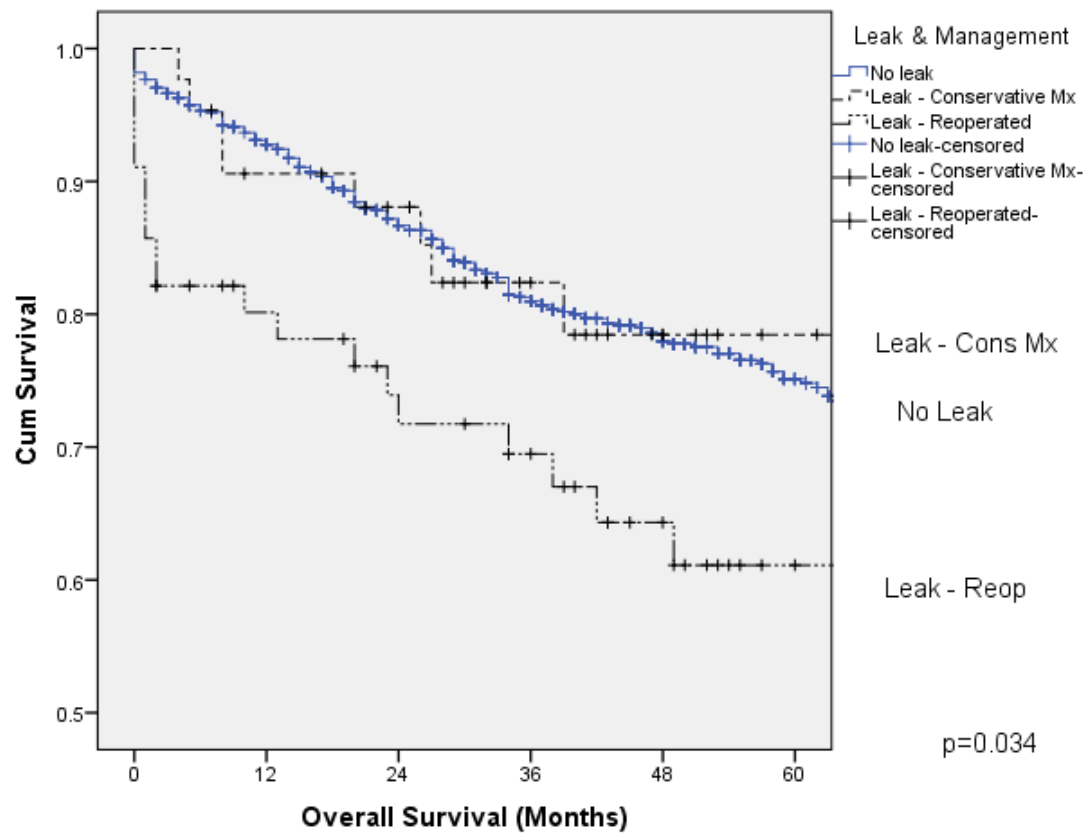


Figure 2.1 KM Curve - Overall survival

Table 2.2 Overall survival - Univariate & multivariate Cox proportional hazard analysis

Variable	Univariate HR	95% CI	P value	Multivariate HR	95% CI	P value
Leak category			0.039			<0.001
No leak	1			1		
Leak – cons	0.90	0.44-1.82	0.759	0.92	0.44-1.19	
Leak - Reop	1.83	1.14-2.92	0.012	2.74	1.66-4.52	
Age			<0.001			<0.001
18-65	1			1		
66-85	1.85	1.36-2.51		1.36	0.93-1.99	
>85	5.48	3.64-8.23		4.04	2.52-6.48	
Gender			0.756			
Male	1					
Female	0.96	0.74-1.25				
Charl Score			<0.001			0.030
0-2	1			1		
>2	2.30	1.63-3.23		1.61	1.05-2.46	
Tumour Site			0.008			0.646
Right colon	1			1		
Left colon	0.59	0.42-0.59		0.46	0.05-4.25	
Rectum	0.82	0.61-1.10		0.64	0.75-5.55	
Stage			<0.001			<0.001
I	1			1		
II	1.48	0.94-2.32		1.16	0.73-1.84	
III	2.46	1.62-3.76		2.06	1.34-3.17	
IV	7.30	4.59-11.62		6.14	3.83-9.85	
S Approach			<0.001			0.001
Open	1			1		
Min Invasive	0.55	0.42-0.73		0.60	0.45-0.79	
Converted	1.07	0.64-1.78		1.05	0.63-1.76	
Anastomosis			0.001			0.104
Ileocolic (r)	1			1		
Colo-colic (l)	0.61	0.43-0.87		1.41	0.150-13.51	
Colo-rectal	0.84	0.63-1.12		1.51	0.17-13.12	
CAA,IPAA,IRA	0.17	0.06-0.47		0.39	0.05-2.85	
Diversion Stoma			0.346			
Yes	1					
No	1.16	0.85-1.56				
Neoadj Chemo			0.864			
Yes	1					
No	1.05	0.59-1.88				

2.4.3 Disease free survival

There were 937 patients with non-metastatic disease at the time of elective surgery and who survived beyond 30 days postoperatively. Amongst these, 86(9.2%) patients suffered anastomotic leaks with 48 of them requiring reoperations. DFS was 24(IQR 10-44), 22(IQR 8-46) and 22 (IQR 7-50) months respectively amongst patients that did not leak, leaked but were managed conservatively and leaked requiring reoperation. (Figure 2.2, Kaplan Meier, log-rank p-value 0.060).

Table 2.3 describes Cox regression analyses investigating the impact of leak on DFS. On multivariate analyses, presence of leak and conservative management indicated a tendency towards worse DFS when compared with those that did not leak [HR 2.07, (95% CI 1.05-4.10), $p=0.058$]. However reoperation did not demonstrate a statistically significant difference in DFS (HR 1.56, 95% CI 0.81-2.99, $p=0.058$).

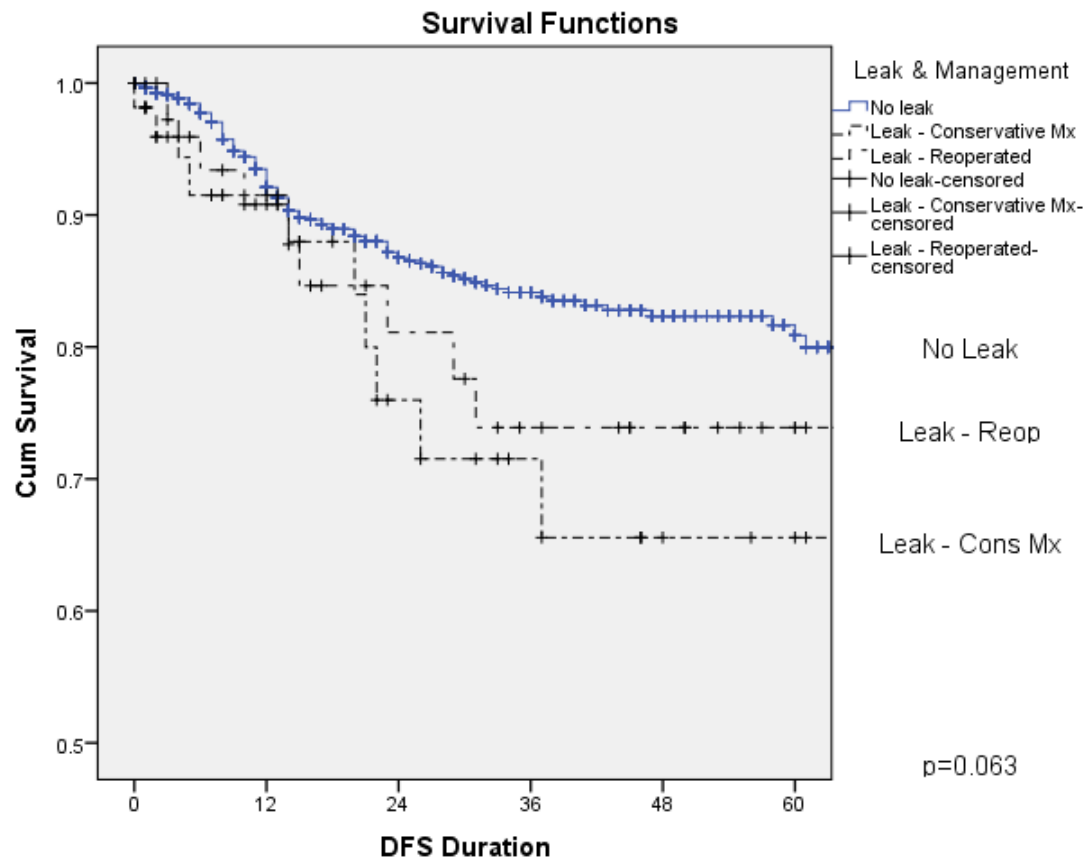


Figure 2.2 KM Curve - Disease-free survival (NB: stage IV excluded)

Table 2.3 Disease-free survival - Univariate & multivariate Cox proportional hazard analysis (Excluding 30-day mortality & stage IV)

Variable	Univariate HR	95% CI	P value	Multivariate HR	95% CI	P value
Leak category			0.066			0.058
No leak	1			1		
Leak – cons	1.91	0.97-3.78	0.062	2.07	1.05-4.10	
Leak - Reop	1.67	0.87-3.12	0.121	1.56	0.81-2.99	
Age			0.032			0.005
18-65	1			1		
66-85	0.74	0.51-1.07		0.74	0.51-1.07	
>85	1.66	0.87-3.17		2.15	1.12-4.14	
Gender			0.519			
Male	1					
Female	1.12	0.79-1.60				
Charl Score			0.688			
0-2	1					
>2	0.93	0.64-1.3				
Tumour Site			0.979			
Right colon	1					
Left colon	0.96	0.62-1.49				
Rectum	1.01	0.66-1.52				
Stage			<0.001			<0.001
I	1			1		
II	1.59	0.76-3.35		1.52	0.72-3.19	
III	6.66	3.47-12.78		6.67	3.47-12.82	
S Approach			0.321			
Open	1					
Min Invasive	0.83	0.57-1.20				
Converted	1.33	0.65-2.70				
Anastomosis			0.723			
Ileocolic (r)	1					
Colo-colic (l)	1.04	0.66-1.64				
Colo-rectal	0.95	0.63-1.46				
CAA,IPAA,IRA	0.65	0.29-1.44				
Diversion Stoma			0.686			
Yes	1					
No	1.09	0.73-1.62				
Neoadj Chemo			0.251			
Yes	1					
No	0.66	0.32-1.35				

There were a total of 16 patients with locoregional recurrences and 109 with distant recurrences. 7 of the 109 had both local and distant recurrences. Recurrence rates and median times to recurrence in each leak category are illustrated in Table 2.4. 22.1%(19/86) of patients who leaked developed a recurrence (3 local and 16 distant), compared to 12.5%(106/851) of patients (13 local and 93 distant) who did not leak.

Table 2.4 Local & distant recurrences in non-stage IV patients surviving beyond POD 30

	No Leak (%)	Leak (%) (Cons+Reop)	Total	Median time to Recurrence (m)	Inter-quartile range (m)
No Recurrence	745 (91.7)	67 (8.3) (29+38)	812	-	-
Local Recurrence	13 (81.2)	3 (18.8) (2+1)	16	12	9-25
Distant +/- local Recurrence	93 (85.3)	16 (14.7) (7+9)	109	13	7.5 -23
Total	851 (90.8)	86 (9.2) (38+48)	937	-	-
Recurrence in leak category (%)	106/851 (12.4%)	19/86 (22.1%)	125/937 (13.3%)		
% Stage I & II	62.9 (535/851)	58.1 (50/86)	62.4 (585/937)		

2.5 Discussion

The principal finding of this study is that patients who develop an anastomotic leak following colorectal cancer resection and have a reoperation to treat it, have worse overall survival than patients who either do not leak or suffer a leak that is managed conservatively. There were more recurrences in the combined leak groups compared to the non-leak group but there were no statistical differences in the disease-free survival between the each of the leak groups (Log-rank $p=0.060$).

The results of the present study are in keeping with a recent report evaluating survival after returns-to-theatre ³⁵³. The authors observed significantly reduced 5-year overall survival (55.3% vs. 66.4%, $p=0.02$) and disease-free survival reaching statistical significance (50.8% vs. 60.8%, $p=0.06$) in reoperated patients. However, an Australian study classifying leaks in a similar fashion to our study, reported that leaks requiring reoperation led to both reduced overall and disease free survival ¹³⁷. Conversely, Mrak and colleagues reported in their retrospective cohort analysis of curative rectal cancer surgery outcome that severity of postoperative complications and type of treatment for a complication, did not demonstrate any significant effect on overall or disease free survival ³⁵⁶.

The above reports together with several others ^{357–359} investigated the negative correlation of anastomotic leakage with survival. It is clear that anastomotic leak and consequent abdominal sepsis are strongly associated with poorer survival

outcome in the perioperative period. It is however uncertain whether abdominal sepsis, or the requirement for reintervention, is associated with poorer oncological outcome in terms of greater predisposition to disease recurrence. Khuri and coworkers demonstrated that postoperative complications that occurred within the first thirty days post-surgery had a significant negative prognostic impact on long-term survival in patients. This was observed when colectomies and seven other high volume procedures in the United States, were analysed using population wide prospectively collected data ³⁶⁰. Such perioperative events may be exacerbated by an anastomotic leak necessitating reoperation. In the current study, KM analysis demonstrated that overall survival is skewed by events occurring in the perioperative period. Nonetheless, cancer recurrence did occur more frequently in patients who leaked and this could not be explained by disease stage at presentation.

The findings of the current study are limited by a number of factors. The relatively short median follow-up period of 40 months is perhaps insufficient to identify differences occurring over the longer term. Furthermore, anastomotic leaks in general, have not had a consensus in definition ^{59,60} and classification ²⁵⁴ in the surgical literature. In this study however, three distinct anastomotic leak groups which are easily distinguishable were utilised as adapted from the International Study Group on Rectal Cancer (Kulu and colleagues. 2013). Leaks were classified based on the type of treatment the patient received in the above classification proposal. Similarly, we categorised patients in our study into those who did not have a leak, had a leak that was managed

conservatively with antibiotics or a radiological drainage, or had a leak that was reoperated on. This series included comorbidity data in the form of Charlson scores, however it is lacking in specific variables such as nutritional and immune status. These parameters may have an independent impact on survival that could not be commented on.

Given that anastomotic leaks occur in the literature ranging from 6-20%^{19,113,361,362}, a larger population sample would have been required to determine the impact of leaks and their subsequent management, on survival as this study's relatively small sample size may have resulted in type II statistical errors and may not have identified significant associations due to insufficient statistical power. It must also be noted that disease-free survival may not have been fully captured in instances when patients may have died with recurrences without having them formally diagnosed. Patient's causes of death were not available for analyses and this may indeed allow more detailed analysis of disease-free survival.

In this series, patients with anastomotic leaks necessitating reoperation demonstrated worse overall survival and no difference in disease free survival when compared to patients that did not leak. Part of the overall survival difference is attributable to events occurring within the early and intermediate postoperative period.

Chapter 3

The impact of adjuvant chemotherapy timing on overall survival following colorectal cancer resection

3.1 Study abstract

Aims: Several studies including two meta-analyses have showed that delay between surgery and adjuvant chemotherapy adversely impacts colorectal cancer survival. This study investigated this impact at a population level over a fifteen-year period in England.

Methods: The Hospital Episode Statistics database was analysed between 1997 and 2012. Colonic cancer and rectal cancer patients were collated and multivariate Cox regression analyses were undertaken to ascertain the relationship between chemotherapy delay and overall survival.

Results: A total of 181 984 patients underwent resection without any reoperation (106 477 (58.5%) having colonic cancer and 75 507 (41.5%) having rectal cancer). In total, 30 836 (16.9%) received adjuvant chemotherapy.

9019 (49.3%), 4573 (25.0%), 2587 (14.1%), 1323 (7.2%) and 804 (4.4%) of 18 306 colonic cancer patients received chemotherapy within 8 weeks, 8-10 weeks, 10-12 weeks, 12-14 weeks and 14-16 weeks, respectively. Sequentially worse overall survival was observed: <8 weeks (ref group); 8-10 wks: Hazard Ratio (HR) 1.09; 10-12 wks: HR 1.13; 12-14 wks HR 1.32 and 14-16 wks: HR 1.32, $p < 0.001$.

5625 (44.9%), 3087 (24.6%), 1940 (15.5%), 1162 (9.3%) and 716 (5.7%) of 12 530 rectal cancer patients received within 8 weeks, 8-10 weeks, 10-12 weeks, 12-14 weeks and 14-16 weeks, respectively. Sequentially worse overall survival was observed: <8 weeks (ref group); 8-10 wks: HR 1.09; 10-12 wks: HR 1.22; 12-14 wks HR 1.23 and 14-16 wks: HR 1.31, $p < 0.001$.

Conclusion: Adjuvant chemotherapy delay adversely impacts colonic and rectal cancer survival. Efforts to prevent complications such as reoperation and to improve access to chemotherapy services are likely to improve survival in this patient cohort.

3.2 Introduction

Colorectal cancer is the fourth most common malignancy occurring in the United Kingdom³⁶³. A multimodal approach is undertaken in its treatment, with resection surgery being the mainstay and adjuvant therapy administered where indicated. Institutional studies and meta-analyses investigating the impact of complications on timing of adjuvant chemotherapy^{364,365} and survival³⁴⁹, and those investigating the association between the delay in chemotherapy and survival³⁵⁰ have been reported. Surgical morbidity leading to reoperation adversely affects short term and long term survival^{366,367}.

However, there is no clear consensus with regard to what is considered timely initiation of adjuvant chemotherapy with time intervals between eight to twelve weeks being suggested as cut-offs for timely therapy, albeit with the proviso that adjuvant chemotherapy should be administered as soon as possible.

This study therefore aimed to investigate the impact of adjuvant chemotherapy delay on overall survival, utilizing 15 years of national population-level epidemiological data of patients undergoing elective colorectal cancer resection.

3.3 Methods

3.3.1 Variables & definitions

The Hospital Episode Statistics (HES) database was analysed between April 1997 and March 2012. HES has been described previously³⁶⁸ and comprises prospectively collected administrative records of patients admitted to hospitals in England. In its current iteration, each admission episode contains, amongst other parameters, up to seven diagnoses including a primary diagnosis and up to four procedures. The former is coded according to ICD-10 (International Classification of Diseases, 10th revision) and the latter according to OPCS-4 (Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures, 4th revision). Comorbidity was assessed using Charlson comorbidity scoring, which is an acknowledged system for quantifying patient comorbidity⁹⁶. This was derived from secondary diagnosis codes in this study. Mortality data were obtained via linkage between HES data and the Office of National Statistics (ONS) datasets. The study was also reported in keeping with the STROBE guidelines³⁶⁹.

3.3.2 Database inclusions and variable coding

All patients undergoing an elective primary colorectal cancer resection between 1st April 1997 and 31st March 2012 were included in the analyses.

Resections were considered to be for cancer if the primary diagnosis for the given admission episode was coded for a colonic or rectal cancer. Patients were grouped into four age categories: 17-54, 55-69, 70-79 and >79 years. The Charlson comorbidity score was categorised into three comorbidity risk categories: 0, 1-4 and >4.

Cancers were categorised depending on the site of lesion: colon or rectum and analysed separately. Episodes including code C78 or C79 (Secondary malignant neoplasm of respiratory/digestive and other organs) were excluded. Any procedure associated with OPCS codes Y50.8 and Y75 was considered to represent a procedure where minimal access surgery had been performed. Failed minimal access (Y71.4) was considered within the minimal access group for analysis purposes. Patients who underwent reoperations in the first 30 days postoperatively were excluded (Table 3.1).

Table 3.1 OPCS-4 & ICD-10 codes

	Code
Colorectal Cancer Diagnoses	C18 – C20 & C21.8
Metastatic Disease Diagnoses (excluding lymph node disease)	C78, C79
Chemotherapy codes	X35.2, X35.8, X35.9, X72, X73
Minimal Access codes	Y50.8, Y75, Y71.4

3.3.3 Outcome variables

3.3.3.1 Timing of adjuvant chemotherapy administration

Adjuvant chemotherapy administration is coded for as an inpatient admission in HES. The first occasion a chemotherapy code (Table 3.1) was observed, was considered to be the time of chemotherapy commencement. We included all chemotherapy episodes up to sixteen weeks post-surgery, as it is unlikely that primary adjuvant chemotherapy would have been commenced beyond that. The impact of adjuvant chemotherapy delay on overall survival was subsequently assessed, by comparing patients grouped into those receiving adjuvant chemotherapy within 8 weeks and subsequent 2-week incremental groupings, up to sixteen weeks.

3.3.3.2 Overall survival

Patient mortality was ascertained from pseudonymised linked data from ONS. ONS linkage was performed on 12 March 2013 and patients were considered to be alive at this date if there was no death registration for them. The impact of delay to adjuvant chemotherapy on overall survival was interrogated utilising multivariate Cox proportional hazard regression analyses.

3.3.4 Statistical Methodology

Univariate Cox regression analysis was undertaken to ascertain significant variables, which impacted overall survival. Variables with a significance of <0.1

on univariate analyses were entered into multivariate models. Thereafter, survival curves were used to demonstrate impact of adjuvant chemotherapy delay on overall survival. Statistical analyses were conducted utilising SPSS version 21.0 (SPSS, Chicago, Illinois, USA).

3.4 Results

3.4.1 Demographics

Between April 1997 and March 2012, a total of 192 706 patients underwent elective colorectal cancer resections. In total, 10 722 (5.6%) had a reoperation within thirty days of their index operation and were excluded. Of the remaining 181 984 patients, 106 477 (58.5%) had a colonic cancer and 75 507 (41.55%) had a rectal cancer. 18 306 (59.4%) of colonic cancer patients and 12 530 (40.6%) of rectal cancer patients received adjuvant chemotherapy. In total, 30 836 (16.9%) received adjuvant chemotherapy.

3.4.2 Colonic Cancer patients

9019/18 306 (49.3%) of these patients received adjuvant chemotherapy within 8 weeks of their operation, 25.0% between 8 to 10 weeks, 14.1% between 10 to 12 weeks, 7.2% between 12 to 14 weeks and 4.4% between 14 to 16 weeks (Table 3.2). Patients were relatively younger in the earlier chemotherapy receipt groups but there were no significant differences in gender distribution. There were significantly less patients with high (>4) comorbidity score in the delayed

chemotherapy groups compared to the within 8 weeks group. However the proportion of those with a Charlson score of zero remained fairly stable throughout the groups. There were significantly fewer patients who underwent minimal access surgery in the most delayed group and patients in the higher socio-economic setting appeared to receive adjuvant chemotherapy earlier.

Table 3.2: 18306 colonic cancer patients who received adjuvant chemotherapy

n (% of category)		0-8 wks	8-10 wks	10-12 wks	12-14 wks	14-16 wks	p-value
Age							<0.001
	18-54	1549 (17.2)	658 (14.4)	342 (13.2)	164 (12.4)	177 (12.7)	
	55-69	4580 (50.8)	2335 (51.1)	1223 (47.3)	612 (46.3)	385 (47.9)	
	70-79	2611 (28.9)	1420 (31.1)	919 (35.5)	483 (36.5)	282 (35.1)	
	>79	279 (3.1)	160 (3.5)	103 (4.0)	64 (4.8)	35 (4.4)	
Gender							0.921
	Male	4898 (54.3)	2448 (53.5)	1390 (53.7)	720 (54.4)	433 (53.9)	
	Female	4121 (45.7)	2125 (46.5)	1197 (46.3)	603 (45.6)	371 (46.1)	
Charlson Score							<0.001
	0	5337 (59.2)	2724 (59.6)	1555 (60.1)	825 (62.4)	492 (61.2)	
	1-4	978 (10.8)	590 (12.9)	357 (13.8)	196 (14.8)	130 (16.2)	
	>4	2704 (30.0)	1259 (27.5)	675 (26.1)	302 (22.8)	804 (22.6)	
Operative Access							<0.001
	Open	7340 (81.4)	3502 (76.6)	2047 (79.1)	1078 (81.5)	681 (84.7)	
	M Access	1679 (18.6)	1071 (23.4)	540 (20.9)	245 (18.5)	123 (15.3)	
IMD tertiles							0.002
	Least Deprived	7215 (80.0)	3665 (80.1)	2028 (78.4)	1044 (78.9)	624 (77.6)	
	Moderately Deprived	1579 (17.5)	791 (17.3)	504 (19.5)	253 (19.1)	165 (20.5)	
	Most Deprived	150 (1.7)	97 (2.1)	48 (1.9)	21 (1.6)	12 (1.5)	
	Missing	75 (0.8)	20 (0.4)	7 (0.3)	5 (0.4)	3 (0.4)	
Total n (% of 18306)		9019 (49.3)	4573 (25.0)	2587 (14.1)	1323 (7.2)	804 (4.4)	

3.4.2.1 Overall Survival in colonic cancer patients

Patients with longer delay to chemotherapy receipt demonstrated sequentially worse survival, with those receiving treatment between 14 to 16 weeks, being 32% more likely to die compare to those who had treatment within 8 weeks (Table 3.3).

Younger age, female gender, a lower Charlson score and minimal access surgery conferred a survival advantage. Patients in moderately deprived areas had a lower overall survival.

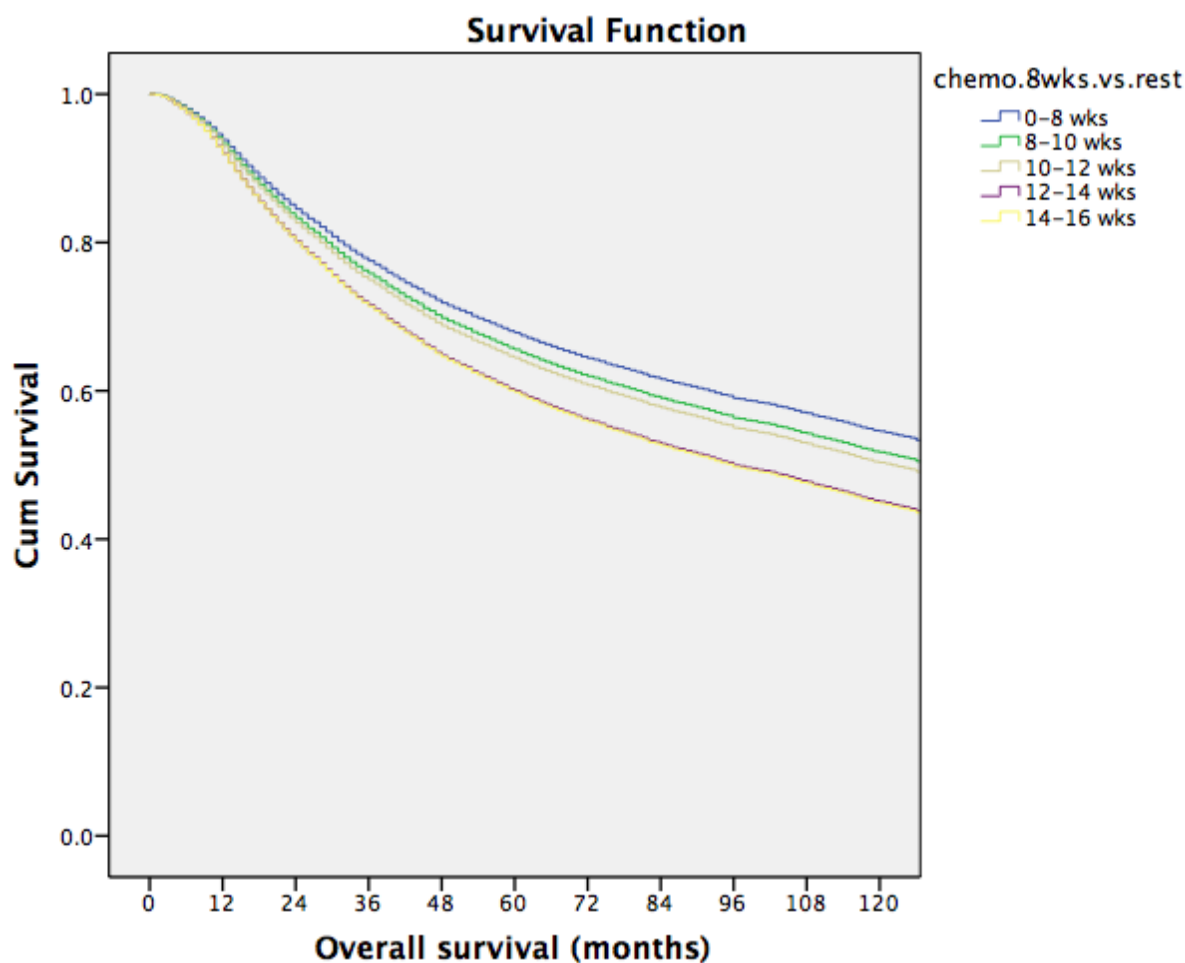
3.4.2.2 Survival analysis in colonic cancer patients

The minimum and maximum follow-up period were 1 month and 189 months respectively. The interquartile range was 19 months to 85 months. 6621/18 306 (36.2%) of these patients died during follow-up. The survival was significantly worse as the delay to adjuvant chemotherapy was sequentially increased. Figure 3.1 details the differing survival trends in the five groups, which were statistically significant (log rank $p < 0.001$).

Table 3.3: Overall survival in 18306 colonic cancer patients undergoing adjuvant chemotherapy

	Univariate			Multivariate		
	Hazard Ratio	95% CI	p value	Hazard Ratio	95% CI	p value
Time to Adjuvant Chemotherapy			<0.001			<0.001
≤8 weeks	1			1		
8-10 weeks	1.10	1.03 to 1.17		1.09	1.02 to 1.16	
10-12 weeks	1.17	1.09 to 1.26		1.13	1.05 to 1.22	
12-14 weeks	1.36	1.25 to 1.49		1.32	1.20 to 1.44	
14-16 weeks	1.34	1.20 to 1.50		1.32	1.19 to 1.48	
Age			<0.001			<0.001
18-54	1			1		
55-69	1.30	1.20 to 1.40		1.28	1.18 to 1.38	
70-79	1.91	1.76 to 2.07		1.85	1.70 to 2.01	
>79	2.81	2.47 to 3.19		2.68	2.35 to 3.04	
Gender			<0.001			<0.001
Male	1			1		
Female	0.86	0.82 to 0.91		0.87	0.83 to 0.91	
Charlson Score			<0.001			<0.001
0	1			1		
1-4	1.19	1.10 to 1.29		1.12	1.03 to 1.21	
>4	1.31	1.24 to 1.38		1.28	1.21 to 1.35	
Operative access			<0.001			<0.001
Open	1			1		
Minimal Access	0.81	0.74 to 0.88		0.81	0.74 to 0.88	
IMD Tertile			0.017			0.003
Least Deprived	1			1		
Moderately Deprived	1.09	1.03 to 1.16		1.11	1.05 to 1.18	
Most Deprived	0.96	0.81 to 1.15		1.00	0.83 to 1.19	

Figure 3.1: Survival curve of colonic cancer patients stratified according to time to initiation of adjuvant chemotherapy



Time to AC (wks)	Overall survival(months)										
	0	12	24	36	48	60	72	84	96	108	120
0-8	9019	7847	6383	5272	4324	3626	3080	2608	2209	1842	1510
8-10	4573	3943	3080	2442	1891	1499	1221	993	794	641	458
10-12	2587	2248	1745	1371	1089	875	714	591	482	377	300
12-14	1323	1139	877	682	560	457	375	309	256	205	162
14-16	804	707	551	435	354	283	217	178	149	123	96

3.4.3 Rectal Cancer patients

5625/12 530 (44.9%) of these patients received adjuvant chemotherapy within 8 weeks of their operation, 24.6% between 8 to 10 weeks, 15.5% between 10 to 12 weeks, 9.3% between 12 to 14 weeks and 5.7% between 14 to 16 weeks (Table 3.4).

Patients were relatively younger in the earlier chemotherapy receipt groups but there were no significant differences in gender distribution. There were significantly less patients with high (>4) comorbidity score in the delayed chemotherapy groups compared to the within 8 weeks group. However the proportion of those with a Charlson score of zero remained fairly stable throughout the groups. The 8-10 week group appeared to have the largest proportion of patients undergoing minimal access surgery compared to the other groups. Patients in the higher socio-economic setting appeared to receive adjuvant chemotherapy earlier.

Table 3.4: 12530 rectal cancer patients who received adjuvant chemotherapy

n (% of category)		0-8 wks	8-10 wks	10-12 wks	12-14 wks	14-16 wks	p-value
Age							<0.001
	18-54	1178 (20.9)	591 (19.1)	330 (17.0)	201 (17.3)	117 (16.3)	
	55-69	3090 (54.9)	1714 (55.5)	1043 (53.8)	583 (50.2)	383 (53.5)	
	70-79	1274 (22.6)	730 (23.6)	520 (26.8)	346 (29.8)	200 (27.9)	
	>79	83 (1.5)	52 (1.7)	47 (2.4)	32 (2.8)	16 (2.2)	
Gender							0.848
	Male	3574 (63.5)	1926 (62.4)	1232 (63.5)	739 (63.6)	449 (62.7)	
	Female	2051 (36.5)	1161 (37.6)	708 (36.5)	423 (36.4)	267 (37.3)	
Charlson Score							<0.001
	0	3408 (60.6)	1903 (61.6)	1154 (59.5)	726 (62.5)	454 (63.4)	
	1-4	526 (9.4)	339 (11.0)	259 (13.4)	136 (11.7)	84 (11.7)	
	>4	1691 (30.1)	845 (27.4)	527 (27.2)	300 (25.8)	178 (24.9)	
Operative Access							<0.001
	Open	4903 (87.2)	2578 (83.5)	1633 (84.2)	1021 (87.9)	611 (85.3)	
	M Access	722 (12.8)	509 (16.5)	307 (15.8)	141 (12.1)	105 (14.7)	
IMD tertiles							0.037
	Least Deprived	4433 (78.6)	2390 (77.4)	1512 (77.9)	902 (77.6)	534 (74.6)	
	Moderately Deprived	1030 (18.3)	627 (20.3)	384 (19.8)	225 (19.4)	159 (22.2)	
	Most Deprived	126 (2.2)	59 (1.9)	36 (1.9)	29 (2.5)	19 (2.7)	
	Missing	47 (0.8)	11 (0.4)	8 (0.4)	6 (0.5)	4 (0.6)	
Total n (% of 12530)		5625 (44.9)	3087 (24.6)	1940 (15.5)	1162 (9.3)	716 (5.7)	

3.4.3.1 Overall Survival in rectal cancer patients

Patients with longer delay to chemotherapy receipt demonstrated sequentially worse survival, with those receiving treatment between 14 to 16 weeks, being 31% more likely to die compare to those who had treatment within 8 weeks (Table 3.5).

Younger age, female gender and a lower Charlson score conferred a survival advantage. Patients undergoing minimal access surgery did not have a survival advantage during the follow-up period of this fifteen-year cohort. Patients in moderately deprived areas had a lower overall survival.

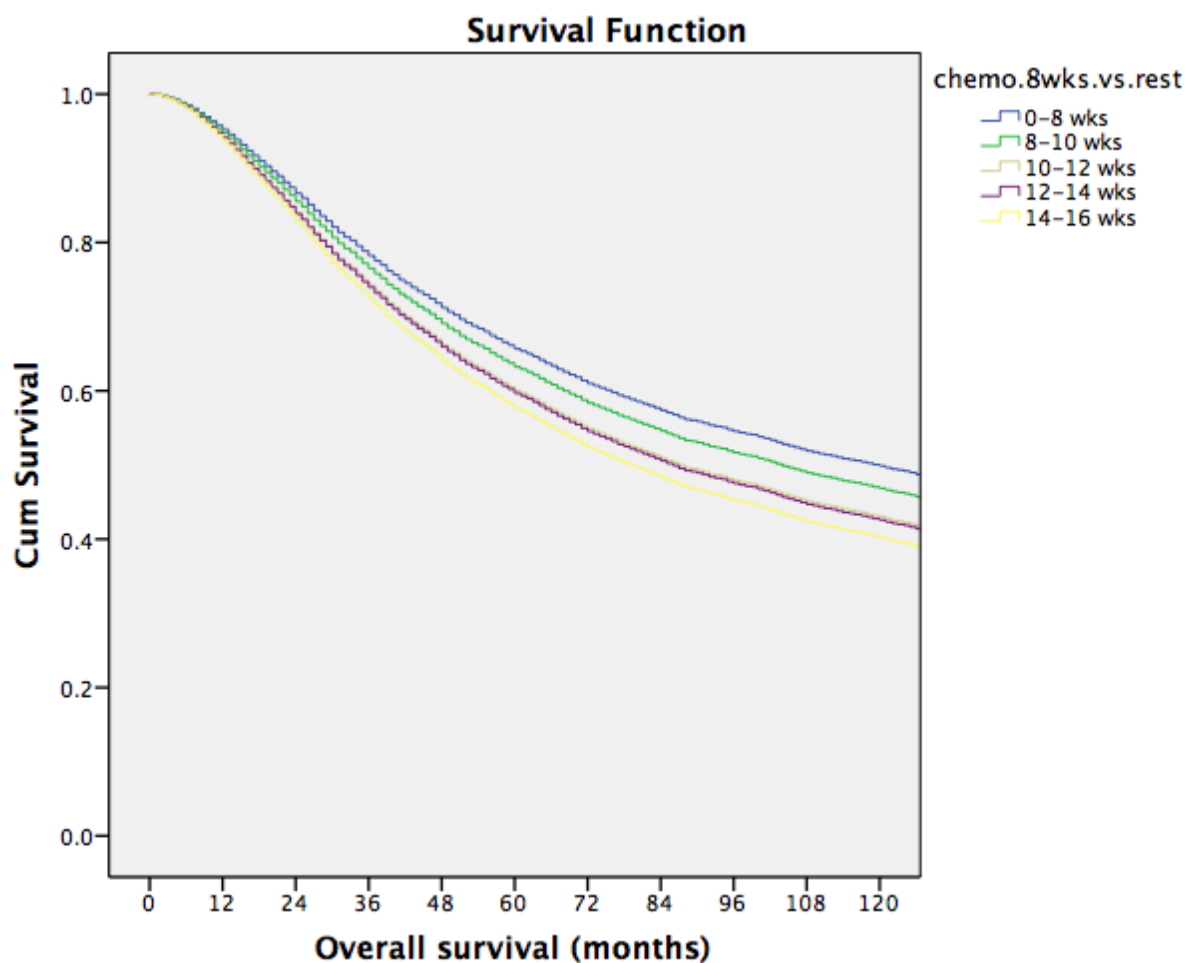
3.4.3.2 Survival analysis in rectal cancer patients

The minimum and maximum follow-up period were 1 month and 184 months respectively. The interquartile range was 22 months to 87 months. 4980/12 530 (39.7%) of these patients died during follow-up. The survival was significantly worse as the delay to adjuvant chemotherapy was sequentially increased. Figure 3.2 details the differing survival trends in the five groups, which were statistically significant (log rank $p < 0.001$).

Table 3.5: Overall survival in 12530 rectal cancer patients undergoing adjuvant chemotherapy

	Univariate			Multivariate		
	Hazard Ratio	95% CI	p value	Hazard Ratio	95% CI	p value
Time to Adjuvant Chemotherapy			<0.001			<0.001
≤8 weeks	1			1		
8-10 weeks	1.09	1.02 to 1.18		1.09	1.01 to 1.17	
10-12 weeks	1.26	1.16 to 1.36		1.22	1.12 to 1.32	
12-14 weeks	1.28	1.17 to 1.41		1.23	1.11 to 1.35	
14-16 weeks	1.33	1.18 to 1.49		1.31	1.17 to 1.47	
Age			<0.001			<0.001
18-54	1			1		
55-69	1.25	1.15 to 1.35		1.23	1.14 to 1.33	
70-79	1.76	1.61 to 1.92		1.72	1.57 to 1.87	
>79	2.52	2.09 to 3.03		2.40	2.00 to 2.89	
Gender			<0.001			<0.001
Male	1			1		
Female	0.85	0.80 to 0.90		0.85	0.80 to 0.90	
Charlson Score			<0.001			<0.001
0	1			1		
1-4	1.25	1.13 to 1.37		1.16	1.06 to 1.28	
>4	1.16	1.09 to 1.23		1.16	1.09 to 1.23	
Operative access			0.053			0.064
Open	1			1		
Minimal Access	0.89	0.79 to 1.00		0.89	0.79 to 1.00	
IMD Tertile			<0.001			<0.001
Least Deprived	1			1		
Moderately Deprived	1.15	1.08 to 1.23		1.16	1.08 to 1.24	
Most Deprived	1.10	0.92 to 1.32		1.00	0.94 to 1.35	

Figure 3.2: Survival curve of rectal cancer patients stratified according to time to initiation of adjuvant chemotherapy



Time to AC (wks)	Overall survival (months)										
	0	12	24	36	48	60	72	84	96	108	120
0-8	5625	5057	4247	3540	2907	2435	2072	1749	1458	1185	939
8-10	3087	2685	2166	1693	1343	1078	883	704	560	446	345
10-12	1940	1703	1340	1065	859	683	556	450	377	292	230
12-14	1162	1023	831	665	533	417	336	267	231	185	143
14-16	716	633	529	405	328	254	203	164	137	121	95

3.5 Discussion

These data, the largest of their kind, demonstrate that adjuvant chemotherapy initiation beyond 8 weeks reduced overall survival in patients, compared to those who received it within 8 weeks of elective colorectal cancer resection. Two-week increments in the delay showed progressively worse overall survival in both colonic cancer and rectal cancer cohorts.

The ideal timing of adjuvant chemotherapy in colorectal cancer management has not been definitively established. Nevertheless it has been reported in a systematic review in 2010 that early initiation within six to eight weeks is likely to lead to better survival and two meta-analyses reported reduced survival with longer delay to adjuvant chemotherapy initiation ^{350,351}. In the current population-based study, we have similarly shown that patients had a sequentially poorer survival, the longer the delay to adjuvant chemotherapy.

Adjuvant chemotherapy regimens for colorectal cancer have evolved over the fifteen-year period of analysis. This may have impacted to differing extents on overall survival, regardless of whether a delay in adjuvant chemotherapy delivery occurred. In the United Kingdom, regimens based on 5-fluorouracil (5-FU) and folinic acid (L-FA) with or without levamisole (LV) (QUASAR) ³⁷⁰ were most commonly utilised until approximately 2005 and thereafter regimens combined the former with oxaliplatin (MOSAIC) ³⁷¹. Although the HES dataset does not provide information with regards to specific drugs utilised, we noted that rates of chemotherapy receipt, proportion of patients receiving timely

chemotherapy and subsequent impact on overall survival were similar between the two approximated time periods (1997–2005 and 2006–2012).

Reasons for delay in initiation of adjuvant chemotherapy can be clinical, service related or patient preference. Clinical factors such as postoperative infections, other medical complications and reoperation, may prevent transition to adjuvant chemotherapy or delay its initiation. A recent study utilising the American National Cancer Database observed that postoperative complications resulted in 16.8% of stage III cancer resection patients not receiving adjuvant chemotherapy. The same study also observed a delay of up to 65% in the time to initiation of chemotherapy in those with serious complications such as anastomotic leakage ³⁵². Furthermore, another recent institutional study also reported a reduced benefit when adjuvant chemotherapy was commenced beyond eight to ten weeks postoperatively ³⁷². Conversely, other investigators have not observed survival differences associated with early and late chemotherapy initiation ³⁷³.

Our observational cohort study is in keeping with the notion that prompt/early adjuvant chemotherapy where it is indicated will improve overall survival in the patient. Therefore it is pertinent that all measures are taken to prevent reoperation or significant complication in the postoperative period. Careful patient selection, preoperative patient optimisation and good intraoperative decision making, may be important in this aspect.

This population study benefits from a large cohort of patients over an extended period of time. However it has several limitations pertaining to the utilisation of administrative datasets such as Hospital Episodes Statistics (HES). Administrative health data has its specific limitations which have been described previously ³⁷⁴. The database used in the current study does not include cancer stage (although the majority of patients who received chemotherapy would be stage III or possibly high-risk stage II), which is an important prognostic determinant of both overall and disease-free survival.

Furthermore, other clinico-pathological factors such as histological grade, nodal status, margin clearance and intraoperative factors such as blood loss are not available. This dataset also does not have any recurrence data and therefore we were not able to interrogate disease-free survival. Subsequent interventions such as liver metastectomies are also not accounted for in these analyses. Although we were able to assess overall survival, cancer specific deaths were not ascertainable. Cancer and non-cancer related deaths are not accurately distinguishable in the Office of National Statistics' death registration data that is linked to the HES database. HES data are also not able to distinguish patients who may have been/should be offered chemotherapy but did not receive it for alternative reasons (frailty, high-risk comorbidities or patient preference). We elected to analyse all patients in our 15-year database who received adjuvant chemotherapy within 16 weeks of the cancer surgery and we also excluded patient who underwent a reoperation.

We also excluded patients who had secondary metastasis codes (ICD-10) to further reduce heterogeneity of the cohort. This is likely to represent elective colorectal cancer patients, with stage III disease, who received chemotherapy as a primary adjuvant treatment. We are however not able to discern patients who may have had adjuvant chemotherapy indicated but did not receive it due to various reasons such as patient frailty or preference, and postoperative clinical factors.

Over the study period, the indications for adjuvant chemotherapy would have also evolved to include high risk stage II ^{375,376}, albeit with equivocal evidence base ^{375,377} and patients with greater comorbidity as increased experience and research in oncology, and refinement and introduction of new regimens and agents occur. Furthermore, the number of cycles each patient received was also not available. Although the receipt of adjuvant chemotherapy is documented in HES, data on the number of cycles received, type of chemotherapy agent and whether cycles were completed were not available. This is a further limitation of this study that adds bias to our results and may explain patient survival outcome differences.

The advent of minimal access surgery may have also allowed less surgical morbidity, faster recovery and indeed earlier initiation of adjuvant chemotherapy and subsequent survival advantage. Our analyses include a period when minimal access surgery was being implemented and being actively improved on. Therefore its impact on postoperative recovery and subsequent timely or

delayed adjuvant chemotherapy receipt or in fact non-receipt of chemotherapy may not be clear.

The above reasons contribute to the heterogeneous population being studied and although the analyses have been adjusted for some factors, not all variables have been so and this adds to the limitations of this study. Nevertheless, this dataset permits longitudinal overall survival analyses of the largest national cohort of patients to date, over a long period of time.

We have shown utilising a population database that early adjuvant chemotherapy significantly increases overall survival in both colonic and rectal cancer, which has a lasting impact up to 10 years postoperatively. Regardless of its causation, it can be seen that chemotherapy delay independently reduces overall survival and therefore, a targeted approach to reduce this delay is essential. Prevention and prompt proactive management of surgical and medical complications are important in preventing this delay. Furthermore, early access to oncological services and service design to ensure its prompt delivery must be in place.

Lastly, patient counseling on the importance of early adjuvant chemotherapy must also be actively pursued. This study emphasises the importance ensuring prompt administration of adjuvant chemotherapy in patients undergoing elective colorectal cancer resection. Consequently, defining strategies that permit timely

access to oncology services is a potential area for quality improvement in England.

Chapter 4

Adjuvant chemotherapy initiation within 8 weeks of elective colorectal resection improves overall survival regardless of re-operative status

4.1 Study abstract

Aims: Reoperation after colorectal resection may delay receipt of adjuvant chemotherapy. This study investigated the dual impact of a reoperation and adjuvant chemotherapy delay on overall survival.

Methods: The English HES database was analysed between 1997 and 2012. Patients were divided into colon and rectal cancer cohorts and subsequently subdivided into four groups. (Reoperation within 30 days)

A: No chemotherapy delay (<8 weeks) & No reoperation

B: No chemotherapy delay & Reoperation

C: Chemotherapy delay & No reoperation

D: Chemotherapy delay & Reoperation.

Multivariate logistic and Cox regression was undertaken to investigate the relationship between chemotherapy delay and reoperation, and their combined effect on OS.

Results:

Colon cancer: Groups A, B, C and D had 9019(47.9%), 144(0.8%), 9287(49.3%) and 386(2.0%) patients respectively. On multivariate Cox regression, Group B did not show a significant difference ($p=0.321$) in OS compared to the reference category (Group A). Groups C (HR: 1.16, CI 1.10-1.21, $p<0.001$) and D (HR 1.33, CI 1.02-1.74, $p=0.037$) both showed significantly worse OS compared to Group A.

Rectal cancer: Groups A, B, C and D had 5625(42.8%), 163(1.2%), 6905(52.5%) and 459(3.5%) patients respectively. On multivariate Cox regression, Group B did not show a significant difference ($p=0.157$) in OS compared to Group A. Groups C HR: 1.17, CI 1.11-1.24, $p<0.001$] and D (HR 1.38, CI 1.19-1.60, $p<0.001$) both showed significantly worse OS compared to Group A.

Conclusion: Adjuvant chemotherapy initiation within eight weeks significantly increases overall survival regardless of reoperation status in both colon and rectal cancer patient cohorts.

4.2 Introduction

Colorectal cancer, as previously noted, is the fourth most common malignancy occurring in the United Kingdom³⁶³. A multimodal approach is undertaken in its treatment, with resection surgery being the mainstay and adjuvant therapy administered where indicated. Colorectal resection carries risk of surgical morbidity requiring reoperation in the immediate postoperative period. This may delay receipt of adjuvant chemotherapy^{367,378} and this in turn may or may not adversely impact upon survival³⁵³.

Institutional studies and meta-analyses investigating the impact of complications on timing of adjuvant chemotherapy^{364,365} and survival³⁴⁹, and those investigating the association between the delay in chemotherapy and survival³⁵⁰ have been reported. Surgical morbidity leading to reoperation adversely affects short term and long term survival^{366,367}. However, the relationship between reoperative status and delay in adjuvant chemotherapy receipt, and their combined impact on overall survival is not clear.

This study aimed to investigate this specific relationship utilizing 15 years of population-level epidemiological data of patients undergoing elective colorectal cancer resection.

4.3 Methods

4.3.1 Variables & definitions

The Hospital Episode Statistics (HES) database was analysed between April 1997 and March 2012. HES has been described previously³⁶⁸ and comprises prospectively collected administrative records of patients admitted to hospitals in England. In its current iteration, each admission episode contains, amongst other parameters, up to seven diagnoses including a primary diagnosis and up to four procedures. The former is coded according to ICD-10 and the latter according to OPCS-4. Mortality data were obtained via linkage between HES data and the Office of National Statistics (ONS) datasets. The study was also reported in keeping with the STROBE guidelines³⁶⁹

4.3.2 Database inclusions and variable coding

All patients undergoing an elective primary colorectal cancer resection between 1st April 1997 and 31st March 2012 were included in the analyses.

Resections were considered to be for cancer if the primary diagnosis for the given admission episode was coded for a colonic or rectal cancer. Patients who had an additional metastasis codes (C78 and C79) at primary resection were deemed to be palliative and not curative, and excluded from analyses. Patients were divided into those who had a tumour in the colon or the rectum and analysed independently. Patients were grouped into four age categories: 17-54,

55-69, 70-79 and >79 years. Comorbidity was assessed using Charlson comorbidity index (CCI), which is an acknowledged system for quantifying patient comorbidity⁹⁶. This was derived from secondary diagnosis codes in this study. The Charlson comorbidity score was categorised into three comorbidity risk categories: 0, 1-4 and >4. Deprivation scores were derived and divided into tertiles, utilising pseudonymised postcode data of patients from the HES database as per the UK government's index of multiple deprivation study³⁷⁹. Any procedure associated with OPCS codes Y50.8 and Y75 was considered to represent a procedure where minimal access surgery had been performed. Failed minimal access (Y71.4) was considered within the minimal access group for analysis purposes (Table 4.1). Reoperations within 30 days of index operation, including defunctioning procedures and re-laparotomy were also collated.

4.3.3 Outcome variables

4.3.3.1 Timing of adjuvant chemotherapy administration

Adjuvant chemotherapy administration is coded for as an inpatient admission in HES. The first occasion a chemotherapy code (Table 4.1) was observed, was considered to be the time of chemotherapy commencement. We included all chemotherapy episodes up to sixteen weeks post-surgery, as it is unlikely that primary adjuvant chemotherapy would have been commenced beyond that. Adjuvant chemotherapy receipt within eight weeks was considered timely.

Patients who received adjuvant chemotherapy between eight and sixteen weeks were considered to have a delay in adjuvant chemotherapy.

Table 4.1: OPCS-4 & ICD-10 codes

	Code
Colorectal Cancer Diagnoses	C18 – C20 & C21.8
Metastasis (Lymph nodes not included)	C78 – C79
Chemotherapy codes	X35.2, X35.8, X35.9, X72, X73
Minimal Access codes	Y50.8, Y75, Y71.4

4.3.3.2 Reoperation status

Reoperation was defined as any abdominal or pelvic operation, including examination under anaesthesia or procedure for a wound complication, occurring within 30 days of the index surgery.

4.3.3.3 Predictors of adjuvant chemotherapy delay

The impact of discrete categorical variables, including reoperative status, was investigated using logistic regression, in the colon and rectal cancer cohorts.

4.3.3.4 Overall survival

Patient mortality was ascertained from pseudonymised linked data from ONS. ONS linkage was performed on 12 March 2013 and patients were considered to be alive at this date if there was no death registration for them.

Overall survival was analysed in the below four distinct groups to ascertain the impact of reoperation & adjuvant chemotherapy delay, utilising multivariate Cox regression analyses.

Within the separate cohorts, patients were subsequently divided into four distinct groups:

A: No adjuvant chemotherapy delay & No reoperation

B: No adjuvant chemotherapy delay & Reoperation

C: Adjuvant chemotherapy delay & No reoperation

D: Adjuvant chemotherapy delay & Reoperation

4.3.4 Statistical Methodology

Demographic data, including age, gender, Charlson score, tumour site, operative access and deprivation (Index of Multiple Deprivation) categories were collated and analysed.

The impact of discrete categorical variables on adjuvant chemotherapy delay in colon and rectal cancer patients, were tested with univariate logistic regression and those with a significance of $p < 0.1$ were subsequently loaded into a multivariate model. Similarly, the impact of discrete categorical variables on overall survival in each group of patients listed above were tested with univariate Cox regression analysis and those with a significance of $p < 0.1$ were subsequently loaded into a multivariate model. The survival curve for each group was plotted to demonstrate survival differences. A p value of < 0.05 was denoted to be significant in multivariate analysis. All statistical analyses were conducted utilising SPSS version 21.0 (SPSS, Chicago, Illinois, USA).

4.4 Results

4.4.1 Overall demographics

Between April 1997 and March 2012, a total of 192,706 patients underwent elective colorectal cancer resections. In total, 10722 (5.6%) had a reoperation within thirty days of their index operation. 31988 (16.6%) of patients received adjuvant chemotherapy [14951 (46.7%) within eight weeks and 17037 (53.3%) beyond eight weeks. In the cohort of patients who did not receive adjuvant chemotherapy, the reoperation rate was 6.0% (9570/160,718) and in the cohort who did receive adjuvant chemotherapy, the reoperation rate was 3.6% (1152/31988). Patients who received adjuvant chemotherapy (n=31988) were divided into colon and rectal cohorts and subsequently each cohort was further split into four distinct groups (Figure 4.1 & Table 4.2).

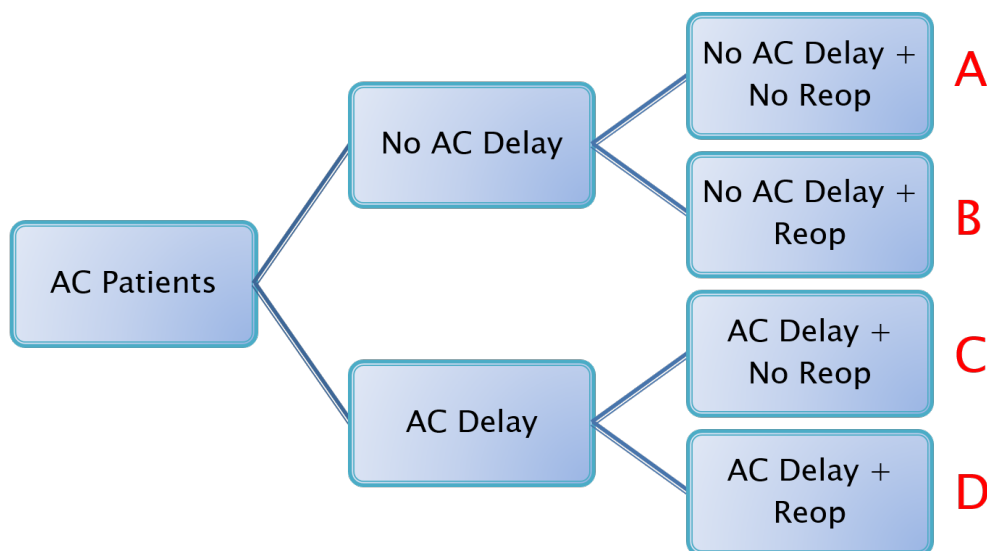


Figure 4.1 Adjuvant chemotherapy & reoperative status