An investigation into the relationship between the postoperative systemic inflammatory response, complications, and oncologic outcomes following surgery for colorectal cancer

By

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A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

To

The University of Glasgow

From research conducted in the Academic Unit of Surgery, School of Medicine, University of Glasgow

Abstract

Colorectal cancer is the second most common cause of cancer death in the United Kingdom (UK). At present, surgery remains the cornerstone of its management and is the mainstay of curative treatment. However, surgery for colorectal cancer is associated with significant postoperative morbidity and mortality. These postoperative complications, whether classified by their type or severity, are associated with poorer quality of life, increased socioeconomic and direct healthcare costs, and poorer oncologic outcomes.

The stress response to surgery is a neurohormonal and immune response to trauma which seeks to stop haemorrhage, prevent infection, and promote healing. However, an inappropriately exaggerated postoperative systemic inflammatory response is now understood to be associated with infective complications following surgery for colorectal cancer. It is thought that this may occur through the suppression of the adaptive immune system by this overwhelming innate response. However, it's effect on the longer term and oncologic outcomes is less clear. In addition, the factors which influence this postoperative systemic inflammatory response are unclear. Furthermore, it remains to be determined whether attenuation of the postoperative systemic inflammatory response will improve short and long term outcomes following surgery for colorectal cancer.

The work presented in this thesis further examines the relationship between the postoperative systemic inflammatory response, postoperative complications, and long term oncologic outcomes following surgery for colorectal cancer. Several perioperative factors which might influence the postoperative systemic inflammatory response are examined. Finally, the question as to whether attenuation of the postoperative systemic inflammatory response might result in improved outcomes following surgery for colorectal cancer is examined.

The magnitude of the postoperative systemic inflammatory response, in particular, exceeding C-reactive protein (CRP) concentrations of 150mg/L on postoperative days 3 or 4, has been reported to be associated with the development of infective type postoperative complications. Chapter 3 examined the relationship between the postoperative systemic inflammatory response and complication severity, reporting that exceeding these CRP thresholds was associated with major complications as defined by Clavien Dindo grades 3 to 5.

Although postoperative complications are recognised to have a negative prognostic impact, the relationship between the postoperative systemic inflammatory response and long term oncologic outcome is less clear. The results of Chapter 4 suggest that an exaggerated postoperative systemic inflammatory response has a negative prognostic impact independent of complications following surgery for colorectal cancer.

There is already some evidence to suggest that patient and operative factors such as the use of laparoscopic surgery, body mass index (BMI), comorbid disease, and the presence of preoperative systemic inflammation influence the postoperative systemic inflammatory response. Chapters 5 to 11 examined some other important patient and perioperative factors which might have an influence on the postoperative systemic inflammatory response. Chapter 5 reported that BMI and visceral obesity measured by preoperative CT scans are associated with the magnitude of the postoperative systemic inflammatory response and complications in female patients only. Chapter 6 reported no significant association between poorer exercise tolerance, a lower anaerobic threshold as measured by cardiopulmonary exercise testing (CPEX), and the magnitude of the postoperative systemic inflammatory response in a small number of patients. Chapter 7 reported no association between the formation of a temporary defunctioning stoma (at the time of anterior resection for rectal cancer), and the magnitude of the postoperative systemic inflammatory response. Chapter 8 reported that operation duration is not directly associated with the postoperative systemic inflammatory response, instead suggesting that the surgical approach is more important. Chapter 9 reported no association between perioperative blood transfusion and the magnitude of the postoperative systemic inflammatory response, but did find a significant association between preoperative inflammation and anaemia. Chapter 10 reported no association between preoperative neoadjuvant chemoradiotherapy (nCRT) and the magnitude of the postoperative systemic inflammatory response in patients undergoing surgery for rectal cancer. Chapter 11 compared the postoperative systemic inflammatory response of patients undergoing surgery for colorectal cancer in the UK and Japan, using propensity scoring to match patients from each country by various demographic, pathological, and perioperative variables. The results suggest a significant difference in the magnitude of the postoperative systemic inflammatory response, possibly dependent on ethnicity, which appears to be confirmed on further examination of the literature.

Chapter 12 examined the possibility of a new paradigm of postoperative care following surgery for colorectal cancer. At present the investigation of potential complications

following surgery is primarily reactive in nature and based on markers of patient physiology such as heart rate, core body temperature, blood pressure etc. Chapter 12 proposed the use of CRP on day 4 to prompt early investigation of such potential complications by computed tomography (CT) in the presence of an exaggerated postoperative systemic inflammatory response. The results suggest that such a postoperative care protocol could result in the earlier and more accurate diagnosis of postoperative complications.

Chapters 13 to 15 examined the use of single dose preoperative corticosteroids for the attenuation of the postoperative systemic inflammatory response and whether it might improve short term complications following surgery for colorectal cancer. Meta-analysis of the existing randomised controlled trials in gastrointestinal cancer surgery in Chapter 13 reported that corticosteroids result in lower postoperative CRP concentrations and fewer postoperative complications, but only in patients undergoing oesophageal and hepatic surgery and not in patients having a colorectal resection. In Chapter 14, a propensity score matched analysis of the GRI cohort of patients given dexamethasone at the induction of anaesthesia, for the prevention of postoperative nausea and vomiting (PONV), reported a significant reduction in postoperative CRP concentrations and complications. Finally, Chapter 15 set out a protocol for a randomised controlled trial of preoperative dexamethasone to assess dose response with relation to the magnitude of the postoperative systemic inflammatory response.

In summary, the postoperative systemic inflammatory response may impact on the short and long term outcomes of patients undergoing surgery for colorectal cancer. Attenuation of this postoperative systemic inflammatory response might reduce the rate of postoperative complications, although the impact of such strategies on long term outcomes is as yet unknown. Future research in this area might examine various methods of attenuating the postoperative systemic inflammatory response; including anaesthetic techniques, the use of minimally invasive surgery, and pharmacological techniques such perioperative steroids and other anti-inflammatory drugs, and their impact on short and long term outcomes after surgery for colorectal cancer.

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Acknowledgements

Thank you to my friends and family, especially my wife Claire, daughter Eilidh and son Matthew, for putting up with me during this period of research.

Thanks to my brother Callum for giving his time and expertise in proof reading this work

Thanks to Professor Paul Horgan for allowing me to complete this period of research and for providing me with a salary during it.

Thanks to Professor Donald McMillan for providing, in abundance, his time, guidance, and expert editorial eye during the creation of this thesis.

Thanks to my colleagues and the other research fellows within our team who were a constant source of encouragement, wit, and reasons for procrastination.

Final thanks should go to the clinicians and patients of the Glasgow Royal Infirmary Department of Coloproctology, without whom there would be no such research.

Author's Declaration

The work presented in this thesis was undertaken during a period of research between 2014 and 2017 in the University of Glasgow Academic Unit of Surgery, at Glasgow Royal Infirmary, during which time I maintained the colorectal cancer database. The work was completed whilst working as a Specialty Registrar in General Surgery in the West of Scotland Deanery between 2017 and 2018.

I declare that the work presented in this thesis was undertaken by myself, except where indicated below:

- Data regarding postoperative complications and the postoperative systemic inflammatory response prior to 2014 were collected by the respective research fellows maintaining the database at the time: Mr Campbell Roxburgh, Mr Colin Richards, Ms Michelle Ramanathan, Mr James Park. I retrospectively categorised all complication data by Clavien Dindo grade and applied new threshold values prior to my analysis, interpretation, and presentation.

- Assistance with the capture and analysis of CT scan images used to derive values of body composition was provided by Dr Douglas Black, Specialty Registrar in Radiology, West of Scotland Deanery (Chapter 6).

- Assistance with data collection was provided by Mr Bo Khor, undergraduate medical student, University of Glasgow (Chapters 7 and 10).

- Data regarding the time of patients entering and leaving theatre (Chapter 7) were supplied by Mr Stephen Leonard, Theatre Utilisation Data Coordinator, Anaesthetics and Theatres, NHS Greater Glasgow and Clyde.

- The Dokkyo Medical University postoperative colorectal resection database (Chapter 11) is collected and maintained by Professor Mitsuru Ishizuka, who permitted its use.

Publications

The work presented in this thesis has resulted in the following published papers:

McSorley ST, Ramanathan ML, Horgan PG, McMillan DC. Postoperative C-reactive protein measurement predicts the severity of complications following surgery for colorectal cancer. Int J Colorectal Dis 2015;30(7):913-917

McSorley ST, Horgan PG, McMillan DC. The impact of the type and severity of postoperative complications on long-term outcomes following surgery for colorectal cancer: a systematic review and meta-analysis. Crit Rev Oncol Hematol 2016;97:168-177

McSorley ST, Horgan PG, McMillan DC. The impact of preoperative corticosteroids on the systemic inflammatory response and complications following surgery for gastrointestinal cancer: a systematic review and meta-analysis. Crit Rev Oncol Hematol 2016;101:139-150

McSorley ST, Watt DG, Horgan PG, McMillan DC. Postoperative systemic inflammatory response, complication severity, and survival following surgery for colorectal cancer. Ann Surg Oncol 2016;23(9):2832-2840

McSorley ST, Jones I, McMillan DC, Talwar D. Quantitative data on the magnitude of the systemic inflammatory response and its relationship with serum measures of iron status. Trans Res 2016;176:119-126

Khor BY, McSorley ST, Horgan PG, McMillan DC. The relationship between systemic inflammation and stoma formation following anterior resection for rectal cancer: a cross-sectional study. Int J Surg 2017;37:79-84

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complications following surgery for colorectal cancer. Ann Surg Oncol 2017;24(8):2104-2112

McSorley ST, Black DH, Horgan PG, McMillan DC. The relationship between tumour stage, systemic inflammation, body composition and survival in patients with colorectal cancer. Clin Nutr 2018;37(4):1279-1285

Kelly AU, McSorley ST, Patel P, Talwar D. Interpreting Iron studies. BMJ 2017 doi: 10.1136/bmj.j2513

The work presented in this thesis has resulted in the following published letters:

McSorley ST, Roxburgh CS, Horgan PG, McMillan DC. Re: Dexamethasone versus standard treatment for postoperative nausea and vomiting in gastrointestinal surgery: a randomised controlled trial (DREAMS Trial). BMJ 2017 [Epub] http://www.bmj.com/content/357/bmj.j1455/rr-0 as of 25/04/2017

McSorley ST, Mansouri D, Horgan PG, McMillan DC. Comment on “The important role for intravenous iron in perioperative patient blood management in major abdominal surgery: a randomized controlled trial”. Ann Surg 2018;267(3):e49

Presentations

The work presented in this thesis has resulted in the following presentations:

Postoperative C-reactive protein measurement predicts the severity of complications following surgery for colorectal cancer. Digestive Diseases Week, Washington DC, USA 2015 (poster)

Complication type and severity have an adverse effect on long term oncological outcome following surgery for colorectal cancer. Digestive Diseases Week, Washington DC, USA 2015 (oral)

The relationship between systemic inflammation and postoperative outcomes following neoadjuvant chemoradiotherapy for rectal cancer. ASCO GI Cancer Symposium, San Francisco, USA 2016 (poster)

The impact of preoperative dexamethasone on the postoperative systemic inflammatory response and complications following surgery for colorectal cancer. ASCO GI Cancer Symposium, San Francisco, USA 2016 (poster)

The relationship between CPET, the postoperative systemic inflammatory response, and complications following surgery for colorectal cancer. ACPGBI, Edinburgh, UK 2016 (poster)

The relationship between systemic inflammation and stoma formation following anterior resection for rectal cancer. West of Scotland Surgical Association, Glasgow, UK 2016 (poster)

Dedication

Dedicated to the memory of Stewart Smith, my friend. This thesis describes the illness which took his life in the prosaic, dry and objective language required of medical research. He is a constant reminder to me of the personal story underlying each case, patient and statistic. His bravery and good humour lifted us in those dark moments and made the most of what time we had.

Definitions/Abbreviations

5-FU 5-Fluorouracil

AICR American Institute for Cancer Research

AJCC American Joint Committee on Cancer

APC Adenomatous Polyposis Coli

APCS Antigen Presenting Cells

APR Abdominoperineal resection

AR Anterior Resection

AT Anaerobic Threshold

ATP Adenosine Triphosphate

ASA American Society of Anesthesiology

ATE Average Treatment Effect

BMI Body Mass Index

CARS Compensatory Anti-inflammatory Response Syndrome

CD Cluster Determinant

C-D Clavien Dindo Grade

CEA Carcino-Embryonic Antigen

CI Confidence Interval

CIMP CpG Island Methylator Phenotype

CLR Crohn's Like Reaction

CNS Central Nervous System

COX Cyclo-Oxygenase

CPET/CPEX Cardiopulmonary Exercise Testing

CRM Circumferential Margin

CRLM Colorectal Liver Metastases

CRUK Cancer Research United Kingdom

CRP C-reactive protein

CSS Cancer Specific Survival

CT Computed Tomography

CVA Cerebrovascular Accident

DDC Deleted in Colorectal Cancer

DFS Disease Free Survival

DMU Dokkyo Medical University

DNA Deoxyribonucleic Acid

ECG Electrocardiogram

EGFR Epidermal Growth Factor Receptor

ELAPE Extralevator Abdominoperineal Excision

EMR Endoscopic Mucosal Resection

ERAS Enhanced Recovery After Surgery

ESR Erythrocyte Sedimentation Rate

FAP Familial Adenomatous Polyposis

FDG PETCT Fluoro-Deoxy-Glucose Positron Emission Tomography Computed Tomography

FID Functional Iron Deficiency

FIT Faecal Immunochemical Test

gFOBT guaiac Faecal Occult Blood Tests

GFR Glomerular Filtration Rate

GI Gastrointestinal

GPI Gloucester Prognostic Index

GMS Glasgow Microenvironment Score

GPS Glasgow Prognostic Score

GRI Glasgow Royal Infirmary

H&E Haematoxylin and Eosin

H2RA H2 Receptor Antagonist

HIF Hypoxia Inducible Factor

HNPCC Hereditary Non-Polyposis Colorectal Cancer/Lynch syndrome

HPA Hypothalamic-Pituitary Axis

HR Hazard Ratio

HU Hounsfield Units

IBD Inflammatory Bowel Disease

ICCC Intra-class Correlation Coefficient

ICU Intensive Care Unit

IGF-1 Insulin-like Growth Factor 1

IHC Immunohistochemistry

IL Interleukin

IQR Interquartile Range

ISD Information Services Division

LDH Lactate Dehydrogenase

LH Left Hemicolectomy

LMR Lymphocyte to Monocyte Ratio

MCT Monocarboxylate Transporter

MDT Multi-Disciplinary Team

MI Myocardial Infarction

MMP Matrix Metalloproteinases

MMR Mismatch Repair

MO Myopenic Obesity

MRI Magnetic Resonance Imaging

MSI Microsatellite Instability

MSS Microsatellite Stable

nCRT neoadjuvant Chemoradiotherapy

NHS National Health Service

NICE National Institutes for Health and Clinical Excellence

NK Natural Killer cells

NLR Neutrophil to Lymphocyte Ratio

NPS Neutrophil Platelet Score

NPV Negative Predictive Value

NSAID Non-Steroidal Anti-Inflammatory Drug

OR Odds Ratio

OS Overall survival

PLR Platelet to Lymphocyte Ratio

POD Postoperative Day

PPV Positive Predictive Value

PRCs Packed Red Cells

RAAS Renin Angiotensin Aldosterone System

RH Right Hemicolectomy

ROI Region of Interest

RSI Remote Site Infection

SD Standard Deviation

SFA Subcutaneous Fat Area

SFI Subcutaneous Fat Index

SIGN Scottish Intercollegiate Guidelines Network

SIR Systemic Inflammatory Response

SIRS Systemic Inflammatory Response Syndrome

SMA Skeletal Muscle Area

SMD Skeletal Muscle Radiodensity

SMI Skeletal Muscle Index

SSI Surgical Site Infection

T2DM Type 2 Diabetes Mellitus

TAM Tumour Associated Macrophage

TAMIS Trans-Anal Minimally Invasive Surgery

TC Total Colectomy

TCR T-Cell Receptor

TEM Trans-anal microsurgery

TGF Transforming Growth Factor

TFA Total Fat Area

TFI Total Fat Index

TME Total Mesorectal Excision

TNF Tumour Necrosis Factor Alpha

TNM Tumour Nodes Metastasis

TS Thymidylate Synthase

TSP Tumour Stroma Percentage

UC Ulcerative Colitis

UICC Union for International Cancer Control

UK United Kingdom

USA United States of America

USS Ultrasound Scan

UTI Urinary Tract Infection

VEGF Vascular Endothelial Growth Factor

VFA Visceral Fat Area

VFI Visceral Fat Index

VO Visceral Obesity

VO_2 oxygen consumption

VTE Venous Thromboembolism

WCC White Cell Count

WCRF World Cancer Research Fund

WHO World Health Organisation

1 Introduction

1.1 Epidemiology of colorectal cancer

1.1.1 In the United Kingdom

Colorectal cancer is the fourth most common cancer amongst men and women in the UK, and is the second leading cause of cancer death behind lung cancer. In 2013, there were around 41,000 new cases of colorectal cancer in the UK, which accounts for around 12% of all new cancer diagnoses (CRUK, 2013). In the period of time 2011-2013 its incidence had increased 5% when compared to 2001-2003, with a slightly higher rate of new cases in men (56%) (CRUK 2013). Over half of all new cases each year are diagnosed in those over 70 years old.

As of 2011, in both sexes, only around 59% of those diagnosed with colorectal cancer survived 5 years or longer, however this figure increases to over 90% in stage I disease and drops to less than 10% in those with stage IV disease. Furthermore, survival at 5 years following diagnosis with colorectal cancer continues to improve, having been only 49% in 2001 (CRUK 2011). Alongside ongoing improvements in treatment, a significant contributor to this is thought to be surgical subspecialisation, with the surgical treatment of colorectal cancers now only performed by specialist colorectal surgeons (Oliphant et al. 2013). Earlier presentation and diagnosis may also play a part in this survival improvement, and with the ongoing introduction of screening programmes throughout the UK this may come to be a more important factor.

In Scotland around 4,000 new cases of colorectal cancer are diagnosed each year. The statistics relating to increasing incidence, distribution by sex, and proportion of patients alive at 5 years are comparable to those for the UK as a whole (NHS ISD 2016).

1.1.2 Worldwide

In 2008 it was estimated that there were over 1.2 million new cases of colorectal cancer, with an estimated worldwide prevalence of over 3 million people in 2006 (Ferlay et al. 2010). The highest rates occur in the developed world: Europe, North America and Australasia, with a lower incidence in South East Asia and South America, and the lowest in Africa (Kamangar et al. 2006). However, nations outside of those traditionally defined as “the West” are seeing an increase in the incidence of colorectal cancer, presumably due to changes in lifestyle and exposure to other risk factors (Ferlay et al. 2013a).

In Europe, colorectal cancer has a fairly similar distribution to that of the UK, comprising 13% of all new cancer diagnoses, however the UK has been reported to have poorer rates of survival (Sant et al. 2009). It has been suggested that this may relate to greater delayed presentation and poorer treatment outcomes in the UK, however care must be taken in interpretation of these findings due to significant differences in risk factor exposure, the use of screening programmes, diagnostic methods, and treatment protocols between countries. Indeed, significant variation in both the incidence of, and survival with, colorectal cancer, is found between other European countries and not just with the UK (Ferlay et al. 2013b).

1.2 Aetiology of colorectal cancer

Colorectal cancer, as it is presently understood, is a heterogeneous condition which is likely to represent an umbrella for a number of different diseases with varying genetic origins. It is thought to occur over a relatively long period time with the accrual of genetic alterations gradually causing normal epithelium to become dysplastic then overtly malignant.

The majority of colorectal cancers (98%) are adenocarcinomas, whilst the remainder are of either adenosquamous or adenocarcinoid carcinoma type histology. In addition, a variety of benign tumours and hamartomas can affect the colon and rectum however are usually not considered colorectal cancer. Rectal cancers are the most common single site with around 35-40% of all newly diagnosed tumours, followed by around 30% in the sigmoid and descending colon. Colorectal cancers spread through multiple mechanisms including direct invasion of adjacent organs, via the portal venous system, lymphatics, and transcoelomic means.

Between 10% and 20% of colorectal cancers will occur in patients who have a similarly affected first degree relative (Burt et al. 2005). Of this group, around one in four will be found to have a specific inherited genetic mutation which predisposes them to the disease (Ponz de Leon et al. 2004). The remainder, and majority of new cases of colorectal cancer, are sporadic in nature and a mixture of genetic and environmental factors are thought to contribute to the development of the disease in these cases (Brenner et al. 2014). A number of different carcinogenesis pathways have been described, mainly through work on the hereditary forms of colorectal cancer, each of which have different implications for clinical management and outcomes (Sadanandam et al. 2013).

1.2.1 Adenoma carcinoma sequence

Dysplastic adenomatous polyps of the colon and rectum are by far the most common premalignant precursor lesion in sporadic colorectal cancer (Jass 2007). The original multi-step model which describes the development of these adenomas and the progression of dysplasia to invasive malignancy through the accrual of specific somatic genetic mutations, known as the “adenoma carcinoma sequence”, was first described by Fearon and Vogelstein over twenty-five years ago (Vogelstein et al. 1988). The entire process is heavily associated with chromosomal instability, i.e. changes in both the number and

structure of chromosomes, and loss of heterozygosity through point mutation, rendering the individual susceptible to deletion of a remaining functional proto-oncogene or tumour suppressor gene (Lengauer et al. 1997).

The first step in the traditional sequence is deletion of the adenomatous polyposis coli (APC) gene which gives rise to the colorectal adenoma itself, and is a defect found in 70% of these types of polyps (Kinzler et al. 1996). Subsequent mutations in the K-ras oncogene promotes both growth and progressive dysplastic change of the polyp, followed by loss of the p53 tumour suppressor gene which allows progression to the final part of the sequence: adenocarcinoma (Fearon 2011).

This model, although valuable, is now recognised to be over simplistic. Even within those sporadic tumours which develop from adenomatous polyps, it is now recognised that the accrual of mutations in a variety of oncogenes and tumour suppressor genes such as src, myc, wnt, E-Cadherin, SMAD4, and many others, is likely to be an important factor and also explains the variation in genetic profiles found between colorectal cancers (Wood et al. 2007, Chittenden et al. 2008)

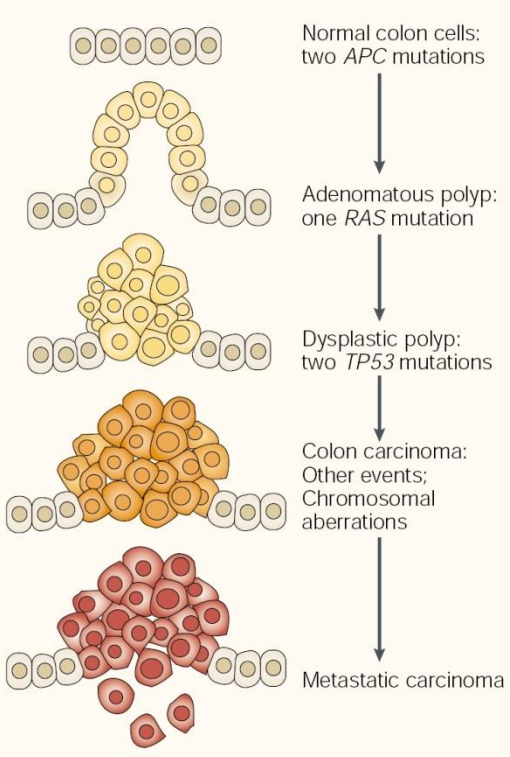

Figure 1-1:The adenoma carcinoma sequence (adapted from Fearon et al. 1990)

1.2.2 Microsatellite instability

High frequency microsatellite instability (MSI-H) is found in both around 15% of sporadic colorectal cancers and in the majority of patients with Hereditary Non-Polyposis Colon Cancer (HNPCC) (Aaltonen et al. 1993, Thibodeau et al. 1998). These microsatellites are repetitive sequences of DNA found randomly throughout the human genome. Microsatellite instability is thought to be caused by deficient or defective DNA mismatch repair (MMR) and is associated with an accumulation of base pair mismatches and alteration in the length of the microsatellite sequences following DNA replication. The same MMR deficiency is thought to allow the accumulation of mutations which are associated with carcinogenesis.

Tumours are described as having high frequency microsatellite instability (MSI-H) if 2 or more of 5 validated microsatellites (D2S123, D5S346, D17S250, BAT-25 and BAT-26) are found to be unstable, having low frequency microsatellite instability (MSI-L) if one is found to be unstable, whilst the remainder are classified microsatellite stable (MSS) (Boland et al. 1998).

In HNPCC (described in more detail below), mutations in one of six DNA MMR genes (MLH 1, MSH 2, MSH 3, MSH 6, PMS 1 and PMS2) can give rise to MSI (Papadopoulos et al. 1997). In contrast, in sporadic colorectal cancers with the MSI-H phenotype, MMR deficiency is thought to arise as an epigenetic phenomenon, due to MLH-1 silencing by hypermethylation of its gene promoter region (Kane et al. 1997).

Sporadic MSI-H colorectal cancers, in general, tend to be found in the right colon, in the elderly, are more likely to have associated synchronous lesions, and are less likely to have associated metastases at diagnosis (Jung et al. 2012). MSI-H tumours are associated with a significant local lymphocytic inflammatory, or “Crohn’s like”, response (Dolcetti et al. 1999). It has been suggested that this relates to the creation of multiple tumour epitopes in the form of truncated proteins resulting from DNA MMR errors (Schwitalle et al. 2008). It is postulated that this is why MSI-H tumours are associated with better prognosis (Popat et al. 2005, Galon et al. 2006) and that microsatellite status may predict treatment response, although the present evidence for this is somewhat conflicting (Bertagnolli et al. 2009).

1.2.3 Hypermethylation and the hyperplastic/serrated polyp pathway

Hyperplastic colonic polyps have long been known about and, until fairly recently, were considered almost universally benign. Some, in particular serrated adenomas, are now thought to represent premalignant precursor lesions for a type of colorectal cancer which does not follow the traditional adenoma carcinoma sequence, but is more closely associated with cancers which occur through microsatellite instability (Bettington et al. 2013). Indeed, it is thought that the silencing of tumour suppressor genes through hypermethylation of promoter and regulatory regions leads to eventual carcinogenesis rather than mutation of the genes themselves (Ferracin et al. 2008). More specifically in colorectal cancer, specific epigenetic hypermethylation gives rise to the CpG Island Methylator Phenotype (CIMP) (Issa 2004). In particular, hypermethylation of the MLH 1 gene promoter region gives rise to sporadic MSI-H tumours as discussed above, with a similar pathological and clinical phenotype (Herman et al. 1998). It must also be noted that CIMP positivity can be found in MSS colorectal cancers. However, the considerable overlap between MSI and CIMP, along with their relationships with the oncogenes BRAF and K-ras (discussed in detail later), is in part what has lead researchers to attempt to classify colorectal cancers into discrete molecular subtypes as described below.

1.2.4 Molecular subtypes of colorectal cancer

As already stated, colorectal cancer is a heterogeneous disease in terms of its genetics, pathology, and response to therapy. Recent consensus has been reached on the categorisation of colorectal cancer into four discrete subtypes based on patterns of genetic abnormality and gene expression: MSI Immune, Canonical, Metabolic, and Mesenchymal (Table 1.1) (Guinney et al. 2015). The aim of this work is to make collaboration and comparison across future preclinical and clinical studies in colorectal cancer easier. However, concerns have been raised that the presence of variability in gene expression even within different areas of a single tumour, so called tumour heterogeneity, may undermine this proposed categorisation (Dunne et al. 2016).

Table 1-1: Consensus molecular subtypes of colorectal cancer (adapted from Guinney et al. 2015)

CMS 1 **MSI Immune**	**CMS 2** **Canonical**	**CMS 3** **Metabolic**	**CMS 4** **Mesenchymal**
14%	37%	13%	23%
MSI, CIMP high, hypermutation BRAF mutations	SCNA high	Mixed MSI status, SCNA low, CIMP low K-ras mutations	SCNA high
Immune infiltration	WNT and MYC activation	Metabolic deregulation	Expanded tumour stroma, TGF-β activation, angiogenesis

CMS colorectal molecular subtype, MSI microsatellite instability, SCNA somatic copy number alterations, CIMP CpG island methylator phenotype

1.3 Inherited forms of colorectal cancer

Inherited forms of colorectal cancer account for around 5% of all new cases in the developed world, and their understanding has lead to much of what is known regarding carcinogenesis pathways in colorectal cancer (Jasperson et al. 2010).

1.3.1 Familial adenomatous polyposis

Familial adenomatous polyposis (FAP) is an autosomal dominant condition, the underlying genetic abnormality being germline mutation of the APC tumour suppressor gene (Segditsas et al. 2006). Almost all affected patients will develop colorectal cancer by middle age if left untreated, due to the development of hundreds of colonic adenomas, some of which will inevitably undergo malignant transformation following the adenoma carcinoma sequence (Fearnhead et al. 2002). Despite prophylactic colectomy, cancer is still a major cause of death in these patients due to the association between FAP and extra-colonic lesions including desmoids tumours, pancreatic mucinous lesions, and hepatoblastoma (Belcehtz et al. 1996).

1.3.2 Hereditary non-polyposis colon cancer

Hereditary non-polyposis colon cancer (HNPCC, or Lynch syndrome), is an autosomal dominant inherited condition which confers those affected a 60-80% lifetime risk of colorectal cancer (Lynch et al. 1999). As already discussed, HNPCC is caused by germline mutations in one or more of 6 genes associated with DNA mismatch repair (MMR): MLH 1, MSH 2, MSH 3, MSH 6, PMS 1 and PMS 2, causing HNPCC tumours to have high frequency microsatellite instability (MSH-H) and the associated "Crohn's like" inflammatory infiltrate (Boland et al. 2010). Patients with HNPCC are more likely to have a right sided lesion, synchronous disease, and are at increased risk of extracolonic malignancy, in particular endometrial, ovarian, gastric, ureteric, hepatobiliary, and small bowel tumours (Watson et al. 1994). Diagnosis of HNPCC is based on assessment of the patient and their family history using one of two commonly used guidelines; the Revised Bethesda Guidelines (Umar et al. 2004) and the Amsterdam II Criteria (Vasen et al. 1999), followed by laboratory testing to identify specific genetic mutations. There is some evidence to suggest that the broader Revised Bethesda Guidelines more accurately identify those patients with underlying deficient MMR (Jung et al. 2016).

1.3.3 Hamartomatous polyposis syndromes

The hamartomatous polyposis syndromes represent a rarer group of mostly autosomal dominantly inherited diseases associated with the development of colorectal cancers and extracolonic tumours (Calva et al. 2008). The group of disease includes Juvenile Polyposis, Peutz-Jeghers disease, and PTEN Hamartoma Tumour Syndrome (of which Cowden's disease predominates in adults), which carry a colorectal cancer risk of 39-68%, 39-57%, and 18% respectively (Campos et al. 2015). The mechanism by which hamartomatous polyps progress to invasive malignancy is closely linked to the activity of each of the causal mutations but lies outside of those carcinogenesis pathways already discussed.

1.4 Acquired risk and preventative factors for colorectal cancer

Unlike some cancers, e.g. lung, in which a single acquired risk factor accounts for the majority of sporadic new cases, multiple risk factors and preventative factors are thought to relate to the aetiology of colorectal cancer. Indeed, many of these factors are interrelated and co-exist, some having an additive or multiplicative impact on risk (Brenner et al. 2014).

1.4.1 Age

Increasing age is a significant risk factor for sporadic colorectal cancer, with over 50% of new cases in those over 70 years of age (CRUK). Indeed, ageing is associated with a number of cancer types, and there are several theories as to why this might be the case (Smith et al. 2009). Increasing age allows for an increasing total exposure to environmental factors associated with the development of cancer. Methylation of DNA occurs to greater extent as time passes, which may relate to the length of time exposed to oxidative stressors, and can result in gene silencing (Adams et al. 2015). At a chromosomal level telomeres degrade with time. These chromosomal caps are thought to protect the structural integrity of chromosomes and so their shortening may allow for chromosomal instability (Hackett et al. 2003).

1.4.2 Diet

The hypothesis that the contact of carcinogens within digested food-stuff with the colorectal mucosa might increase the risk of colorectal cancer was first postulated in the 1970's following observational studies suggesting that diets higher in fibre, with faster colonic transit, were associated with reduced incidence of colorectal cancer (Burkitt 1971, Armstrong et al. 1975). However, prospective studies published since have reported conflicting results and a more recent large meta-analysis of these prospective studies reported that, after adjustment for other known risk factors, dietary fibre was not independently associated with colorectal cancer incidence (Park et al. 2005). However, other elements of diet are thought to represent a significant modifiable risk factor in colorectal cancer through the same mechanism.

A recent meta-analysis of prospective studies investigating both fresh red meat and processed meat consumption reported that both types of food were associated with

increased risk of colonic and rectal cancer, with a non-linear dose-response relationship (Chan et al. 2011). Indeed, the World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) consensus statement suggests that individuals should limit their intake of red meat, processed meats, and animal fat (AICR 2007).

In contrast there is good evidence that the consumption of essential fatty acids, especially through fish oil and diets relatively high in fish, is associated with a modest reduction in the risk of colorectal cancer (Wu et al. 2012). These fish oil omega fatty acids are thought to reduce colorectal carcinogenesis by anti-inflammatory action, through inhibition of cyclo-oxygenase (COX), and direct effects on colonic mucosal cell proliferation (Caygill et al. 1996, Larsson et al. 2004). In addition, a meta-analysis of prospective studies has reported that diets high in fruit and vegetables are associated with reduced incidence of colorectal cancer (Aune et al. 2011), although the evidence for individual antioxidant vitamins A, C, and E, and the group of carotenoids, is less clear (Murtaugh et al. 2004, Mannisto et al. 2007). Furthermore, a pooled analysis of 9 prospective observational studies has reported an association between dietary vitamin D and calcium supplementation and a reduced risk of colorectal cancer (Ma et al. 2011). However, a recent randomised controlled trial of vitamin D in women who had just completed colonoscopy found no reduction in the risk of adenomatous polyp recurrence at follow up surveillance colonoscopy (Baron et al. 2015). It may be that vitamin D reduces the risk of malignant progression of existing polyps rather than reducing polyp formation.

1.4.3 Obesity

Increasing body mass index (BMI), particularly into the obese category of >30kg/m^2, is now well recognised to be associated with increased risk of colorectal cancer (Ma et al. 2013). Central obesity especially seems to have an important role, with the appearance of a dose-response relationship between waist circumference and colorectal cancer risk (Moghaddam et al. 2007). Obesity is strongly related to other risk factors for colorectal cancer including diabetes, diet, exercise, and deprivation. However, obesity may well contribute to colorectal carcinogenesis in its own right. Adipocytes, particularly those of visceral fat found in central obesity, are neurohormonally and immunologically active cells. It has been suggested that they chronically produce cytokines and pro-inflammatory mediators which may influence carcinogenesis (McMillan et al. 2006). In addition, leptin, produced by adipocytes as part of the satiety response, may be involved in the development of colorectal cancer (Frezza et al. 2006).

1.4.4 Exercise

Although levels of physical activity are often related to other colorectal cancer risk factors such as obesity, age, smoking, and cardiovascular disease, in the case of colorectal cancer there also appears to be a protective effect independent of these confounders (Colditz et al. 1997). Indeed, several meta-analyses have reported that exercise and physical activity reduce the risk of developing colorectal cancer (Wolin et al. 2007, Boyle et al. 2012). The WCRF and AICR consensus statement suggests that any increase in levels of physical activity should confer some degree of risk reduction (AICR 2007). Hypotheses as to why this should be the case include faster colonic transit in the physically active, exercise induced immunomodulation, and hormonal changes e.g. lower levels of circulating prostaglandins in those who are active (Samad et al. 2005).

1.4.5 Alcohol

Several recent meta-analyses have reported that alcohol intake is associated with colorectal cancer risk in a dose dependent manner (Fedirko et al. 2011, Bagnardi et al. 2015). There are several possible mechanisms by which alcohol may have its carcinogenic effect including its metabolites, particularly acetaldehyde (Boffetta et al. 2006), impairment of folic acid absorption (Hamid et al. 2009), and alterations in production of oestrogens and androgens (Singletary et al. 2001).

1.4.6 Smoking

Tobacco smoking is associated with the production of numerous harmful and carcinogenic compounds, some of which are recognised to impact on the gastrointestinal tract epithelium (Jensen et al. 2012). A meta-analysis of 106 observational studies reported a significant association between cigarette smoking and the development of colorectal cancer, related to the number of pack years, but only becoming statistically significant after 3 decades of smoking history (Botteri et al. 2008).

1.4.7 Systemic inflammation

It is now clear that cancer, including that of the colon and rectum, and inflammation are intimately linked. Indeed, the presence of inflammation is now considered a hallmark of cancer, primarily as a factor promoting growth and metastases (Hanahan et al. 2011). Furthermore, the presence of systemic inflammation has been shown to predict poorer prognosis in a variety of cancers independent of stage (McMillan 2013). In addition to its impact on established cancer, described in more detail below, there is good evidence to suggest that the presence of inflammation is associated with the subsequent development of colorectal cancer (Erlinger et al. 2004). Clinical trials of anti-inflammatory medications have been shown to reduce the risk of development of colorectal cancer in high risk groups, discussed in more detail below (Burn et al. 2011). However, systemic inflammation is also associated with numerous other risk factors for colorectal cancer including obesity, diabetes mellitus, and cardiovascular disease (Freeman et al. 2002, Choi et al. 2013, Stancel et al. 2016). Therefore, it remains unclear whether systemic inflammation is an independent risk factor for the development of colorectal cancer or whether it is related in a greater degree to other associated factors.

1.4.8 Medication

A number of medications have been found to affect colorectal cancer risk, several of which have been key in elucidating potential mechanisms of carcinogenesis or disease progression.

1.4.8.1 Aspirin and non-steroidal anti-inflammatory drugs

Evidence that the non-steroidal anti-inflammatory group of drugs (NSAIDs) might reduce the risk of formation of colorectal adenomas, and colorectal cancer, was first reported in patients with the heritable forms of the disease (Giardiello et al. 1993), and in the CAPP trials of aspirin (Burn et al. 2011). These findings have been extended to sporadic forms of the disease, with reduction in risk apparent after around 10 years of exposure (Vinogradova et al. 2007). NSAIDs primarily act via inhibition of the cyclo-oxygenase (COX) pathway, and one potential mechanism of action is that the resultant reduction in prostaglandin synthesis has anti-proliferative effects alongside a reduction in platelet activation, reducing downstream cytokine release (Cha et al 2007). The more selective COX-2 inhibitors have been found to be similarly efficacious, which is of interest as a proportion of colorectal

cancers over express COX-2 (Harris et al. 2008). In addition, NSAIDs are believed to interact with the Wnt/β-catenin/NF-κB and PI3K/AKT pathways (Grosch et al. 2006). Furthermore, it is thought that NSAIDs may have direct effects on the local microenvironment and inflammatory response, described in more detail below (Park et al. 2014a). Despite such promising results, concerns regarding adverse drug events have prevented the adoption of these drugs as primary chemoprevention (US Preventive Services Task Force 2007).

1.4.8.2 Statins

The HMG-CoA reductase inhibitors, or "statins", are a group of drugs primarily used for the treatment of hypercholesterolaemia and in cardiovascular secondary prevention. They have, however, been found to be associated with a modest reduction in the risk of colorectal cancer (Bonovas et al. 2007, Bardou et al. 2010). These anti-carcinogenic effects are thought to relate to statins' pleiotropic effects on cell proliferation, cellular response to oxidative stress, angiogenesis, and inflammation (Park et al. 2014a). Some of these pathways are mediated via downstream activity of HMG-CoA reductase, and some are independent of this pathway (Hindler et al. 2006, Coogan et al. 2007).

1.4.8.3 H2 receptor antagonists

Several studies have examined the potential survival benefit from the use of H2 receptor antagonists (H2RAs), such as cimetidine, in patients with colorectal cancer, with a recent Cochrane review suggesting a modest survival benefit as an adjuvant therapy in patients with resected disease (Deva et al. 2012). The underlying mechanism for this action is yet to be fully accounted for. H2RAs have been shown to increase the bioavailability of 5-fluorouracil (5-FU), a common adjuvant chemotherapeutic agent (Harvey et al. 1984). In addition, H2RAs have been shown to impact T-lymphocyte and natural killer cell (NK) activity at both the local and systemic levels (Nielsen et al.1995, Kelly et al. 1999). Furthermore, histamine is associated with cyclo-oxygenase dependent inflammatory pathways, and it may be that H2RAs reduce the risk of cancer recurrence through this pathway (Cianchi et al. 2005).

1.4.8.4 Metformin

Metformin is a widely used drug which reduces peripheral insulin resistance in patients with type 2 diabetes mellitus (T2DM). It has been shown to reduce the risk of developing colorectal cancer, and of disease recurrence, particularly in diabetic patients (He et al. 2016). Metformin is thought to have multiple modes of action which relate to the mechanisms by which diabetes increases the risk of colorectal cancer (discussed in more detail below). These include the inhibition of growth factors such as insulin, insulin-like growth factor 1 (IGF-1), and leptin via the AMPK pathway (Sedhev et al. 2015).

1.4.9 Acquired conditions associated with colorectal cancer

1.4.9.1 Inflammatory bowel disease

The group of inflammatory bowel diseases (IBD) of which Crohn's disease and ulcerative colitis (UC) predominate form one of the single largest risk factors for colorectal cancer outside of the heritable forms and family history (Jess et al. 2012a). Indeed, it is thought that around 1 in 6 deaths in patients with UC (Jess et al. 2012b), and 1 in 12 deaths in patients with Crohn's disease are due to colorectal cancer (Jess et al. 2004). Although patients with IBD tend to develop colorectal cancer at an earlier age than other sporadic cases of colorectal cancer, their prognosis once diagnosed is the same as those patients without IBD (Rhodes et al. 2002). IBD is a chronic inflammatory disease of the gastrointestinal tract, therefore it is thought that the chronic exposure to pro-inflammatory cytokines leads to dysplasia and eventual carcinogenesis as described above. Indeed, studies suggest that the degree of local inflammation, determined at endoscopy and by histology, relates to the risk of development of colorectal cancer (Rutter et al. 2004, Nieminen et al. 2014)

1.4.9.2 Diabetes mellitus

A recently updated meta-analysis of observational studies reports a significantly higher incidence of colorectal cancer amongst patients with diabetes mellitus (DM) (Wu L et al. 2013). Furthermore, patients with DM who develop colorectal cancer are more likely to die of the disease than those without, although no distinction was made between types 1 and 2 DM (Jiang et al. 2011). In particular, type 2 diabetes is associated with peripheral insulin resistance and compensatory hyperinsulinaemia. This in turn leads to higher

circulating insulin-like growth factors (IGFs) which are thought to inhibit apoptosis and promote proliferation of colonocytes (Wu et al. 1995, Giovannuci 2001). Furthermore, insulin resistance is associated with the production of proinflammatory cytokines including TNF-α, IL 6, and leptin, which are thought to have a role in colorectal carcinogenesis as described above (Fernandez-Veledo et al. 2009). There is significant overlap between type 2 DM and obesity, which is also associated with colorectal cancer, and similar mechanisms are likely to be involved.

1.5 Clinical presentation of colorectal cancer

At present, colorectal cancer will be diagnosed in one of three clinical settings; elective presentations, emergency presentations, and through screening of asymptomatic individuals. In the elective setting this usually occurs following either referral to a colorectal surgical clinic, or direct referral to investigation by the General Practitioner based on symptoms. Emergency presentations include acute abdominal pain as a result of colonic perforation or obstruction, and significant rectal bleeding. Resection for colorectal cancer performed in the acute or emergency setting is associated with higher postoperative mortality and poorer 5 year disease free survival (Anderson et al. 1992, McArdle et al. 2004, Oliphant et al. 2014). In the past, emergency presentation might have accounted for between 30% and 40% of new colorectal cancer diagnoses, a proportion which has been in slow but steady decline (Ananda et al. 2016). This is most probably due to multiple factors including public education regarding symptoms of colorectal cancer, referral pathways for primary care, and the introduction of screening.

1.5.1 Symptoms and signs

Elective presentations of new colorectal cancer usually occur due to one, or a combination, of three symptoms: change in bowel habit, abdominal pain or rectal bleeding (Keddie et al. 1968). These symptoms are also common to a variety of other benign colorectal pathologies and therefore diagnosis based on symptoms alone is difficult. For example, change in bowel habit alone has a positive predictive value (PPV) of only 9% for colorectal cancer, however, when combined with rectal bleeding, and increasing age the PPV increases considerably to 35% (Thompson et al. 2007). This clearly still allows for considerable diagnostic error. In some cases, patients present with either symptomatic or asymptomatic iron deficiency anaemia, discussed in more detail below. Less commonly, patients present with clinical signs such as a palpable rectal or abdominal mass, or signs of metastatic disease.

1.5.2 Diagnostic investigations

Colonoscopy (flexible fibreoptic examination of the lumen of the colon following osmotic laxative bowel preparation) is considered the gold standard method for the diagnosis of colorectal cancer in both the symptomatic and in the asymptomatic screening populations.

In addition to lesion visualisation and location, colonoscopy allows for tissue biopsy of any lesions encountered, and even curative endoscopic resection of small polyp cancers. It is however an invasive test and is associated with a colonic perforation rate of around 1 in 2000 tests (Lorenzo-Zuniga et al. 2010).

Computed tomography (CT) colonography (also known as CT pneumocolon and virtual colonoscopy) has superseded double contrast barium enema in the radiological diagnosis of colorectal cancer in the UK. It requires osmotic laxative bowel preparation and the creation of a pneumocolon by rectal catheter insufflation. It has been shown to be as sensitive as colonoscopy in diagnosing established colorectal cancers and polyps larger than 10mm (Halligan et al. 2005, Pickhardt et al. 2011). It has a more favourable short term complication profile than colonoscopy and is able to detect extra-colonic abnormalities (Veerappan et al. 2010). However, if a colonic lesion is detected then the patient will require to undergo colonoscopy to obtain tissue. In addition, a CT colonogram will expose a patient to a not insignificant radiation dose (Liedenbaum et al. 2008). Its use as a potential primary screening tool is currently being investigated, although its use is indicated within the Scottish Bowel Cancer Screening Programme in certain circumstances as described below (de Wijkerslooth et al. 2010).

At present in Scotland, faecal blood based tests including guaiac faecal occult blood tests (gFOBT) and faecal immunochemical tests (FIT) are used only within screening (discussed below) and are not used as diagnostic tests in symptomatic patients.

1.5.3 Scottish Bowel Cancer Screening Programme

The Scottish Bowel Cancer Screening Programme was introduced in a staged manner across Scotland from 2007 onward and is coordinated centrally by the Scottish Bowel Screening Centre in Dundee. All men and women aged between 50 and 74, registered with a General Practitioner in Scotland, are invited to participate. An opt-in system is in place for those patients over the age of 74 who wish to take part in screening. Participants are sent a gFOBT kit and asked to provide 2 samples from 3 separate faecal specimens. These are placed on 6 oval windows, classified as positive if 5 out of 6 windows are positive, and weakly positive if 1- 4 windows are positive. In the case of a weakly positive or inconclusive result, a FIT is completed. The cut-off levels for a positive result for the gFOBT and FIT tests are 600µg Hb/g faeces and 10 µg Hb/g faeces respectively (Fraser et al. 2012). In the case of a negative test the patient is re-invited 2 years later at their next

screening round. Following a positive test result, the local health board is contacted and are responsible for arranging further investigation. Individuals are pre-assessed and undergo colonoscopy if this is deemed suitable. If colonoscopy is unsuccessful then bowel imaging by CT colonography is performed. Early evidence from this screening programme suggests a shift toward earlier disease stage at diagnosis (Mansouri et al. 2015). This should eventually lead to improved survival in colorectal cancer patients, although concerns remain regarding lead time bias and the lack of impact on overall life expectancy in the population as a whole (Hewitson et al. 2007).

1.6 Multidisciplinary management of colorectal cancer

The Scottish Intercollegiate Guideline Network (SIGN) recommend that all patients diagnosed with colorectal cancer be discussed at a specialist colorectal oncology multi-disciplinary team (MDT) meeting, before and after surgery and oncology treatments, composed of specialists likely to be involved in the patient's staging, perioperative, and oncologic care (SIGN 2016). This can include, but is not limited to, a colorectal surgeon, oncologist, radiologist, pathologist, and nurse specialist with subspecialty interest in colorectal cancer. Indeed, there is evidence that the use of MDTs in treatment decision making and planning is associated with improved surgical and long term outcomes for patients with colorectal cancer (Burton et al. 2006, MacDermid et al. 2009).

1.6.1 Neoadjuvant chemoradiotherapy

In the UK, preoperative, or neoadjuvant chemoradiotherapy (nCRT), is primarily indicated in rectal cancers in which there is concern immediate surgical resection would leave involved circumferential margins (CRM) within the pelvis (SIGN 2016). However, nCRT is also often given to patients with T3 or T4 rectal cancers, or where local nodal disease is evident on the staging CT or MRI (Engstrom et al. 2009). In some cases, the use of nCRT can allow anal sphincter preservation in a tumour, which at diagnosis involves the sphincter complex, or would not allow for a clear margin without excision of the sphincters in primary surgery. In the USA, the indications are wider and its use more common. In addition, chemotherapy regimens and external beam radiation dosing strategies vary, and there is yet to be conclusive evidence as to which, if any, is superior in terms of involved CRM rates and longer term outcomes (NICE 2014).

In general, a radio-sensitising chemotherapy agent such as capecitabine, or 5-flurouracil (5-FU) is given, followed by a pre-planned number of fractions of radiotherapy. The high energy photons generated cause both direct damage to DNA and cause the production of reactive oxygen species leading to further DNA and cellular damage. The greatest impact is felt by the metabolically and mitotically active tumour cells, however damage is also caused to surrounding healthy tissue leading to the more common side effects such as skin toxicity, radiation proctitis, enteritis, and cystitis.

Complete clinical (i.e. no tumour on digital or endoscopic examination) and pathological (at the resected specimen) responses can be achieved in around 10-15% of patients in

reported series of nCRT for rectal cancer (Habr-Gama et al. 2010). This represents a potentially significant move away from surgery for certain rectal cancer patients, although the long-term outcomes and appropriate management pathways are at present under investigation.

1.6.2 Surgery

Surgical resection remains the cornerstone of curative management for colorectal cancer. The tumour is resected along with a minimum 5cm margin (or 1cm distally in low rectal cancers) of healthy bowel along with the lymphatic and blood supply, taken as near their origin as possible, within its segment of mesocolon. The last few decades have seen total mesorectal excision (TME) emerge as the gold standard oncologic resection for all rectal cancers due to the significant reduction in local recurrence achieved (Heald et al. 1986). Rectal cancers involving the sphincter complex, or within 8cm of the anal margin, usually require abdominoperineal resection (APR), with excision of the sphincters and formation of an end colostomy. Those with circumferential, margin threatening disease, may require more radical extralevator (ELAPE) and exentrative procedures (Jones et al. 2016). The use of minimally invasive surgical techniques, including laparoscopic surgery and robotic surgery, have been shown to be equivalent to traditional open surgery in terms of long term oncologic outcomes (Kim et al. 2014, Vennix et al. 2014, Jaap Bonjer et al. 2015). Minimally invasive transanal techniques such as TEM and TAMIS have been reported to have acceptable local recurrence rates in early invasive low rectal cancers when completely excised, however, the lack of lymph node tissue within the resected specimen means that distant recurrences can occur unexpectedly (Sajid et al. 2014).

At the time of resection, the decision on whether to create a primary anastomosis, to create a permanent stoma, or indeed to create a temporary stoma to defunction a primary anastomosis will be dependent on numerous patient, anatomical, and tumour factors. Evidence suggests that the more distal an anastomosis the greater the risk of anastomotic dehiscence, and that temporary loop ileostomies may reduce both the likelihood and severity of any subsequent leak (Montedori et al. 2010). Other factors which may encourage temporary stoma formation are those associated with anastomotic leak such as male sex, comorbidities, BMI, prolonged surgery, nCRT, and intraoperative blood loss (McDermott et al. 2015).

1.6.3 Adjuvant chemotherapy

Adjuvant chemotherapy is currently recommended for patients found to have Union for International Cancer Control (UICC) stage III and above (i.e. that with at least lymph node involvement), or high risk stage II disease (SIGN 2016). High-risk stage II disease is most commonly defined as that without any lymph node involvement but with one of the following pathological characteristics which form the Gloucester Prognostic Index (GPI): peritoneal involvement, venous invasion, involved margins, and tumour perforation (Petersen et al. 2002, Morris et al. 2007). In addition, adjuvant therapy is commonly offered to those with T4 disease, and sometimes to patients with an inadequately resected, or sampled, number of lymph nodes, commonly defined as less than 12 (Benson et al. 2004).

Adjuvant chemotherapy has been shown to produce a 10% absolute risk reduction in terms of overall survival in patients with stage III disease (Moertel et al. 1995). It is most commonly commenced at around 6 weeks following surgery to allow for wound healing and initial recovery. There is limited evidence that delay beyond this period is associated with poorer long-term outcomes (Dahl et al. 2009). Regimens commonly include capecitabine, an oral preparation of 5 FU which irreversibly inhibits the enzyme thymidylate synthetase, required for DNA replication. Platinum based oxaliplatin, on the other hand, causes DNA crosslinking which leads to cellular apoptosis.

1.6.4 Follow up of resected disease

There is limited evidence that intensive follow up after surgery for colorectal cancer is associated with small improvements in overall survival (Jeffery et al. 2007). In general, the nature and timing of follow up investigation varies by the risk of disease recurrence as estimated by pathological stage. However, the quality of the evidence is relatively poor. This is partly reflected in the differences between the NICE and SIGN guidelines with regard to follow up (NICE 2014, SIGN 2016). While both bodies agree that a combination of carcinoembryonic antigen (CEA), CT, and colonoscopy should be used, there is debate with regard to timing. The table below shows an example of a follow up protocol which in fact borrows from both the NICE and SIGN guidelines.

Table 1-2: Example of follow up after surgery for colorectal cancer (adapted from the West of Scotland Cancer Network 2016)

Follow-up Pathway	Patient Group	Risk Stratification	Follow-up Year 1			Follow-up Year 2		Follow-up Year 3		Follow-up Year 4	Follow-up Year 5
			6w	6m	1yr	18m	2yr	30m	3yr	4yr	5yr
Patient-directed	Significant co-morbidities	Not fit for adjuvant therapy or further surgery in the event of recurrence	Clinic * ¥	Clinic * ¥	Clinic Discharge ¥						
Post - Surgical Active Follow-up §	Dukes A	Low Risk	Clinic	Clinic CEA	Clinic CT CAP CEA †		Clinic CT CAP CEA		Clinic CT CAP CEA * ¥		Colonoscopy CEA
	Dukes B	Low Risk									
	High Risk Dukes B Dukes C	Missed adjuvant treatment window but would be fit for intervention if required									
Intensive post adjuvant treatment (or offered)	Dukes B	High Risk	Clinic	Clinic CEA	Clinic CT CAP CEA †	Clinic CEA	Clinic CT CAP CEA	Clinic CEA	Clinic CT CAP CEA	CEA	Colonoscopy CEA
	Dukes C	High Risk									

NOTES: * Discharge, as appropriate
† Colonoscopy if not had full colon visualised pre-operatively
¥ Patient and GP should have access to easy referral back to the service via the colorectal CNS in the event of any colorectal concerns
§ Patients who have been identified as requiring regular colonscopic surveillance eg for Lynch syndrome, should continue to receive this

1.6.5 Metastatic disease

Around 20% of patients with colorectal cancer will be found to have extracolonic, or metastatic, disease at presentation. In a small number of these patients, curative treatment options, usually a combination of surgery and oncologic therapies, are pursued. The most common site of colorectal cancer metastasis is the liver. Patients with resectable liver metastases can undergo either synchronous colorectal and liver resection (de Santibanes et al. 2010) or staged resection, usually with the primary lesion being resected first and the liver lesion resected after recovery from the initial surgery (Choti et al. 2002). In addition to cytotoxic adjuvant chemotherapy, cetuximab, a monoclonal antibody targeting the epidermal growth factor receptor (EGFR), has been shown to improve survival in patients with liver metastases and locally advanced disease who are found to have unmutated (or wild type) K-ras (Karapetis et al. 2008).

1.6.6 Palliative treatment

Approximately 80% of those patients with metastatic disease at presentation are found to be unsuitable for management with curative intent due to a number of factors including disease burden, comorbid state, and performance status (Mella et al. 1997). Although there is some evidence that palliative resection of the primary lesion is associated with longer median survival (Park et al. 2013), modern palliative treatment is far more likely to be based on medical treatment options. Palliative cytotoxic chemotherapy has been demonstrated to improve survival in both locally advanced and metastatic colorectal cancer, however not all patients desire this treatment option due to potential toxicities (de

Gramont et al. 2000). Radiotherapy, usually targeted toward pelvic lesions, has proven useful in the management of both pain and bleeding (Bae et al. 2011). In addition, there are still non-resective palliative surgical options such as defunctioning via stoma, intestinal bypass, and colonic stenting, aimed usually at preventing symptoms of intestinal obstruction (Costi et al. 2014). If patients are judged to be unsuitable even for these treatment options, they are referred for best supportive care through palliative care and hospice specialist services.

1.7 Staging colorectal cancer

1.7.1 Preoperative Staging modalities

Preoperative staging is conducted with the aim of determining the optimal management strategy for newly diagnosed patients and, at present, is primarily based on imaging techniques. These techniques, along with the diagnostic colonoscopy, aim to inform the clinicians of the location and size of the tumour, its relation to surrounding structures, and whether there is evidence of nodal or distant metastases. CT of the chest, abdomen, and pelvis is warranted in all cases of colorectal cancer. Additional magnetic resonance imaging (MRI) of the liver may be performed to assess any indeterminate lesions (SIGN 2011). ^{18} Fluorine Fluorodeoxyglucose Positron Emission Tomography Computed Tomography (^{18}F FDG-PETCT) is a biological imaging technique which can be used in the preoperative staging of colorectal cancer patients (O'Connor et al. 2011). ^{18}F FDG-PETCT measures the relative net glucose uptake in tumours, which are much more metabolically active than surrounding normal tissue, using a nuclear tracer. This technique is primarily used to characterise lesions which are indeterminate on CT and MRI imaging but can also detect occult metastatic disease (Jadvar et al. 2009).

Furthermore, in rectal cancers, i.e. tumours within 15cm of the dentate line, MRI of the pelvis is recommended to assess the degree of local, especially circumferential, invasion, the proximity to the anal sphincters and determine the presence of local nodal involvement. It has also been suggested that endoanal ultrasound scanning (USS) may be used in the assessment of rectal cancers, particularly to differentiating T1 and T2 lesions when local excision is being considered. However due to its operator dependency, it is recommended to be used in addition, rather than as an alternative (SIGN 2011).

1.7.2 Histopathology based staging

Following surgical resection, the tumour specimen is processed, usually after formalin fixation, and reported by a pathologist following the Royal College of Pathologists guidelines (Williams et al. 2007). This pathological stage is the most important prognostic indicator and also determines to a large extent whether the patient receives subsequent adjuvant treatments. Staging based on local and distant spread from bowel to lymph nodes in the resected specimen, as a prognostic marker in colorectal cancer, was first described

by Dukes and subsequently modified to include distant organ spread (Dukes et al. 1958, Turnbull et al. 1967). Currently in the UK, the 5th edition of tumour node metastases (TNM) staging system, produced by the American Joint Committee on Cancer (AJCC) and adopted by the UICC, is used. The most recent, 7th edition, of the TNM system is estimated to upstage patients from lymph node negative to node positive disease in around 3% of cases, however this has been estimated to have little additional prognostic value and does not have as established a body of evidence of reliability as the 5th edition (Nagtegaal et al. 2011, Ueno et al. 2012). Several prefixes can be added to the components of the TNM stage, including "c" which denotes clinical staging without pathology from a resected specimen, "p" which denotes pathological staging from the resected specimen, and "y" which denotes the use of neoadjuvant therapy.

Table 1-3: Pathological staging and colorectal cancer specific survival (adapted from CRUK)

Dukes stage	TNM stage	T stage	N stage	M stage	5 year CSS (%)
A	I	T1 – T2	N0	M0	95
B	II	T3 – T4	N0	M0	80
C1	III	T1 – T4	N1	M0	66
C2	III	T3 – T4	N1 - N2 plus apical node	M0	
D	IV	T1 – T4	N0 – N2	M1	7

CSS: cancer specific survival, T1: invades submucosa, T2: invades muscularis, T3: invades through muscularis but not serosa, T4: invades through serosa and/or into adjacent organs, N1: 1-3 lymph nodes involved, N2: >3 lymph nodes involved, M1: distant metastatic disease present

1.8 Pathological and tumour characteristics associated with outcomes

Although tumour stage is the single most important prognostic factor in colorectal cancer, a number of other pathological, metabolic, molecular, and genetic characteristics of the tumour are known to have additional prognostic value. This information can be used to stratify patients in terms of treatment and in some cases has yielded targeted therapies.

1.8.1 Pathological characteristics

A number of pathological features of the resected specimen have been shown to be associated with higher stage disease and poorer survival in patients with colorectal cancer. Poorly differentiated tumours have a more invasive phenotype than well and moderately differentiated tumours, being significantly more likely to have associated nodal involvement (Derwinger et al. 2010) and poorer prognosis in both colonic (O'Connell et al. 2004) and rectal cancers (McDermott et al. 1984).

Tumour budding, the presence of small detached groups of viable tumour cells outside of the main lesion, is thought to represent the invasive front of the tumour, with some believing it to be an important part of the endothelial to mesenchymal transformation pathway, and a marker of local invasiveness. Indeed, increased presence of tumour budding has been reported to be associated with poorer survival in patients with node negative disease (van Wyk et al. 2015).

Venous invasion has been reported to be of particular prognostic significance in patients with node negative disease (Roxburgh et al. 2010). The use of elastica staining by immunohistochemistry (IHC) to identify blood vessels within the resected specimen has been shown to both increase the incidence of reported venous invasion and increase its prognostic ability (Roxburgh et al. 2011). The invasion of tumour cells into, and along, the local nerve sheaths, known as perineural invasion, has been reported to be associated with local recurrence and poorer prognosis, particularly in rectal cancer (Liebig et al. 2009). However, its presence is not routinely reported in current UK practice.

Both tumour involvement of the serosa (the outermost layer of the colonic wall) and true tumour perforation through it, are recognised to be high risk pathological features

associated with local and distant recurrence and poor survival (Benson et al. 2004, Stewart et al. 2007). In addition, tumour involvement of the longitudinal or circumferential surgical margin, defined as R1 (microscopic viable tumour cells within 1mm of the cut edge) or R2 (grossly visible tumour at the cut edge), are strongly associated with local disease recurrence (Birbeck et al. 2002).

Due in part to the number and variety of adverse pathological features, Petersen and colleagues developed a scoring system for prognosis (Petersen et al. 2002). Patients are graded from 0 to 5 based on pathological characteristics, with a score of 2 or more denoting high risk, with an estimated 50 % survival at 5 years (Morris et al. 2007). In addition to prognostic value, many UK MDTs use this Petersen, or Gloucester Prognostic Index (PI, GPI), to identify high risk Stage II patients who are then offered adjuvant treatment in the absence of nodal disease.

Table 1-4: Gloucester Prognostic Index (adapted from Petersen et al. 2002)

Pathological characteristic	Score
Peritoneal involvement	1
Extramural venous invasion	1
Margin involvement	1
Tumour perforation	2

1.8.2 Tumour metabolism and necrosis

The Warburg effect is the name given to the process by which tumour cells generate a significant proportion of their energy through the uptake and the breakdown of glucose by glycolysis even in the presence of normal tissue oxygenation. Although anaerobic glycolysis is a far less efficient method of producing adenosine triphosphate (ATP) from glucose when compared to aerobic cellular respiration, the reduced reliance on a reliable oxygen supply may allow for cell proliferation in the hostile environment created by host responses (Heiden et al. 2009).

In patients with colorectal cancer, higher glucose metabolism, as determined by ^{18}F FDG-PETCT, has been associated with markers of tumour proliferation (Riedl et al. 2007, Deng

et al. 2015), lower likelihood of down staging following neoadjuvant chemoradiotherapy (Calvo et al. 2013) and poorer long-term survival (Shi et al. 1991, Lau et al. 2014, Marcus et al. 2016). As tumours grow they release factors which promote the ingrowth of blood vessels, a process known as angiogenesis. One of the key mediators released is vascular endothelial growth factor (VEGF), which has been shown to be associated with reduced recurrence free survival in colorectal cancer at meta-analysis (Des Guetz et al. 2006).

The presence of tumour necrosis has been reported to be associated with poorer disease specific survival in colorectal cancer (Pollheimer et al. 2010, Richards et al. 2012a). Tumour necrosis is a common finding in solid tumours, and is thought to be generated by tumour growth rate outstripping blood supply, leading to ischaemia. In colorectal cancer, tumour necrosis has been reported to be associated with other adverse prognostic factors such as increasing tumour size and poor differentiation (Gao et al 2005, Pollheimer et al. 2010). In addition, some studies have reported an inverse association between tumour necrosis and the local inflammatory response (Gao et al. 2005, Knutsen et al. 2006). Furthermore, tumour necrosis has been associated with the preoperative host systemic inflammatory response in patients undergoing surgery for colorectal cancer (Richards et al. 2012a).

Tumour metabolism, angiogenesis, and tumour necrosis are clearly important processes in the growth of the primary tumour and in the development of distant metastases. However, their inter-relationship, the exact mechanisms by which they influence prognosis, and their associations with the local and systemic host immune responses remain unclear.

1.8.3 Molecular and genetic markers

A variety of molecular and genetic markers have been proposed as prognostic markers in colorectal cancer, although only a relative few, namely carcinoembryonic antigen (CEA) and K-ras, have been adopted into widespread clinical practice.

CEA is widely used as a tumour marker in colorectal cancer, particularly in the detection of recurrent disease during follow up after surgery (Graham et al. 1998). This is despite there being very little evidence as to the impact of this kind of use on survival (Duffy 2001). CEA has also been considered for use in both a screening and diagnostic role in colorectal cancer, however its poor discriminatory ability has prevented its adoption in either clinical scenario (Begent 1984, Fletcher 1986)

K-ras, a member of the RAS family, is one of the most commonly mutated oncogenes in colorectal cancer (and in several other adenocarcinomas) associated with uncontrolled cell proliferation (Forrester et al. 1987). Studies have reported a variable impact on prognosis based on K-ras mutation status (Andreyev et al. 1998, Andreyev et al. 2001, Westra et al. 2004). However, K-ras has found clinical use in determining the utility of the anti-EGFR monoclonal antibody cetuximab in patients with locally advanced and metastatic disease. Indeed, EGFR is itself an oncogene, associated with cellular adhesion and metastatic disease. Cetuximab has been shown to increase median survival in this group of patients, but only in those without K-ras mutation (Karapetis et al. 2008).

Several other genetic and molecular markers have been considered for their prognostic value including: p53 mutation, deleted in colorectal cancer (DDC), indices of cellular proliferation (most notably Ki67), carbohydrate antigen 19-9 (Ca 19-9), thymidylate synthase (TS), and matrix metalloproteinases (MMP). However, heterogeneity in results with regard to prognostic impact has limited their use to trials in colorectal cancer (Graziano et al. 2003).

1.9 The immune response to colorectal cancer and host factors associated with outcomes

It is increasingly recognised that colorectal cancer outcomes are not only determined by the intrinsic characteristics of the tumour itself, but also by the patient. Some of these factors, such as age and the presence and severity of comorbidity, may have their impact through the ability or otherwise of the patient to tolerate those treatments which are available. Other host factors, such as the host immune response to cancer, may have a more direct impact on the tumour biology and response to treatment. The host immune response, at the local and systemic levels, represents the body's intrinsic natural ability to detect, prevent and eradicate cancer. As already discussed, inflammation and cancer are closely associated in terms of both carcinogenesis and in established cancer as one of the acquired key components of tumour biology which allow it to survive, proliferate and disseminate (Hanahan et al. 2011). Indeed, host systemic inflammation is so closely linked to disease progression and metastases in cancer that it has been referred to as the "tip of the iceberg" (McAllister et al. 2014). In addition, such is the evidence regarding the impact of the host immune response on colorectal cancer outcomes that there have been calls to both stage and treat this host response to determine if there is, and treat, any dysregulation (Diakos et al. 2014, Roxburgh et al. 2014).

1.9.1 The host immune response

The immune system is the body's method of detecting and removing organisms identified as non-self, primarily pathogens such as bacteria, yeasts, fungi, and helminths. It also targets host cells which display non-self antigens, including cells infected by viruses, and cancer cells. This process of cancer immunosurveillance, or immunoediting as it has been more recently described, is thought to be a continuous one, with the appearance of individual malignant cells presenting cancer-specific antigens which are for the most part identified and destroyed by the immune system (Dunn et al. 2004). In some cases, however, the cancer cells are not completely destroyed by the immune system and reach a stable existence, or equilibrium, within the host. Subsequent evasion of the immune system allows growth at the primary site and eventual distant dissemination, and is thought to be a key step in the development of established cancer (Dunn et al. 2002).

The immune system is vastly complex and relatively poorly understood, with numerous components, each of which have multiple and complex interactions. Numerous tissues form part of the immune system as a whole, including lymph nodes, the spleen, bone marrow and liver, alongside the considerable portion resident in circulation. However, these can be thought of as falling into one of two broad parts: the innate (or non-specific) immune system and the adaptive (or acquired) immune system.

The innate immune system generates a non-specific response to pathogens and tissue injury. The epithelium lined body surfaces (i.e. the skin, gastrointestinal tract, respiratory tract and genitourinary tract) form a first-line barrier defence. If they are breached or injured the innate immune system is activated. It is comprised of both circulating humoral factors (namely the complement cascade), and cellular components including phagocytes (neutrophils and macrophages), granulocytes (basophils, eosinophils, and mast cells), and directly cytotoxic natural killer cells (NK). The response is generated and directed through the production of small molecules known as cytokines and chemokines, as a direct result of tissue injury or following contact with a pathogen (Janeway et al. 2002). Initially pro-inflammatory mediators recruit a rapid and effective innate response, following which anti-inflammatory mediators cause it to wane and allow the restoration of normal tissue structure and function (Janeway 2001). In most circumstances, activation of the innate immune system also leads to activation of the adaptive immune system, e.g. through antigen presentation by phagocytes.

The adaptive immune system provides a more specific response to pathogens and other non-self antigens, including cancer cells, and in addition provides the immune system's stored "memory" of previous encounters with specific antigens. The adaptive immune system is composed primarily of the lymphocytes, which mature in either the bone marrow (B cells) or thymus (T cells). These lymphocytes tend to become activated through the presentation of non-self antigens by a group of cells known as antigen presenting cells (APCS) of which the neutrophils and macrophages of the innate immune system form a part. B cells form part of the humoral immune system and, following activation, produce antibodies against the specific antigen encountered. These antibodies can have direct toxic effects on pathogens but also recruit the innate immune system following antibody-antigen binding, both as opsonins which encourage phagocytosis and by activating the complement cascade. T cells have their action through the binding of the T cell receptor (TCR) with non-self antigens. T cell subsets are classified by the presentation of specific membrane proteins linked to TCR binding, called cluster determinants (CD). The subset of T cells

which are the primary effectors of this specific cell mediated immune response are the cytotoxic T cells (CD8+), which upon TCR binding produce cytotoxins. A number of other subsets of T cells exist, each with specific roles including antigen presentation (CD4+ helper T cells), antigen memory (CD45R0+ memory T cells), and regulation of the adaptive immune response (FOXP3+ T regs).

In general, the adaptive immune system is regarded as that which has the most important role to play in cancer immunoediting. Indeed, it is thought that innate immune driven inflammation can promote tumour progression, in part through suppression of the adaptive response (Qian et al. 2010).

1.9.2 The local inflammatory response

For a considerable time, the local inflammatory response, i.e. the extent and type of intra- and peri-tumoural immune infiltration, has been thought to relate to the effectiveness of the host's antitumour immunity and thus disease prognosis (House et al. 1979). As time goes on it is increasingly appreciated that the interaction between tumour cells, the local inflammatory infiltrate, and the tumour microenvironment (the medium in which the tumour cells develop or otherwise) is important in terms of prognosis and as a potential therapeutic target. In general, the presence of a strong, adaptive or lymphocytic inflammatory infiltrate at the local level is associated with a good prognosis (Jass 1986). This has been defined in multiple ways as described in more detail below. In contrast, local infiltration by cells of the innate response, including tumour associated macrophages (TAMs) and neutrophils, is thought to result in a pro-tumour environment and poorer prognosis (Kim et al. 2016).

1.9.2.1 Crohn's like reaction

Following on from the work of Jass, the term "Crohn's like reaction" (CLR) was coined to describe aggregates of lymphocytes around the tumour which were associated with improved prognosis in colorectal cancer (Graham et al. 1990). It is of interest that this CLR is now often described in the context of MSI-H tumours, and that this has in part led to MSI-H and CIMP tumours falling into the "Immune" colorectal cancer subtype.

1.9.2.2 Klintrup-Makinen grade

The Klintrup-Makinen grade is a semi-quantitative method of grading the generalised inflammatory infiltrate, primarily at the invasive margin, using haematoxylin and eosin (H&E) stained slides (Klintrup et al. 2005). The initial study reported a significant association between a high grade inflammatory infiltrate and improved prognosis in colorectal cancer patients, a finding which has since been externally validated (Roxburgh et al. 2009).

1.9.2.3 Galon Immunoscore

The Galon Immunoscore utilises immunohistochemistry and assigns scores based on the density of CD8+ and CD3+ T cells in the tumour and at the invasive margin. Those patients with a strong infiltrate at both locations have been shown to have a better prognosis, and a reduced risk of colorectal cancer recurrence after surgery than those with weaker infiltrates (Galon et al. 2006, Mlecnik et al. 2011). There is some evidence to suggest that this method of assessing the local adaptive immune response provides greater prognostic accuracy than that of the Klintrup-Makinen grade alone (Park et al. 2016a).

1.9.2.4 The tumour microenvironment

The tumour microenvironment forms the true interface between cancer and host. It is composed of the infiltrating immune cells, blood vessels, and the extracellular matrix and supporting cells of the tumour stroma. An expanded tumour stroma has been reported to be associated with poorer prognosis, however the mechanism by which it may facilitate tumour progression has not been fully elucidated. Several theories include factors from the stroma influencing local and systemic inflammation, tumour pH, and tumour metabolism (Park et al. 2016a). Tumour cells favour glycolysis as a method of glucose metabolism, even in the presence of normoxia (Vander Heiden et al. 2009). Indeed, this phenomenon termed the Warburg effect may be facilitated by the tumour-supporting stroma. It has previously been reported that in patients with colorectal cancer, increased tumour cell expression of enzyme pathways associated with anaerobic metabolism and lactate extrusion - including lactate dehydrogenase isoenzyme 5 (LDH 5), hypoxia inducible factor (HIF) and monocarboxylate transporter 1 (MCT1) - was associated with an increase in the ability of cancer associated fibroblasts to uptake and oxidise lactate, suggesting a reciprocal role in supporting tumour cell metabolism (Giatromanolaki et al. 2007).

1.9.2.5 The Glasgow Microenvironment Score

As already discussed, the presence of a strong inflammatory cell infiltrate, as assessed by the Klintrup-Makinen grade and by the Galon Immunoscore, is associated with improved survival in colorectal cancer (Richards et al. 2014). Recently, the degree of tumour stroma expansion, as defined by tumour stroma percentage (TSP), has been reported to further stratify survival in those patients with a weak inflammatory cell infiltrate as defined by the Klintrup-Makinen grade (Table 1.2), leading to the creation of the Glasgow Microenvironment Score (GMS) (Park et al. 2015, Park et al. 2016a).

Table 1-5: The Glasgow Microenvironment Score (GMS) and its association with 5 year survival following surgery for stage I-III colorectal cancer (adapted from Park et al. 2015)

GMS	K-M	TSP	5 year CSS
0	strong	-	89%
1	weak	low	75%
2	weak	high	51%

GMS Glasgow Microenvironment Score, K-M Klintrup-Makinen grade, TSP tumour stroma percentage, CSS cancer specific survival

1.9.2.6 Faecal calprotectin

Calprotectin is a calcium and zinc binding protein of the S-100 family which is found in both serum and stool. It has both antimicrobial and apoptotic properties and is associated with gastrointestinal inflammation (Sherwood 2012). Indeed, faecal calprotectin is now a widely clinically used biomarker primarily in the monitoring of inflammatory bowel disease (Mowat et al. 2016). The use of faecal calprotectin in the diagnosis and disease monitoring of colorectal cancer has also been studied, however no consensus exists as to its use and its place amongst other established methods of screening, detection, and monitoring (Kristinsson et al. 1998, Limburg et al. 2003, Hoff et al. 2004).

1.9.3 The systemic inflammatory response

The systemic inflammatory or “acute phase” response is a significant mobilisation, predominantly of the non-specific innate immune system, as a result of tissue injury or the presence of pathogens (Gabay et al. 1999). It temporarily replaces normal homeostasis and is, at first, a useful process which aims to neutralize pathogens and promote tissue healing before anti-inflammatory processes become dominant and the acute phase wanes. Systemic inflammation involves numerous cell types, cytokines, and acute phase proteins.

The process is regulated by a balance of cytokine production at different times, with pro-inflammatory cells such as neutrophils and macrophages, and cytokines such as interleukin (IL) 1, IL 6, tumour necrosis factor (TNF) α and IGF-1 balanced by the anti-inflammatory regulatory cells and cytokines, such as IL 4 and IL 10. In some cases, however, the balance between pro- and anti-inflammatory processes is lost, leading to prolonged and excessive inflammation which can be deleterious in its effects and is discussed in more detail below (Bone 1999). The presence of a prolonged and inappropriate systemic inflammatory response has been described in a variety of solid tumours and is almost universally associated with poor prognosis (McMillan 2013). This response may be produced and maintained through the production of proinflammatory cytokines and mediators by the tumour cells themselves as they bid to proliferate and invade, or by the peritumoural and intratumoural infiltrating cells of the immune system (Burke et al. 1996, Koong et al. 2000). It is hypothesised that the presence of an innate inflammatory response inhibits the more useful, in terms of anti-tumour activity, adaptive immune response (Roxburgh et al. 2013). The presence and magnitude of the systemic inflammatory response has been measured and defined in numerous ways and using many individual or combined components of the immune response, as discussed below.

1.9.3.1 C-reactive protein

C-reactive protein (CRP) is one of the family of pentraxins, discovered in 1930 and so named due to its reactivity with the pneumococcal C-polysaccharide (Gabay et al. 1999). It is a positive acute phase protein (Figure 1.2), and is perhaps currently the most widely clinically used marker of the systemic inflammatory response, although others such as erythrocyte sedimentation rate (ESR), white cell count (WCC) and procalcitonin are also in use. CRP is produced by hepatocytes following IL 6 secretion by macrophages and T cells. Its physiological role is to bind to lysophosphatidylcholine expressed on the surface of dying or damaged cells and some bacterial cell membranes. It acts as an opsonin and also activates the complement cascade, aiding further recruitment of the innate immune system. The presence of a raised preoperative CRP, at a variety of concentrations, in resectable colorectal cancer has widely been reported to be associated with poorer prognosis independent of disease stage (Nozoe et al. 1998, Nielsen et al. 2000, McMillan et al. 2003). Furthermore, CRP concentrations in the postoperative period have been reported to be associated with anastomotic leak and other infective complications following colorectal resection as discussed later.

1.9.3.2 Albumin

Albumin is the most prevalent plasma transport protein and a negative acute phase reactant (Figure 1.2). Low preoperative concentrations of serum albumin have been reported to be associated with poor prognosis in resected rectal and colon cancer (Longo et al. 1998, Cengiz et al. 2006).

1.9.3.3 The Glasgow Prognostic Scores

The Glasgow Prognostic Scores combine preoperative threshold values of serum CRP (>10mg/L) and albumin (<35g/L) to stratify the prognostic significance of each component. Both the original score (GPS) and modified GPS (Table 1.3) are independently prognostic in colorectal cancer and a variety of solid tumours (McMillan 2013). Indeed, the mGPS has recently been reported to stratify prognosis within patients of the same TNM stage (Park et al. 2016b). Furthermore, with the development of high-sensitivity serum CRP determination, the high sensitivity mGPS (hs-mGPS) has also been described using a CRP threshold of 3mg/L (Proctor et al. 2013). In particular, it has gained favour in studies conducted in Asian populations, as prior reports suggest a much lower incidence of cancer related inflammation in this particular ethnic group when the traditional CRP thresholds were applied (Kobayashi et al. 2010, Jiang et al. 2012).

Table 1-6: The original and modified Glasgow Prognostic Scores and their association with survival in patients following surgery for colorectal cancer (modified from McMillan et al. 2007)

Biochemical results	Points allocated	3 year CSS (%)
GPS		
CRP <10mg/L and albumin >35g/L	0	90
CRP <10mg/L and albumin <35g/L	1	94
CRP >10mg/L and albumin >35g/L	1	62
CRP >10mg/L and albumin <35g/L	2	50
mGPS		
CRP <10mg/L	0	91
CRP >10mg/L and albumin >35g/L	1	75
CRP >10mg/L and albumin <35g/L	2	52

GPS Glasgow Prognostic Score, mGPS modified Glasgow Prognostic Score, CRP C-reactive protein

1.9.3.4 White cell count

Total circulating white cell count (WCC) is a common laboratory measure of the systemic inflammatory response and itself has been reported to be associated with mortality in patients with cancer (Shankar et al. 2006). In addition, the components of the circulating white cell population, along with a number of ratios and scoring systems based on their concentrations, have been reported to be prognostic.

1.9.3.5 Neutrophils and the neutrophil lymphocyte ratio

Neutrophils make up the majority of the circulating white cell population and are the key effector cells of the innate immune system. The ratio of neutrophils to lymphocytes (NLR) is an indicator of the magnitude of an immune response and an indicator as to whether it is predominantly innate or adaptive. NLR, in particular at ratios of greater than 3, or in other reports greater than 5, has been reported to be prognostic in colorectal cancer independent of stage (Guthrie et al. 2013). However, more recent evidence suggests that neutrophils are the most important component of the two, and that lymphocytes add little extra prognostic value (Watt et al. 2015a).

1.9.3.6 Platelets and the platelet lymphocyte ratio

Thrombocytosis is, in itself, a sensitive marker of systemic inflammation, and its ratio with lymphocytes (PLR) is associated with prognosis in several gastrointestinal cancers (Smith et al. 2008).

1.9.3.7 Monocytes and the lymphocyte monocyte ratio

The lymphocyte monocyte ratio (LMR) represents another method of assessing the magnitude and balance of a cancer immune response which has been reported to be of greater prognostic value in resected colorectal cancer when compared to the mGPS, NLR, and PLR (Chan et al. 2016). However, the primary endpoint in that particular study was overall survival and a more useful comparison in terms of disease specific survival has yet to be published.

1.9.3.8 Neutrophil platelet score

The neutrophil platelet score (NPS) combines two components of the innate immune response, each with prognostic significance, and has been reported to further stratify survival independent of stage (Watt et al. 2015b).

Table 1-7: The Neutrophil Platelet Score (NPS) and its association with survival in patients with resected colorectal cancer (adapted from Watt et al. 2015)

Haematological results	Points allocated	5 year CSS (%)
Neutrophils < $7.5x10^9$/L and platelets < $400x10^9$/L	0	79
Neutrophils > $7.5x10^9$/L or platelets > $400x10^9$/L	1	69
Neutrophils > $7.5x10^9$/L and platelets > $400x10^9$/L	2	65

CSS cancer specific survival

1.9.4 Cancer cachexia

Disease progression in cancer is often associated with a gradual process of involuntary loss of weight, muscle mass, and function, an entity known as cachexia (Aapro et al. 2014). Indeed, cancer cachexia is recognised to be a poor prognostic factor in a variety of tumours (Trajkovic-Vidakovic et al. 2012). Definitions of cancer cachexia have traditionally focused on loss of weight or changes in body mass index (BMI), however as the overall weight of the world's population increases, measures of body composition have been recognised to be more useful (Martin et al. 2013). In particular, it has been recognised that the loss of both the quantity and quality of lean tissue is especially prognostic in colorectal cancer (Malietzis et al. 2016a). Furthermore, recent evidence suggests that systemic inflammation may be a key underlying mechanism driving this catabolic process, however its exact nature is uncertain (Douglas et al. 2014, Malietzis et al. 2016b).

1.9.5 Anaemia

Anaemia is commonly defined as haemoglobin (Hb) concentrations of <11g/dL in women and <13g/dL in men (WHO 2004). Anaemia has been reported to be present preoperatively in as many as 80% of patients with advanced disease (Knight et al. 2004), and is associated with both poorer outcomes (Leitchle et al. 2011) and poorer response to chemotherapy (Tampellini et al. 2006). Classically, colorectal cancer has been associated with iron deficiency anaemia secondary to frank or occult gastrointestinal blood loss. Iron

deficiency is defined as: serum ferritin <15μg/L, transferrin saturation <16%, or an Hb increase of 1g/dL after 1-2 months of iron supplementation (although values vary with pregnancy and ethnicity) (WHO 2001). However, systemic inflammation is associated with functional iron deficiency (FID). FID is a state in which iron is inadequately incorporated into erythroid precursors despite sufficient iron stores. This may occur in patients with infectious, inflammatory or malignant conditions and is a major component of the anaemia of chronic disease (Thomas et al. 2013). This process is believed to be mediated by the inhibition of the iron transport protein ferroportin due to the influence of IL 6 on hepcidin, a key regulator of iron homeostasis (vonDrygalski et al. 2013). Diagnosis of iron deficiency becomes problematic as ferritin and iron study results are affected by systemic inflammation. Therefore, many patients with colorectal cancer who are inflamed may in fact have FID rather than true iron deficient anaemia, although there is little data to this effect in terms of either the degree of derangement of measures of iron status, or the prevalence within patients with colorectal cancer.

1.10 The postoperative systemic inflammatory response in colorectal cancer

The body's natural response to any physical trauma, including that of surgery, is to initiate a stereotypical neurohormonal and inflammatory response. If this response is appropriate in terms of both its duration and magnitude, it seeks initially to stabilise the patient's physiology and then promote healing: the return to normal tissue structure and function (Cuthbertson 1979). However, if the duration of the response is too long, or the magnitude of the response too great, this can have a negative impact on short- and long-term outcomes following surgery for colorectal cancer.

1.10.1 Local response to surgery

The complex local response to tissue injury is usually divided into four phases: coagulative, inflammatory, proliferative, and remodelling (Stadelmann et al. 1998a). The initial phase is that of haemostasis through activation of the clotting cascade, followed by the creation of a locally pro-inflammatory environment. The processes of vasodilatation, cellular adhesion, and diapedesis, enhanced by factors released by damaged cells and activation of the complement cascade, encourage the influx of neutrophils and macrophages to the injured area. These myeloid cells neutralize any pathogens which have entered the area and remove damaged cells and tissue. This is almost immediately followed by an anti-inflammatory response which causes the inflammatory phase of the wound healing process to wane. During the proliferative and remodelling phases, fibroblasts and myofibroblasts are recruited to produce collagen and elastin, in the case of granulation tissue, and where possible stem cell division replaces tissue like for like. A number of factors can contribute to delayed healing of such wounds including insufficiency of the local vascular supply, diabetes mellitus, infection, and immunosuppressive and anti-inflammatory drugs (Stadelmann et al. 1998b).

1.10.2 Systemic inflammatory or "stress" response to surgery

Alongside the local response to trauma, a combined systemic neuroendocrine and inflammatory response occurs to varying degrees (Baigrie et al. 1992). As with the local inflammatory response, the evolutionary goal of this process is to return the patient to normal homeostasis and promote healing. Initially, activation of the clotting cascade leads

to thrombocytosis. Activation of the sympathetic nervous system, through direct effects and the release of catecholamines by the adrenal medulla, initially causes cardiovascular responses, such as tachycardia and vasoconstriction, and respiratory responses, such as tachypnoea and increased tidal volumes. Changes in renal perfusion lead to the activation of the renin-angiotensin-aldosterone system (RAAS) which leads to increased reabsorption of filtered sodium and water with the net result of oliguria. The hypothalamic-pituitary-adrenal (HPA) axis is activated, leading to the production of the stress hormone cortisol by the adrenal cortex. Pro-inflammatory cytokines are released by damaged tissue and by activated cells of the innate immune system, which in turn lead to an increase in the number of circulating neutrophils and macrophages. Pro-inflammatory cytokines such as TNF α, IL 1 and IL 6, drive rapid changes in the synthesis of the positive and negative acute phase proteins by the liver, including CRP, albumin, transferrin, and ferritin. Catabolism of lean tissue provides the required energy and substrates.

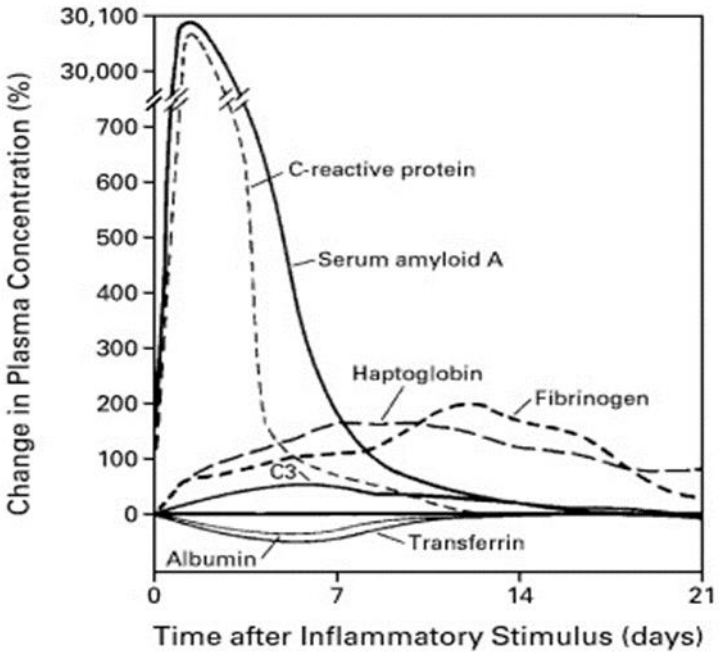

Figure 1-2: Change in plasma concentrations of some acute phase proteins after a moderate inflammatory stimulus (adapted from Gabay and Kushner 1999)

Plasma concentrations of IL 6 and CRP have been shown to be reliable and reproducible markers of the magnitude of the postoperative systemic inflammatory/stress response following surgery across a wide variety of operation types and surgical specialities (Watt et al. 2015c). They have been shown to be superior to various other cytokines, acute phase proteins, white blood cell and haematological parameters, and circulating stress hormones in stratifying the magnitude of surgical trauma across various operations and surgical

specialities. IL 6 peaks at around 24 hours postoperatively, but due to costs and techniques has not been adopted into wide-spread clinical practice as of yet, remaining a research tool (Sakamoto et al. 1994). CRP, in contrast, is routinely measured and available in the clinical setting, usually peaking between 48 and 72 hours after surgery.

As with the local response, a systemic anti-inflammatory response then replaces the pro-inflammatory, allowing a gradual return to normal homeostasis and physiology.

1.10.3 Immunologic dissonance

In some cases, the balance between the pro- and anti-inflammatory responses is lost (immunologic dissonance) and the systemic inflammatory response becomes either overwhelming or persistent. The exaggerated pro-inflammatory response drives cardiovascular, respiratory and metabolic effects which can lead to the development of the Systemic Inflammatory Response Syndrome (SIRS), shock, and end organ dysfunction (Bone et al. 1992).

The Compensatory Anti-Inflammatory Response Syndrome (CARS), in contrast, can lead to a relative state of immunosuppression (Bone 1996). In the immediate postoperative period, this can lead to a greater susceptibility to infective complications. Furthermore, in the case of colorectal cancer, this state is thought to promote tumour recurrence and metastasis (Colotta et al. 2009). One of the mechanisms by which this is hypothesised to happen is through neutrophil dysfunction (Leliefeld et al. 2016). The impact of immunological dissonance is thought to render neutrophils less effective in terms of their innate anti-pathogen activity, and also causes them to suppress adaptive anti-tumour effector cells.

Table 1-8: Criteria for the Systemic Inflammatory Response Syndrome (SIRS): score >1 (adapted from Bone et al. 1992)

Physiological parameter	Threshold	Score
Temperature	>38C or <36C	1
Heart rate	>90 beats per minute	1
Respiratory rate	>20 breaths per minute or -$PaCO_2$ <32mmHg	1
White cell count	>12 or <4 x10^9/L	1

C Celsius, *$PaCO_2$* partial pressure of carbon dioxide

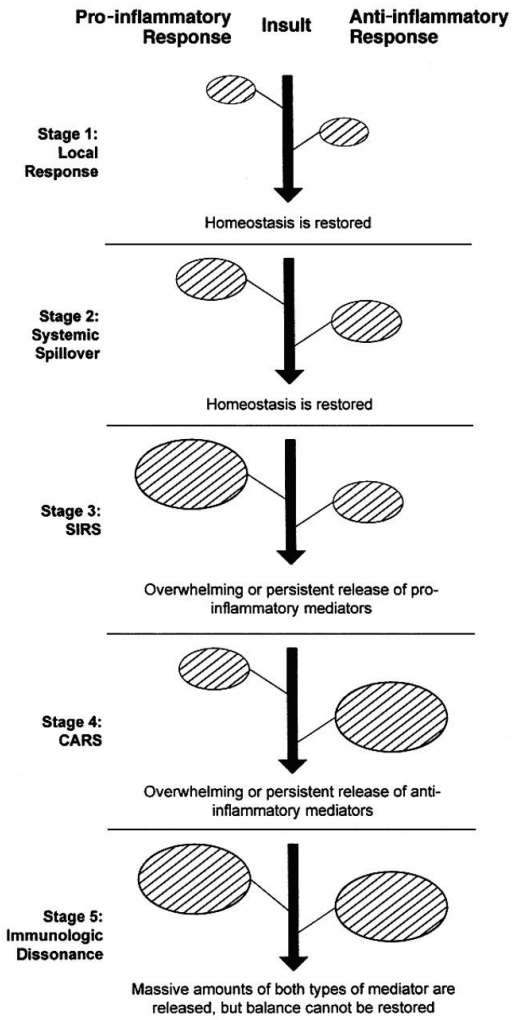

Figure 1-3: Outline of the processes leading to the Systemic Inflammatory Response Syndrome (SIRS), Compensatory Anti-Inflammatory Response Syndrome (CARS) and immunologic dissonance after surgery (adapted from Bone 1996)

1.10.4 Factors known to modulate the postoperative systemic inflammatory response

If the magnitude of the postoperative systemic inflammatory response is thought to have an impact on both complications and disease recurrence after surgery for colorectal cancer then an understanding of those factors, modifiable and non-modifiable, which determine or modify it is clearly desirable.

There is good evidence that laparoscopic and other minimally invasive surgical techniques results in a lower postoperative systemic inflammatory response than traditional open abdominal surgery across a variety of specialities including colorectal surgery (Watt et al. 2015c). Whether this simply relates to the smaller abdominal wounds required, or whether other factors such as the use of carbon dioxide for insufflation, or the no-touch isolation technique generally used, remains unclear.

There is some interest in factors surrounding perioperative care that might be targeted in a bid to modify the postoperative systemic inflammatory response. A number of general anaesthetic agents including propofol, and volatile anaesthetics, are thought to have an impact on both the immune system in the perioperative period and long-term oncologic outcomes (Piegeler et al. 2016). The use of regional anaesthetic technique may be important, with both the use of epidural anaesthesia in addition to general anaesthesia (Chen et al. 2015), and the use of intravenous lignocaine (Sridhar et al. 2014), reported to be associated with lower postoperative CRP concentrations after abdominal surgery.

Enhanced Recovery After Surgery (ERAS) and other "fast-track" perioperative protocols were introduced with the aim of reducing postoperative length of stay and morbidity, through a reduction in the postoperative stress response, and earlier return to normal function (Lassen et al. 2009). Despite this, there is very little evidence that commonly used components of these protocols actually have any impact on the postoperative systemic inflammatory response (Watt et al. 2015d). Two studies examining the impact of goal directed fluid therapy on postoperative IL 6 after major gastrointestinal surgery reported conflicting results (Wakeling et al. 2005, Noblett et al. 2006). A single randomised controlled trial investigating preoperative carbohydrate loading reported no significant association with postoperative IL 6 or CRP in patients undergoing major abdominal surgery (Mathur et al. 2010). No studies have reported the impact of other ERAS components, including mechanical bowel preparation, antibiotics prophylaxis, early enteral

nutrition, early mobilisation, the avoidance of routine nasogastric and peritoneal drainage, and the postoperative systemic inflammatory response (Watt et al. 2015d).

With regard to patient factors which might influence the magnitude of the postoperative systemic inflammatory response, there is some preliminary evidence that emergency presentation, preoperative systemic inflammation, BMI, and co-morbid state may play a role (Ramanathan 2015). Modifiable patient risk factors present multiple potential targets for intervention, however, the exact nature of these underlying relationships need to be clarified prior to such future studies.

1.10.5 Association with postoperative complications

In line with hypotheses regarding immunologic dissonance, there is increasing evidence that the magnitude of the postoperative systemic inflammatory response is associated with complications following colorectal surgery. In particular, there have been significant attempts to predict the presence of developing complications prior to the onset of obvious clinical symptoms and signs using CRP concentrations in the early postoperative period (Adamina et al. 2015). Much of the focus has been on the early detection of anastomotic leak and infective complications, discussed in more detail below (Platt et al. 2012). Clinically relevant thresholds have been sought, with varying values on varying postoperative days promoted by different interested groups (Ramanathan et al. 2013, Singh et al. 2014a). Such threshold values of CRP have been found to have a high negative predictive value but a poor positive predictive value in terms of both complications and readmission after colorectal surgery (Table 1-9). Furthermore, although laparoscopic surgery has been shown to be associated with a lower postoperative systemic inflammatory response, the postoperative CRP thresholds used for the prediction of postoperative infective complications remain the same as those used in open surgery (Ramanathan et al. 2015b). More recently, a consensus review has suggested that exceeding a CRP concentration of 150mg/L on postoperative days 3 to 5 after colorectal surgery should both prompt further investigation for potential complications, and prevent early discharge from hospital (McDermott et al. 2015). In addition, other studies have investigated the use of other markers associated with the development of postoperative complications, for example procalcitonin, however the IMACORS study reported that CRP was more accurate in the detection of postoperative infective complications following colorectal surgery (Facy et al. 2016). Furthermore, it has long been recognised that albumin is also a marker of the postoperative stress response (Gabay and Kushner 1999) and is associated

with postoperative complications and mortality (Gibbs et al. 1999). It remains to be determined whether albumin, in terms of predicting postoperative complication, offers additional predictive or prognostic value in addition to that of CRP. Indeed, several issues remain to be determined. Is type or severity of complication more important in terms of the postoperative systemic inflammatory response, and longer term outcomes? Also, is there a causal relationship between the magnitude of the postoperative systemic inflammatory response and complications, or is one simply an epiphenomenon of the other?

Table 1-9: Meta-analytic data reporting accuracy of C-reactive protein to detect complications following colorectal (adapted from Singh et al. 2014) and abdominal (adapted from Adamina et al. 2015) surgery

Complication Type	POD	n	Prevalance (%)	CRP cut off (mg/L)	AUC	Sens (%)	Spec (%)	NPV (%)	PPV (%)
Anastomotic leak									
	3	2,126	7.9	172	0.81	76	76	97	21
	4	1,987	9.1	124	0.80	79	70	97	21
Infective complication									
	3	507	38	169	0.70	61	70	82	46
	4	624	34	96	0.76	76	61	86	45

POD postoperative day, *CRP* C-reactive protein, *AUC* area under the curve, *NPV* negative predictive value, *PPV* positive predictive value, *Sens* sensitivity, *Spec* specificity

1.11 Complications following surgery for colorectal cancer

Surgical resection continues to be the mainstay of treatment for colorectal cancer. However, it is associated with a significant level of postoperative complication and morbidity. These postoperative complications are associated with increased postoperative mortality, poorer quality of life after surgery, and a significant health care and societal cost (Ghaferi et al. 2011). It has also been increasingly recognised that these postoperative complications may not only have negative implications for short-term outcomes, but also for oncologic outcomes (Law et al. 2007a, Law et al. 2007b, Mirnezami et al. 2011) and long-term survival (McArdle et al. 2005, Khuri et al. 2005, Pucher et al. 2014). Postoperative complications can be described as "deviation from the normal postoperative course" (Dindo et al. 2004). They have been classified in a number of ways. Variation in classification of complications has important implications in both clinical and research practice due to the ability to directly compare outcomes, and with regard to the underlying mechanisms linking complications to short and long-term outcomes.

1.11.1 Classification by type

Complications have been traditionally classified by type, in a descriptive manner. Following this, particular interest arose in infective type complications, with studies reporting that this sub group of complications had a negative impact on long-term oncologic outcomes (Law et al. 2007a, Nespoli et al. 2004). Some further considered the site of infection (Law et al. 2007a, Khuri et al. 2005, Miki et al. 2006, Tsujimoto et al. 2010), reporting that intra-abdominal and pulmonary infective complications had a greater impact on long-term outcomes than wound infections.

Table 1-10: Type of complications: accepted definitions of infective complications

Type	Location	Complication	Definition
Infective			
	SSI	wound infection	The presence of pus in the wound either discharging spontaneously or requiring drainage
		anastomotic leak	Anastomotic defect diagnosed radiologically, at endoscopy or laparotomy
		intra-abdominal collection	Surgical or radiologically guided aspiration of pus from abdominal cavity
	RSI	pneumonia	Fever above 38.5C, or SIRS, associated with positive chest x-ray findings
		septicaemia	SIRS with positive blood culture
		UTI	Lower urinary tract symptoms, or fever, with positive urinalysis and/or urine culture
Non-infective			
	wound	seroma	Sterile superficial wound collection without fever or surrounding cellulitis
		dehiscence	Deep or superficial separation of the wound without fever, pus or surrounding cellulitis
	surgical site	haemorrhage	Bleeding requiring radiological or operative intervention
	cardiac	MI	Myocardial ischaemia causing ECG changes and raised cardiac enzymes/markers
		arrhythmia	New, resting ECG arrhythmia, requiring medical intervention
	vascular	VTE	Deep or pulmonary venous thrombosis with clinical symptoms, confirmed radiologically
		CVA	Persistent focal neurological deficit with radiological evidence of cerebral vascular territory infarction
	urinary	renal failure	Oliguria/anuria with decreasing GFR, with or without need for renal replacement therapy
		acute urinary retention	Painful/painless anuria with inability to void requiring urinary catheterisation
	GI	ileus	Paralytic/non-mechanical small bowel obstruction

SSI: surgical site infection, RSI: remote site infection, SIRS: systemic inflammatory response syndrome, UTI: urinary tract infection, MI: myocardial infarction, ECG: electrocardiogram, VTE: venous thromboembolism, CVA: cerebrovascular accident, GFR: glomerular filtration rate, GI: gastrointestinal

1.11.2 Classification by severity

Postoperative complications are increasingly described by their severity, for example as "minor" and "major" based on pre-defined diagnoses or their perceived significance (Rutegard et al. 2012). In particular, a recently developed method is to describe the severity of a complication objectively based on the action taken by the surgical team to remedy it (Dindo et al. 2004). This Clavien Dindo scale has become increasingly popular and has been validated across various surgical specialities, professionals, and countries (Clavien et al. 2009). Initial applications in other cancer types have shown that increasingly severe complications have a negative impact on long-term outcomes (Petermann et al. 2013).

Table 1-11: Severity of postoperative complications: the Clavien Dindo scale (adapted from Dindo et al. 2004)

Clavien Dindo grade	Description
0	No complication
1	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Acceptable therapeutic regimens are: drugs such as antiemetics, antipyretics, analgesics, diuretics, electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
2	Requiring pharmacological treatment with drugs other than such allowed for grade 1 complications
3	Requiring surgical, endoscopic, or radiological intervention
3A	Intervention not under general anaesthesia
3B	Intervention under general anaesthesia
4	Life threatening complication requiring ICU management including CNS complications
4A	Single organ dysfunction (including dialysis)
4B	Multi organ dysfunction
5	Death

ICU: intensive care unit, CNS: central nervous system

1.11.3 Meta-analysis of impact of complication type and severity on long term outcomes after surgery for colorectal cancer and colorectal liver metastases

This systematic review of published literature was conducted with two primary areas of interest; the impact of type of complications (infective compared to non-infective complications) and the impact of severity of complications (as defined by the Clavien Dindo scale) on long-term outcome following surgery for colorectal cancer. There was also a secondary interest in whether both definitions were capturing the same underlying mechanistic process that was impacting long-term outcomes.

A literature search was made of the US National Library of Medicine (MEDLINE), PubMed, the Cochrane Database of Systematic Reviews (CDSR) and Web of Science (WoS) databases from inception to 22nd October 2014. The following search term was used in free text and medical subject heading (MeSH) "colorectal AND (cancer OR metastases) AND (surgery OR resection) AND (complications OR morbidity) AND ((infective OR infectious) OR (severity OR Clavien OR Dindo)) AND ((long-term AND outcome) OR survival)". This search term was chosen following a number of pilot searches using more inclusive terms that returned large numbers of abstracts which on initial assessment were irrelevant to the present review topic.

The title and abstracts of all studies returned by the search were examined for relevance. Animal and pre-clinical studies were not considered. Review articles, non-English papers, duplicate data sets and abstract only results were excluded. The full text of each study deemed potentially relevant was obtained and analysed. To be included a study had to examine the impact of complications following surgery for colorectal cancer on disease free survival or long-term overall survival in terms of either infective and non-infective type complications, or of severity defined by Clavien Dindo complication scale. Reference lists of included papers were hand searched for additional relevant studies. Selection and extraction was completed by one author (SM) with any uncertainties resolved by discussion with the senior author (DM).

Data analysis was performed using Review Manager version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark,). Meta-analysis of overall and disease free survival was undertaken in terms of complication type and severity

individually. Hazard Ratios (HRs) for each survival outcome, from each study, were combined using a random effects model to account for variability in methodology and complication reporting. The Z test was used to assess the overall impact of complication type and severity on long-term outcomes. Heterogeneity was assessed by the I2 test and two-tailed p-values <0.05 were considered to be statistically significant. Publication bias was assessed using funnel plots. The review methodology and reporting was designed and completed in keeping with the PRISMA statement (Moher et al. 2010)

1.11.4 Impact on long term outcomes

Fourteen studies have reported the impact of postoperative complications by either their type, or severity, on survival after surgery for colorectal cancer, or colorectal liver metastases.

1.11.4.1 Complication type

Two studies (Artinyan et al. 2014, Richards et al. 2011), with 12,498 patients, directly compared infective and non-infective complications and their impact on long-term outcomes after colorectal resection for cancer. The largest study (n=12,075), by Artinyan et al. (2014), examined only the effect on 5 year overall survival, finding a poorer median survival when those with infective complications (32.9 months, HR 1.31, p<0.001) were compared with those with non-infective complications (39.9 months, HR 1.05, p=0.510) and with those with no complications (41.9 months). Richards et al. (2011) (n=423) found no significant impact on either disease free survival (HR 1.06, p=0.762) or overall survival (HR 1.26, p=0.163) when comparing those with infective complications after colorectal resection to those without. Two studies (Farid et al. 2010, Neal et al. 2011), with a total 907 patients examined the effect of infective and non-infective complications on long term outcome after hepatic resection of colorectal liver metastases. Farid et al. (2010) (n=705) reported that both those with infective complications (HR 1.60, p<0.001) and non-infective complications (HR 1.98, p<0.001) had a lower 5 year overall survival compared with those with no complications. They reported a similar decrease in disease free survival amongst those with infective complications (HR 1.53, p=0.004) but not those with non-infective complications (HR 1.25, p=0.099). Neal et al. (2011) (n=202) also found that, when compared to those with no complications, those with infective complications had poorer disease free survival (HR 1.72, p = 0.010) and poorer 5 year over-all survival (HR 1.86, p=0.01). However, no significant difference was found in disease free survival (HR 0.98,

p=0.94) or overall survival (HR 1.37, p=0.4) in those with non-infective complications. Both Farid et al. (2010) and Neal et al. (2011) found that wound infection had no significant effect on disease free survival (p=0.178 and p=0.650 respectively) or overall survival (p=0.658 and p=0.260, respectively). Neal et al. (2011) demonstrated that all other infective complications (i.e. non-wound) decreased disease free survival (p=0.005) and overall survival (p=0.020) significantly. Farid et al. (2010) further divided non-wound complications into respiratory infections and intra-abdominal infections, finding both to have a negative impact on disease free survival (p=0.005 and p=0.039, respectively) and overall survival (p=0.001 and p<0.001).

Table 1-12: Studies comparing the impact of complication type on long term outcome

Type	Author	Country	Year	N	Effect of infective and non-infective complications compared to no complication on outcomes	
					DFS	OS
Colorectal						
	Richards et al.	UK	2011	423	infective: HR 1.06 (p=0.762) non-infective: HR 1.28 (p=0.371)	infective: HR 1.26 (p=0.163) non-infective: HR 1.18 (p=0.499)
	Artinyan et al.	USA	2014	12075	NR	infective: HR 1.31 (p<0.001) non-infective: HR 1.05 (p=0.510)
CRLM						
	Farid et al.	UK	2010	705	infective: HR 1.53 (p=0.004) non-infective: HR 1.25 (p=0.099)	infective: HR 1.60 (p<0.001) non-infective: HR 1.98 (p<0.001)
	Neal et al.	UK	2011	202	infective: HR 1.72 (p=0.010) non-infective: HR 0.98 (p=0.940)	infective: HR 1.86 (p=0.010) non-infective; HR 1.37 (p=0.400)

OS: overall survival, DFS: disease free survival, HR: hazard ratio, NR: not recorded, CRLM: colorectal liver metastases

Meta-analysis of the 3 studies (Richards et al. 2011, Farid et al. 2010, Neal et al. 2011), including 1,330 patients, reporting the impact of complication type on disease free survival, found a statistically significant impact related to infective complications (HR 1.41, 95% CI 1.08–1.83, p=0.01) but not non-infective complications (HR 1.21, 95% CI 0.97–1.52, p=0.09). There was a moderate degree of heterogeneity in data relating to infective complications (I^2=37%) and no heterogeneity in data relating to non-infective complications (I^2= 0%).

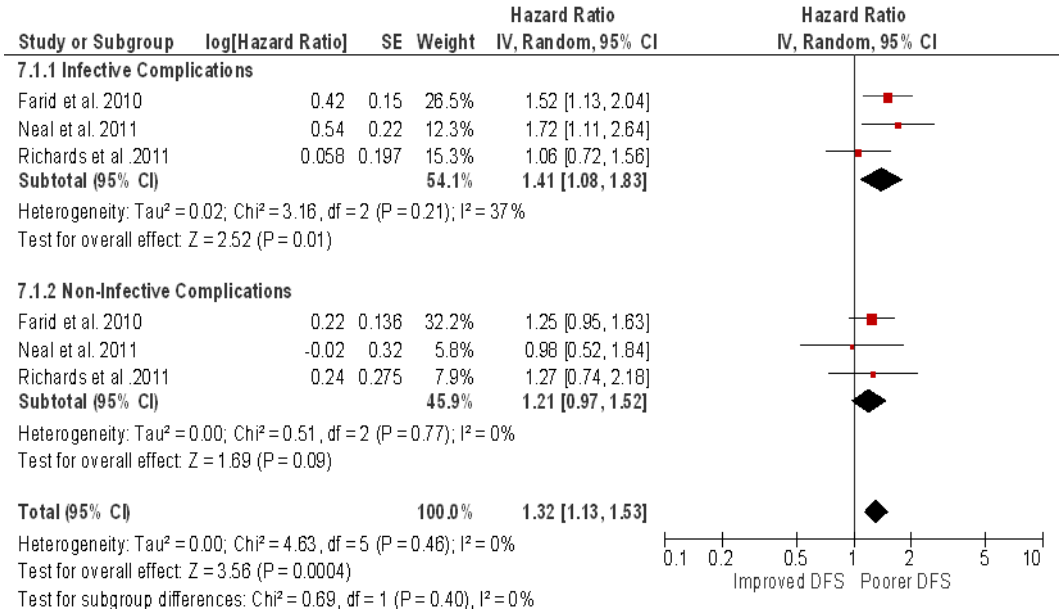

Figure 1-4: Forest plot - impact of complication type on disease free survival

Meta-analysis of the 4 studies (Artinyan et al. 2014, Richards et al. 2011, Farid et al. 2010, Neal et al. 2011), including13,405 patients, reporting the impact of complication type on overall survival, found a statistically significant impact related to infective complications (HR 1.37, 95% CI 1.22–1.55, p<0.001) but not non-infective complications (HR 1.35, 95% CI 0.92–1.97, p=0.12). There was a minimal degree of heterogeneity in data relating to infective complications (I^2=21%) and considerable heterogeneity in data relating to non-infective complications (I^2= 80%).

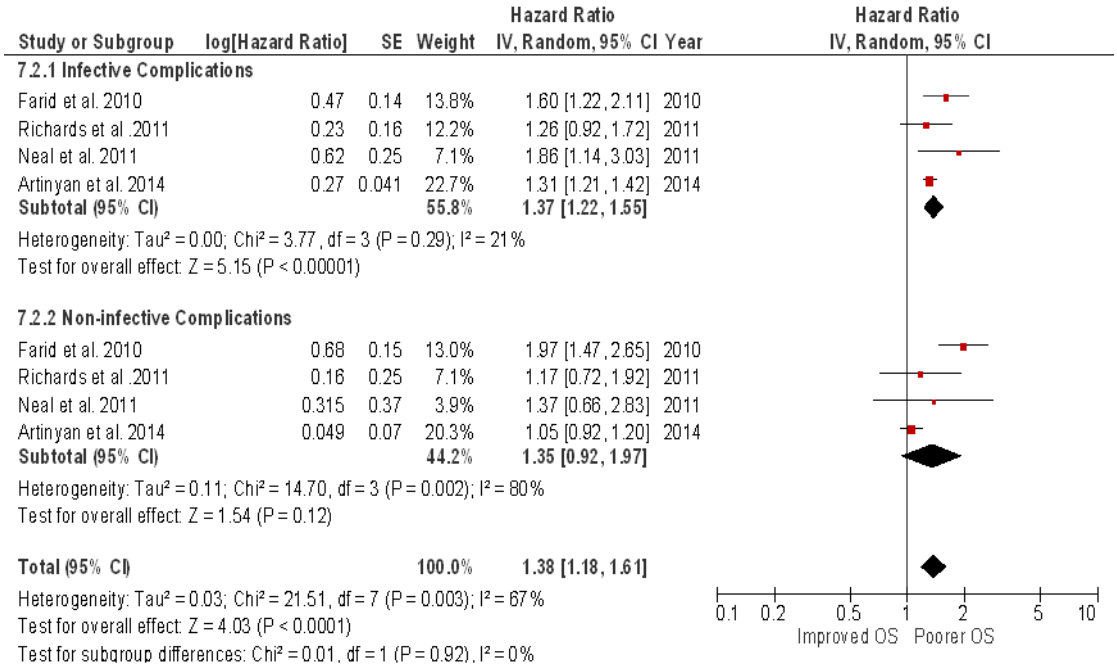

Figure 1-5: Impact of complication type on overall survival

1.11.4.2 Complication severity

Three papers (Mrak et al. 2013, Odermatt et al. 2015, Xia et al. 2014), including 1,879 patients, reported the effect of complication severity on long term outcomes following resection of primary colonic and rectal cancer using the Clavien Dindo scale. Mrak et al.'s (2013) study (n=811) examined curative surgery for rectal cancer only. They excluded those who died within 30 days of surgery (Clavien Dindo grade 5, 1.5%), then divided patients into 3 groups; those with no complication (Clavien Dindo grade 0, 65.5%), minor complications (Clavien Dindo grades 1 and 2, 20.3%) and major complications (Clavien Dindo grades 3 and 4, 12.7%). When the 3 groups were compared they found no significant difference in 5 year disease free survival (65.7% vs. 61.6% vs. 66.8%) or 10 year disease free survival (52.5% vs. 45.1% vs. 59.3%). Furthermore, there was no significant difference in 5 year overall survival (72.4% vs. 68.4% vs. 71.8%), or 10 year overall survival (56.1% vs. 50.1% vs. 61.2%). In contrast, Odermatt et al. (2015), in a similar number of patients (n=844), examined this in patients undergoing curative elective surgery for both colonic and rectal tumours. Patients were grouped into those who had major postoperative complications (Clavien Dindo grades 3B and 4, 4.6%) or did not (Clavien Dindo grades 0 to 3A, 95.4%). They reported a significantly lower 5 year overall survival in those in the major complication group than the remainder (65% vs. 78%, HR 2.42, p=0.009) but not with 5 year recurrence free survival (65% vs. 73%, HR 1.77, p=0.096). Xia et al. (2014) studied patients undergoing laparoscopic resection of colon cancer, excluding rectal lesions and open surgery (n=224). When patients were grouped into Clavien Dindo grades 0–1 and 2–4, a significant effect was found on both 5 year recurrence free survival (82.1% vs. 40.9%, HR 4.25, p<0.001) and 5 year overall survival (78.5% vs. 41%, HR 2.74, p<0.001).

Eight papers (Farid et al., 2010; de Haas et al., 2011; Pang et al.,2015; Lodewick et al., 2014; Tanaka et al., 2010; Mavros et al.,2013; Schiesser et al., 2008; Ito et al., 2008), comprising 4,032 patients, examined the impact of postoperative complications on long-term outcomes using the Clavien Dindo scale in the context of surgery for colorectal liver metastases. Two papers, with 1,010 (de Haas et al. 2011) and 224 patients (Pang et al. 2015) respectively, found no significant impact of the severity of complications on 5 year disease free or overall survival. Lodewick et al.'s (2014) study (n =266) reported a significant reduction in disease free survival when those with grade 3–4 complications were compared to those without complications (19.4% vs. 29.4%,p=0.045) but not for overall survival (36.2% vs. 46.7%, p=0.160).Tanaka et al.'s (2010) study (n =312) reported

a significant reduction in disease free (31.3% vs. 27.8% vs. 11.3%, p<0.010) and overall survival (55.4% vs. 54.5% vs. 33.7%, p<0.010) when those with no complication (Clavien Dindo grade 0), were compared to those with minor (grade 1–2) and major complication (grade 3–4). The remaining four studies (n = 2,220) all reported a significant reduction in both disease free and overall survival when patients with postoperative complications (Clavien Dindo grade 1–4) were compared to those without (Farid et al., 2010; Schiesser et al., 2008; Ito et al., 2008). Furthermore, Tanaka et al. (2010), Mavros et al. (2013), and Farid et al. (2010), reported poorer disease free survival (p=0.016 and p=0.008, respectively) and overall survival (p=0.004 and p=0.022, respectively) with increasing severity of complications when patients were stratified to no complication (Clavien Dindo grade 0), minor complication (grade 1–2), and major complication (grade 3–4). One study did not present hazard ratios for the impact of complication severity on long term outcomes and so was not included in subsequent meta-analysis (Pang et al. 2014).

Table 1-13: Studies investigating the impact of complication severity on long term outcome

Type	Author	Country	Year	N	Effect of C-D complication severity on long-term outcomes	
					DFS	**OS**
Rectal	Mrak et al.	Austria	2013	811	C-D 0: 65.7% C-D 1-2: 61.6% C-D 3-4: 66.8%	C-D 0: 72.4% C-D 1-2: 68.4% C-D 3-4: 71.8%
Colorectal	Odermatt et al.	UK	2015	844	C-D 0-2: 73% C-D 3-4: 65% p=0.096	C-D 0-2: 78% C-D 3-4: 65% p=0.009
Colon	Xia et al.	China	2014	224	C-D 0-1: 82.1% C-D 2-4: 40.9% p<0.001	C-D 0-1: 78.5% C-D 2-4: 41% p<0.001
CRLM						
	Ito et al.	USA	2008	1067	C-D 0: 48% C-D 1-4:41% p=0.0059	C-D 0: 48% C-D 1-4: 41% p<0.001
	Schiesser et al.	Switzerland/ Australia	2008	197	C-D 0: 1.8 yr C-D 1-4: 1.4yr p=0.040	C-D 0: 4.1yr C-D 1-4: 2.1yr p<0.012
	Farid et al.	UK	2010	705	C-D 0: 26% C-D 1-4: 13% p=0.001	C-D 0: 37% C-D 1-4: 24% p=0.026
	Tanaka et al.	Japan	2010	312	C-D 0: 31.3% C-D 1-2: 27.8% C-D 3-4: 11.3% p<0.010	C-D 0: 55.4% C-D 1-2: 54.5% C-D 3-4: 33.7% p<0.010
	de Haas et al.	Netherlands	2011	1010	C-D 0-2: 17% C-D 3-4: 16% p=0.250	C-D 0-2: 52% C-D 3-4: 42% p=0.110
	Mavros et al.	USA	2013	251	C-D 0: 19.7 months C-D 1-4: 11.8 months p=0.005	C-D 0: 53 months C-D 1-4: 36.6 months p=0.009
	Pang et al.	Australia	2014	224	C-D 0-1: 17 months C-D 2-4: 18 months p=0.658	C-D 0-1: 51 months C-D 2-4: 49 months p=0.877
	Lodewick et al.	Netherlands	2014	266	C-D 0: 29.4% C-D 3-4: 19.4% p=0.045	C-D 0: 46.7% C-D 3-4 36.2% p=0.160

C-D Clavien Dindo, *OS* overall survival, *DFS* disease free survival, *CRLM* colorectal liver metastases

Meta-analysis of the 10 studies (Farid et al. 2010, Mrak et al.2013, Odermatt et al. 2015, Xia et al. 2014, de Haas et al. 2011, Lodewick et al. 2014, Tanaka et al. 2010, Mavros et al. 2013, Schiesser et al. 2008, Ito et al. 2008), including 5687 patients, reporting the impact of complication severity on disease free survival, found a statistically significant impact (HR 1.41, 95% CI1.18–1.68, p<0.001) with considerable heterogeneity (I^2= 80%). At subgroup analysis, the three studies of colorectal resection (Mrak et al. 2013, Odermatt et al. 2015, Xia et al. 2014), including 1,879 patients, found that complication severity had no significant impact on disease free survival (HR 1.89, 95% CI 0.83–4.34, p=0.13). However, the 7 studies of liver resection for colorectal metastases (Farid et al. 2010, de Haas et al. 2011, Lodewick et al. 2014, Tanaka et al. 2010, Mavros et al. 2013, Schiesser et al. 2008, Ito et al. 2008), including 3,808 patients, did find a statistically significant impact (HR 1.30, 95% CI 1.11–1.53, p=0.001). There was considerable heterogeneity amongst both the colorectal and liver resection subgroups (I^2=87% and 75%, respectively).

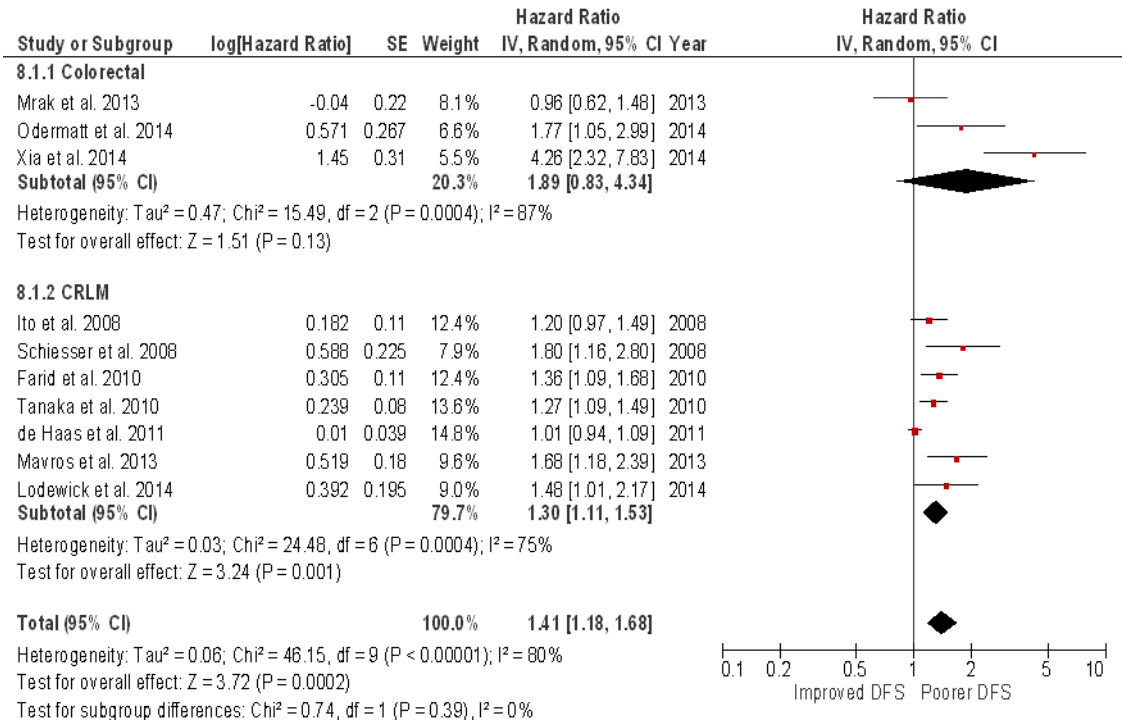

Figure 1-6: Forest plot - impact of complication severity on disease free survival

Meta-analysis of the 10 studies (Farid et al. 2010, Mrak et al. 2013, Odermatt et al. 2015, Xia et al. 2014, de Haas et al. 2011, Lodewick et al. 2014, Tanaka et al. 2010, Mavros et al. 2013, Schiesser et al. 2008, Ito et al. 2008), including 5,687 patients, reporting the impact of complication severity on overall survival, found a statistically significant impact (HR1.45, 95% CI 1.25–1.69, p<0.001) with substantial heterogeneity (I^2= 67%). At subgroup analysis, the three studies of colorectal resection (Mrak et al. 2013, Odermatt et al. 2015, Xia et al. 2014), including 1,879 patients, found that complication severity had no significant impact on overall survival (HR 1.66, 95% CI 0.77–3.56, p=0.19). However, the seven studies of liver resection for colorectal metastases (Farid et al. 2010, de Haas et al. 2011, Lodewick et al. 2014, Tanaka et al. 2010, Mavros et al. 2013, Schiesser et al. 2008, Ito et al. 2008), including 3,808 patients, did find a statistically significant impact (HR 1.43, 95% CI 1.25–1.65, p<0.001). There was considerable heterogeneity amongst both the colorectal and liver resection subgroups (I^2= 84% and 60%, respectively).

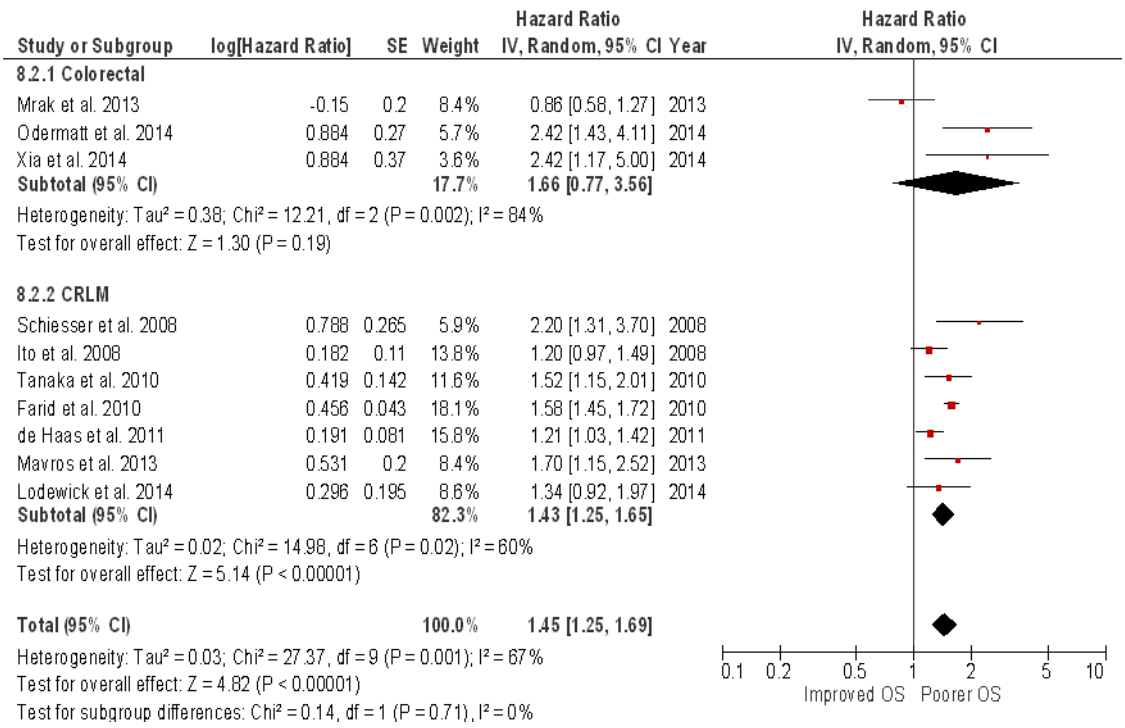

Figure 1-7: Forest plot - impact of complication severity on overall survival

The main limitation of this meta-analysis was the heterogeneity of the included studies in terms of population, complication severity grouping, and long-term outcome measures. In particular, in the analysis of infective and non-infective complications studies reporting resection of colorectal primaries and CRLMs were grouped together. Given the significantly poorer prognosis of patients with CRLM this may have resulted in bias in favour of association with poorer survival. In addition, the majority of studies reporting the impact of complications on survival following resection of CRLMs reported associations between complications and prognostic variables including number of metastases, size of metastases and increasing extent of resection. However, most studies went on to report their findings in terms of survival using a multivariate model accounting for these associations. Furthermore, Xia et al reported that complications of greater severity were associated with a an almost halving of DFS in that patient group, suggesting the possibility of observation or selection bias in that study. Finally, although there is a significant body of literature regarding the type and severity of postoperative complication, to our knowledge only one study (Artinyan et al. 2014) directly compared the two in their effect on long-term outcome, but did not use the Clavien Dindo scale, instead using complication site as a surrogate.

The results of the present review indicate that infective complications have a negative impact on overall and disease free survival following surgery for colorectal cancer and CRLM when grouped together. Complications of greater severity were associated with poorer overall and disease free survival in patients undergoing surgery for CRLM but not primary colorectal surgery. It is likely in these patients that complications of greater severity are infective in nature (e.g. anastomotic leak, collection) however few studies have directly compared the impact of the two methods of categorisation.

2 Summary and Aims

Colorectal cancer is the fourth most common cancer and the second most common cause of cancer death in the UK. Despite advances in treatment, only around half of patients with colorectal cancer are still alive 5 years after diagnosis. Surgery remains the cornerstone of its management, however it is associated with significant rates of postoperative complication and mortality. Although disease stage at diagnosis remains the most important prognostic factor, these postoperative complications are now also recognised to be associated with poorer oncologic outcomes.

The magnitude of the postoperative systemic inflammatory response, in particular exceeding C-reactive protein (CRP) concentrations of 150mg/L on postoperative days 3 or 4, has been reported to be associated with the development of infective type postoperative complications following surgery for colorectal cancer. However, it remains unclear whether the postoperative systemic inflammatory response has a causal relationship with these postoperative complications, or whether it is simply an epiphenomenon of developing infection. One hypothesis is that an exaggerated innate immune response to surgery leads to immunologic dissonance and relative suppression of the adaptive immune system.

If the postoperative systemic inflammatory response is found to have a direct and causal relationship with postoperative complications, and also with long term prognosis, then strategies to manage it will become important in optimising postoperative outcomes in surgery for colorectal cancer. High BMI, comorbid disease, and the presence of preoperative systemic inflammation increase the postoperative systemic inflammatory response. Conversely, only the use of laparoscopic surgery is at present known to objectively reduce the magnitude of the postoperative systemic inflammatory response. If the postoperative systemic inflammatory response is to become a therapeutic target, with the aim of improving short and long term outcomes following surgery for colorectal cancer, then additional methods of attenuation will be required. This might include strategies to preoperatively optimise patients in terms of fitness and pre-existing inflammation, adjustments to surgical and anaesthetic techniques, and the use of drugs including corticosteroids and anti-inflammatories.

The present thesis aims to further examine the relationship between the postoperative systemic inflammatory response, postoperative complications, and long term oncologic outcomes following surgery for colorectal cancer, and specifically to:

1. Determine whether the magnitude of the postoperative systemic inflammatory response is associated with postoperative complications when defined by their severity.

2. Determine whether the postoperative systemic inflammatory response is itself a prognostic factor in patients who have undergone surgery for colorectal cancer.

3. Determine what additional patient and operative variables influence the magnitude of the postoperative systemic inflammatory response, including cardiorespiratory fitness, the use of neoadjuvant chemoradiotherapy prior to surgery for rectal cancer, the formation of a temporary defunctioning stoma, the duration of surgery, and patient ethnicity.

4. Determine whether established thresholds of CRP in the postoperative period might be used along with existing perioperative care strategies to improve the early detection of postoperative complications.

5. Determine whether the use of perioperative corticosteroids is associated with the attenuation of the postoperative systemic inflammatory response, and whether this is associated with improved short-term postoperative outcomes.

3 Postoperative C-reactive protein measurement predicts the severity of complications following surgery for colorectal cancer

3.1 Introduction

Although long-term outcome is mostly related to stage at initial presentation, studies have shown that infective postoperative complications (Artinyan et al. 2014), and in particular anastomotic leak (Mirnezami et al. 2011), have a negative impact on both short and long-term survival following surgery for colorectal cancer.

Postoperative complications have previously been defined as "deviation from the normal postoperative course" (Dindo et al. 2004). They have been classified by type, primarily as infective or non-infective (McArdle et al. 2005, Richards et al. 2011), or by severity using the Clavien Dindo scale (Dindo et al. 2004, Mrak et al. 2013, Clavien et al. 2009).

Two recent meta-analyses (Warschkow et al. 2012a, Singh et al. 2014a), including more than 2,000 patients, have reported the utility of postoperative serum CRP measurement in the early diagnosis of postoperative infective type complications and anastomotic leak after colorectal surgery. A recent comprehensive review suggests that values of CRP above 150mg/L on postoperative days 3-5 are associated with postoperative complications following colorectal surgery and should prompt clinical review (McDermott et al. 2015). Serum albumin has also been investigated, and a concentration below 25g/L on postoperative day 3 has been reported to be associated with the development of infective complications after surgery for colorectal cancer (Platt et al. 2012).

An alternative approach is to classify the severity of the complication based upon the intervention required to treat it (Dindo et al. 2004). A recent retrospective study (Selby et al. 2014), with a small cohort of 127 patients who had undergone elective colorectal cancer surgery, used the Clavien Dindo classification of postoperative complications and reported that the severity of a complication increased with the magnitude of the postoperative day 3 CRP.

The aim of the present study was to examine the relationship between the established postoperative serum CRP and albumin thresholds for the development of infective complications and the severity of complications as defined by the Clavien Dindo classification following elective surgery for colorectal cancer.

3.2 Patients and Methods

3.2.1 Patients

This observational study included patients who underwent elective, potentially curative resection for histologically confirmed colorectal cancer in two hospitals between January 2011 and January 2013. Patients who underwent emergency surgery, who received neoadjuvant chemotherapy or radiotherapy, or who had existing inflammatory conditions, e.g. inflammatory bowel disease and the systemic vasculitides, were excluded.

The decision to perform laparoscopic or open resection was at the discretion of the operating surgeon. All patients received prophylactic antibiotics and venous thromboprophylaxis prior to the induction of anaesthesia as per hospital policy. On each postoperative day, patients were clinically assessed and had blood samples, including serum CRP and albumin, obtained as standard until discharged. Further postoperative investigation and intervention was at the discretion of the patient's surgical team, who were not blind to serum CRP or albumin results.

3.2.2 Methods

All data was collected prospectively in a database, anonymised, and was subsequently analysed. Recorded information included patient demographics, tumour site, TNM stage (TNM, AJCC), surgical approach, complications, preoperative and postoperative serum CRP measurements. Data regarding the nature, severity and management of complications was retrospectively categorised using the Clavien Dindo scale. Any uncertainties were addressed by review of electronic and/or physical case notes. This study was approved as part of surgical audit.

Serum concentrations of CRP (mg/L) were measured using an autoanalyzer (Architect; Abbot Diagnostics, Maidenhead, UK) with a lower detectable limit of 0.2 mg/L, as was serum albumin (normal range 35-50g/L).

The validated Clavien Dindo classification (Clavien et al. 2009), rather than defining the complication itself, assigns a value from 0 (no complication) to 5 (death) based on the intervention required to treat the complication.

The preoperative modified Glasgow Prognostic Score (mGPS), which is associated with cancer specific survival independent of disease stage (McMillan 2013), was calculated in patients for whom preoperative serum CRP and albumin were available.

The neutrophil lymphocyte ratio (NLR), which is associated with cancer specific survival independent of disease stage (Guthrie et al. 2013), was also calculated for each patient for whom preoperative neutrophil and lymphocyte counts were available.

3.2.3 Statistical Analysis

Categorical data regarding patient characteristics were compared using the Chi square test. Data regarding postoperative CRP were non-normally distributed and are presented as medians and ranges. Medians of multiple groups were compared using the Kruskal-Wallis test. The magnitude of CRP by each postoperative day was displayed as 95% confidence intervals of the median. In all tests, a two sided p value <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS version 21 for Windows (Chicago, IL, USA).

3.3 Results

In total, 241 patients were included in the study. 142 (59%) were male and 166 (69%) were over 65 years old. Most had colonic (86%) and node negative (65%) disease. 11 patients (5%) had metastatic disease at the time of surgery, of whom 7 had synchronous hepatectomy to treat liver metastases. The remaining 4 were referred to other specialities for curative surgical management of their metastatic disease following their colorectal surgery. 112 (46%) patients had laparoscopic surgery with a further 11 (5%) having an initial laparoscopic approach but requiring conversion to open surgery.

Of the 241 patients, a complication occurred in 119 (49%) as shown in Table 3-1. The majority of complications required minimal postoperative intervention and fell into Clavien Dindo grades 1 (22, 9%) and 2 (69, 28%). Complications in fewer patients required more significant action, with Clavien Dindo grade 3 representing surgical or radiological intervention (15, 6%) and 4 of critical care requirement or organ failure (6, 3%). Death (Clavien Dindo grade 5) occurred in 7 patients (3%). Of the 119 complications, 94 (79%) were due to either surgical site (65) or remote site (29) infection, and the remaining 25 (21%) were non-infective complications.

The relationship between the severity of complication and the perioperative serial CRP is shown in Figure 3-1. In both cases there was little difference in the median preoperative and first postoperative day CRP. Those who developed a complication then sustained a higher median CRP from postoperative day 2 onward.

Table 3-2 shows patients' perioperative characteristics when grouped by Clavien Dindo grade 0 (no complication), grade 1-2, and grade 3-5 complications. No significant difference was found in age group, gender, TNM stage, or tumour site. A significantly higher proportion of patients who suffered a Clavien Dindo grade 3-5 complication underwent open surgery (16%) compared to those who underwent laparoscopic surgery (7%, $p=0.001$). In addition, a significantly higher proportion of patients who underwent open surgery exceeded the established postoperative CRP threshold of 150mg/L on postoperative days 3 (67% vs. 35%, $p<0.001$) and 4 (53% vs. 39%, $p=0.044$). A significantly greater proportion of patients who suffered a Clavien Dindo grade 3-5 complication had an mGPS score of 2 (44%) than those who experienced a grade 1-2 (19%) or no complication (17%, $p=0.02$). Preoperative neutrophil lymphocyte ratio (NLR) was not significantly associated with the different Clavien Dindo classification groups.

When compared between Clavien Dindo grade groups 0, 1-2, and 3-5 (Table 3-2) there was a significant difference in median CRP on postoperative day 3 (118mg/L vs. 208mg/L vs. 251mg/L, $p<0.001$) and day 4 (98mg/L vs. 161mg/L vs. 243mg/L, $p<0.001$). When compared between Clavien Dindo grade groups 0, 1-2 and 3-5, the established postoperative day 3 CRP threshold of 150mg/L was exceeded by 31%, 54%, and 79% of patients respectively ($p<0.001$). When compared between Clavien Dindo grade groups 0, 1-2 and 3-5, the established postoperative day 4 CRP threshold of 150mg/L was exceeded by 42%, 64%, and 86% respectively ($p<0.001$).

When compared between Clavien Dindo Grade groups 0, 1-2, and 3-5 (Table 3-2) there was a significant difference in median albumin on postoperative day 3 (28g/L vs. 26g/L vs. 23g/L, $p<0.001$) and day 4 (27g/L vs. 25g/L vs. 23g/L, $p<0.001$). When compared between Clavien Dindo grade groups 0, 1-2, and 3-5, the established postoperative day 3 albumin threshold of 25g/L was breached by 23%, 48%, and 64% respectively ($p<0.001$).

3.4 Discussion

The results of the present study demonstrate that established postoperative serum CRP and albumin thresholds, as measured on days 3 and 4 following elective surgery for colorectal cancer, are not only associated wth the type, but also the severity of postoperative complications, as defined by the Clavien Dindo scale. In particular, those patients who required significant surgical or radiological intervention, ITU admission, or who died (grades 3-5) exceeded those thresholds previously defined for the development of infective complications.

In the present study, the proportion of patients in Clavien Dindo grades 1-5 were similar (49%) to that in Selby and colleague's paper (43%) as were the proportions in grades 3-5 at 12% and 11% respectively, although the present study had almost double the number of patients. Similarly, Selby and co-workers included only elective operations for colorectal cancer however it was not clear whether they included patients who had undergone neoadjuvant treatment nor was there data regarding the site of tumours or whether patients underwent laparoscopic surgery.

The use of the postoperative systemic inflammatory response as evidenced by CRP measurement in colorectal cancer surgery to detect infective complications has been applied successfully to other cancer surgery (Dutta et al. 2011, Warschkow et al. 2012b, Warschkow et al. 2012c) and in surgery for benign conditions (Warschkow et al. 2012d). It may be that the findings of the present study with regard to complication severity can also be applied to surgery for other cancers and benign disease.

In the present study, approximately half of the patients underwent laparoscopic surgery. It was of interest that fewer patients who underwent laparoscopic surgery developed Clavien Dindo grade 3 to 5 complications when compared to open surgery. In addition, and in keeping with prior studies, a lower proportion of patients who underwent laparoscopic surgery exceeded the established CRP threshold of 150mg/L on postoperative days 3 and 4 (Wichmann et al. 2005, Ortega-Deballon et al. 2010, Ramanathan et al. 2015b). Given that laparoscopic surgery is recognised to generate a smaller systemic inflammatory response than open surgery (Watt et al. 2015c), it might be hypothesised that there is a causal relationship between the magnitude of the surgical trauma and the severity of complications following surgery for colorectal cancer. Further work investigating the relationship between the magnitude of the postoperative systemic inflammatory response

and the severity of complications in patients undergoing surgery for colorectal cancer is warranted.

Moreover, complications of increasing severity may also lead to poorer long-term outcomes, although only a small number of studies have examined this in the context of the Clavien Dindo classification (Pucher et al. 2014). This raises the possibility that the mechanism by which postoperative complications lead to poorer oncologic outcomes is mediated by the postoperative systemic inflammatory response. However, it remains to be determined whether strategies to reduce the magnitude of the postoperative systemic inflammatory response might also reduce the severity of postoperative complications and/or influence longer term outcomes.

The main limitation of the present study was the relatively small number of patients examined, particularly with regard to those with Clavien Dindo grade 3-5 complications, although the proportion of patients in each grade were similar to that in Selby and colleagues' report with 127 patients. Due to the retrospective nature of the study not all patients had CRP measured on each postoperative day, with almost 20% of included patients not having a recorded postoperative day 4 CRP. Despite BMI being a factor thought to be associated with the postoperative systemic inflammatory response it was not available from both centres and therefore could not be included as a confounder. Using the Clavien Dindo system may lead to some bias as surgeons, anaesthetists, and ward staff may manage a given case or complication differently from one another. The surgical teams caring for each patient were not blind to the postoperative CRP or albumin concentration as it was used as a part of routine clinical care and may have guided, in part, the patient management on which the Clavien Dindo definitions depend.

In summary, there was a direct association between the postoperative systemic inflammatory response, as evidenced by serum CRP and albumin, and the severity of complications following surgery in patients with colorectal cancer.

3.5 Tables and Footnotes

Table 3-1: Frequency of complication by Clavien Dindo grade

Clavien Dindo Grade	N	%
0	122	51
1	22	9
2	69	28
3	15	6
4	6	3
5	7	3
Total	241	100

Table 3-2: Patient characteristics and postoperative systemic inflammation by Clavien Dindo grade

Characteristic	All	Clavien Dindo complication grade			
		0a	1-2b	3-5c	P
Age (<65/65-74/>74)	75/74/92	40/37/45	29/29/33	6/8/14	0.695
Gender (male/female)	142/99	65/57	58/33	19/9	0.183
TNM stage (I/II/III/IV)	58/99/73/11	27/57/34/4	24/32/32/3	7/10/7/4	0.135
Site (colon/rectum)	209/32	110/12	75/16	24/4	0.254
Preop mGPS (0/1/2)	152/20/46	84/7/19	56/11/16	12/2/11	0.02
Preop NLR (≤5/>5)	202/33	102/17	77/12	23/4	0.98
Approach (open/lap)	129/112	50/72	59/32	20/8	<0.001
POD3 CRP (median,range,mg/L)	158(11-601)	118(11-316)	208(35-601)	251(109-346)	<0.001
POD4 CRP(median,range,mg/L)	143(21-528)	98(21-346)	161(25-528)	243(67-403)	<0.001
POD3 CRP>150mg/L (no/yes)	106/119	75/39	27/58	4/22	<0.001
POD4 CRP>150mg/L (no/yes)	102/93	58/26	38/45	6/22	<0.001
POD3 albumin (median,range,g/L)	26(9-40)	28(15-40)	26(12-34)	23(9-33)	<0.001
POD4 albumin (median,range,g/L)	25(10-38)	27(16-38)	25(10-32)	23(11-30)	<0.001
POD3 albumin <25g/L (no/yes)	134/80	82/25	43/39	9/16	<0.001

mGPS preoperative modified Glasgow Prognostic score (0 = CRP<10mg/L, 1 = CRP≥10mg/L and albumin ≥35g/L, 2 = CRP≥10mg/L and albumin <35g/L). NLR preoperative neutrophil lymphocyte ratio. POD postoperative day. a) 0 = no complication, b) 1-2 = complication requiring minor intervention, c) 3-5 = complication requiring significant intervention

3.6 Figures and Legends

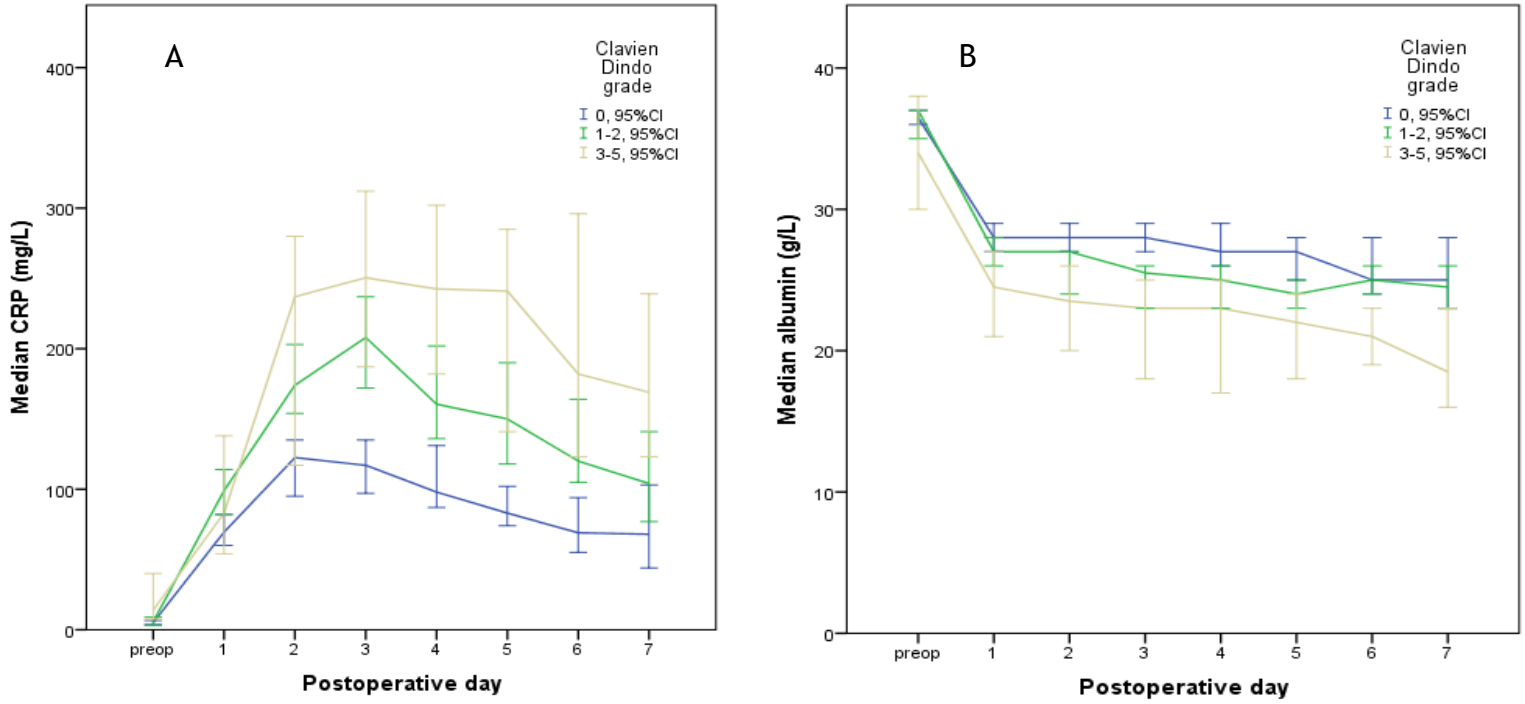

Figure 3-1: (A) perioperative CRP (mg/L) and (B) albumin concentrations on postoperative days 1-7 by Clavien Dindo grade

4 A comparison of the magnitude of the postoperative systemic inflammatory response and complication severity and their impact on survival following surgery for colorectal cancer.

4.1 Introduction

There is good evidence that infective type complications have a significant negative impact on survival following surgery for colorectal cancer (Artinyan et al. 2015), whilst anastomotic leak is associated with disease recurrence (Mirnezami et al. 2011). Fewer studies have examined the impact of complication severity on long-term outcomes, although those which have, reported poorer disease free and overall survival (Xia et al. 2014, Odermatt et al. 2014). Indeed, a recent meta-analysis reported that severe complications had a greater impact on long-term outcomes following surgery for colorectal liver metastases, although the association between Clavien Dindo grade and survival following resection of primary colorectal tumours did not reach statistical significance (McSorley Introduction).

The magnitude of the systemic inflammatory response, as evidenced by postoperative CRP, has been reported to be associated with the development of postoperative infective type complications (Ramanathan et al. 2013, Singh et al. 2014a, Platt et al. 2012). As discussed in the previous chapter, two recent studies have examined the relationship between the magnitude of the postoperative systemic inflammatory response, as measured by CRP, and the severity of complications following surgery for colorectal cancer (Selby et al. 2014, McSorley Chapter 3). More recently, a comprehensive review suggested that CRP concentrations above a threshold of 150mg/L on postoperative days 3 to 5 should prompt investigation and or treatment of potential postoperative complications in colorectal surgery (McDermott et al. 2015).

Therefore, it could be assumed that the postoperative systemic inflammatory response does have a negative impact on long term outcomes, through its relationship with postoperative complications. However, two recent studies in oesophagogastric cancer have suggested that CRP concentrations in the postoperative period are significantly associated with long-term outcomes independent of such postoperative complications (Matsuda et al 2015, Saito et al. 2015). To the author's knowledge no study investigating the interaction between the magnitude of the postoperative systemic inflammatory response, complications, and their impact on long-term outcomes has been carried out in colorectal cancer surgery.

Therefore, the aims of the present study were to examine the relationship between the magnitude of the postoperative systemic inflammatory response and complication severity,

and to determine which, if any, had the greatest impact on long-term outcomes following surgery for colorectal cancer.

4.2 Patients and Methods

4.2.1 Patients

This observational study included patients who underwent elective, potentially curative surgery for histologically confirmed colorectal cancer in a single centre between March 2008 and May 2013. Patients with metastatic disease, who underwent palliative procedures, or had existing inflammatory conditions, were excluded.

All patients received prophylactic antibiotics and venous thromboprophylaxis prior to the induction of anaesthesia as per hospital policy. On each postoperative day, patients were clinically assessed and had blood samples, including serum CRP, obtained as standard until discharged. Further postoperative investigation and intervention was at the discretion of the patient's surgical team who were not blind to postoperative blood results.

4.2.2 Methods

All data was collected prospectively in a database, anonymised, and was subsequently analysed. Recorded information included patient demographics, tumour site, TNM stage (TNM, AJCC), surgical approach, whether adjuvant or neoadjuvant treatment was given, whether the presentation was elective or emergency, the presence of complications, preoperative serum CRP, and albumin measurements. Data regarding the nature, severity, and management of complications was retrospectively categorised using the Clavien Dindo scale (Dindo et al. 2004). For patients with multiple complications, the most serious was recorded using both the type and Clavien Dindo grade. Any uncertainties were addressed by review of electronic and/or physical case notes. Date and cause of death were cross-checked with the Registrar General (Scotland). Death records were complete until 30th June 2015 which served as the censor date. The study was approved by the West of Scotland Research Ethics Committee, Glasgow.

Serum concentrations of CRP (mg/L) were measured using an autoanalyzer (Architect; Abbot Diagnostics, Maidenhead, UK) with a lower detectable limit of 0.2 mg/L, as was serum albumin (normal range 35-50g/L). The preoperative modified Glasgow Prognostic Score (mGPS) was calculated from preoperative serum CRP and albumin (McMillan 2013).

4.2.3 Statistical Analysis

Categorical data regarding patient characteristics were compared using the Chi square test and Chi square test for linear association where appropriate. Patients who underwent colonic resection were analysed as a subgroup due to significant differences in postoperative complication rates between those with colonic and rectal cancers. Those patients who died within 30 days of surgery or during the same admission (Clavien Dindo grade 5 complications) were excluded from survival analysis. Univariate and multivariate survival data were analysed using Cox's proportional hazards model. Variables associated with disease specific or overall survival at a significance level of $p < 0.1$ on univariate analysis were included in multivariate modelling using backward conditional regression where a two sided p value < 0.05 was considered statistically significant. Disease specific survival was defined as time from date of surgery to date of cancer specific death. Overall survival was defined as time from date of surgery to date of death from any cause. Statistical analyses were performed using IBM SPSS version 22 for Windows (Chicago, IL, USA).

4.3 Results

4.3.1 Patients

377 patients were included having undergone potentially curative surgery for colorectal cancer in the absence of metastatic disease. The majority were male (55%), over 65 years old (68%), with colonic (63%) and node negative disease (66%). 110 patients (29%) had a laparoscopic resection with the remainder having open surgery. Amongst the 138 patients with rectal cancer, 65 (47%) with locally advanced or margin threatening disease had neoadjuvant treatment, of which 10 (15%) were subsequently found to have had a pathological complete response. Of all included patients, 29% went on to have adjuvant treatment following surgery.

4.3.2 Complications

Of 377 patients, 138 (37%) experienced complications (Table 4-1). 4 patients (1%) died within 30 days of surgery or during the same admission. When classified using the Clavien Dindo scale, 108 (30% of all patients) were grade 1-2 (i.e. required minor intervention) and 26 (6%) were grade 3-4 (i.e. necessitated major intervention). When patient's demographic, pathological, and clinical characteristics were compared across complication severity (Table 4-2), male gender ($p<0.01$), ASA score ($p<0.05$), smoking status ($p<0.05$), and rectal cancer ($p<0.05$) were significantly associated with Clavien Dindo grade. There was a significant association between complication severity and the proportion of patients breaching the established CRP threshold of 150mg/L on postoperative days 2 ($p=0.004$), 3, and 4 (both $p<0.001$).

4.3.3 Follow up

After exclusion of postoperative mortality (4, 1%), death due to any cause occurred in 81 patients (22%) with 53 (14%) being cancer specific. The median follow up for patients alive at the time of their censoring was 46 months (range 24-86 months).

4.3.4 Disease Specific Survival

On univariate analysis (Table 4-3), age (HR 1.54, 95% CI 1.08-2.21, $p=0.018$), ASA score (HR 1.69, 95% CI 1.16-2.46, $p=0.007$), TNM stage (HR 2.50, 95% CI 1.63-3.85, $p<0.001$), mGPS (HR 1.67, 95% CI 1.23-2.26, $p=0.001$), breaching the established CRP threshold of 150mg/L on postoperative day 3 (HR 1.84, 95% CI 1.01-3.35, $p=0.047$), and

postoperative day 4 (HR 2.53, 95% CI 1.43-4.48, p=0.001), infective complications (HR 2.02 (95% CI 1.16-3.52) and complication severity (HR 1.66, 95% CI 1.13-2.43, p=0.009), were associated with disease specific survival and included in multivariate analysis. On multivariate analysis (Table 4-3), ASA score (HR 1.52, 95% CI 1.01-2.28, p=0.044), mGPS (HR 1.49, 95% CI 1.08-2.07, p=0.016), TNM stage (HR 2.46, 95% CI 1.52-3.96, p<0.001), and breaching the established CRP threshold of 150mg/L on postoperative day 4 (HR 2.00, 95% CI 1.12-3.59, p=0.020) remained independently associated with poorer disease specific survival. Breaching the established CRP threshold of 150mg/L on postoperative day 3 was not included in multivariate analysis as it was directly associated with breaching the established CRP thresholds of 150mg/L on postoperative day 4, which had a greater statistical significance on univariate analysis.

4.3.5 Overall survival

On univariate analysis (Table 4-3), age (HR 1.83, 95% CI 1.36-2.48, p<0.001), ASA score (HR 1.92, 95% CI 1.41-2.61, p<0.001), mGPS (HR 1.52, 95% CI 1.18-1.96, p=0.001), TNM stage (HR 1.70, 95% CI 1.25-2.31, p=0.001), breaching the established CRP threshold of 150mg/L on postoperative day 2 (HR 1.99, 95% CI 1.22-3.26, p=0.006, postoperative day 3 (HR 1.76, 95% CI 1.08-2.85, p=0.022), and postoperative day 4 (HR 2.02, 95% CI 1.27-3.20, p=0.003), and adjuvant treatment (HR 0.64, 95% CI 0.37-1.09, p=0.098) were associated with overall survival and included in multivariate analysis. On multivariate analysis (Table 4-3), ASA score (HR 1.49, 95% CI 1.05-2.10, p=0.024), TNM stage (HR 2.12, 95% CI 1.45-3.09, p<0.001), breaching the established CRP threshold of 150mg/L on postoperative day 4 (HR 2.14, 95% CI 1.34-3.41, p=0.001), and adjuvant treatment (HR 0.33, 95% CI 0.17-0.64, p=0.001) all remained independently associated with overall survival. Breaching the established CRP threshold of 150mg/L on postoperative day 3 was not included in multivariate analysis as it was directly associated with breaching the established CRP thresholds of 150mg/L on postoperative day 4, which had a greater statistical significance on univariate analysis.

4.3.6 Colonic resection

When the subgroup of 239 patients who underwent surgery for colonic cancer were considered, 79 (33%) experienced complications (Table 4-4). No patients died within 30 days of surgery or during the same admission. When classified using the Clavien Dindo scale, 63 were grade 1-2 and 16 were grade 3-4. When patients' demographic,

pathological, and clinical characteristics were compared across complication severity (Table 4-4) only smoking status (p=0.047) was significantly associated. There was a significant association between complication severity and the proportion of patients breaching the established CRP threshold of 150mg/L on postoperative days 2 (p=0.032), 3 (p=0.002), and 4 (p=0.005).

On multivariate analysis (Table 4-5) mGPS (HR 1.81, 95% CI 1.20-2.72, p=0.005), TNM stage (HR 2.28, 95% CI 1.23-4.21, p=0.009), and breaching the established CRP threshold of 150mg/L on postoperative day 4 (HR 2.42, 95% CI 1.13-5.18, p=0.023) were independently associated with disease specific survival after surgery for colonic cancer. ASA score (HR 1.99, 95% CI 1.28-3.10, p=0.002), mGPS (HR 1.53, 95% CI 1.11-2.10, p=0.010) and breaching the established CRP threshold of 150mg/L on postoperative day 4 (HR 2.32, 95% CI 1.29-4.20, p=0.005) were independently associated with overall survival after surgery for colonic cancer.

4.4 Discussion

The results of the present study report a significant association between the magnitude of the postoperative systemic inflammatory response and complication severity following surgery for colorectal cancer. Furthermore, the magnitude of the postoperative systemic inflammatory response, in particular CRP on postoperative day 4, was significantly associated with disease specific and overall survival independent of postoperative complications. These relationships remained in a subgroup of patients who underwent colonic surgery. Therefore, the present results suggest that the magnitude of the postoperative systemic inflammatory response may also be an important factor in relation to long term oncologic outcomes in this group of patients.

The results of the present study are consistent with previous studies showing an association between male gender, preoperative ASA score, smoking status and complication severity following colorectal surgery (McDermott et al. 2015, Kirchoff et al. 2008, Lipska et al. 2006). Moreover, two recent studies reported the association between complication severity and the magnitude of the postoperative systemic inflammatory response in patients with colorectal cancer (Selby et al. 2014, McSorley Chapter 3), and also in patients undergoing surgery for gastric and oesophageal cancer (Matsuda et al 2015, Saito et al. 2015).

A recent meta-analysis reported that complication type and severity were independently associated with poorer oncologic outcomes following colorectal surgery, and liver resection for colorectal cancer (McSorley Introduction). However, the present study is the first to include a measure of the magnitude of the systemic inflammatory response together with the severity of complication in survival analysis following surgery for colorectal cancer. Although the relationship between postoperative infective complications and poorer survival in patients with colorectal cancer has been extensively documented, complication severity using the Clavien Dindo scale provides a validated, objective framework for the definition of such postoperative complications (Clavien et al. 2009).

Taken together, the implications of these results are important. They would suggest that the mechanisms that link the magnitude of the postoperative systemic inflammatory response, postoperative complications, and poorer oncological outcomes are inflammatory in aetiology (Powell et al. 2015). In previous work, it has been reported that the presence of preoperative systemic inflammation, as measured by the mGPS, but not postoperative

complication, was associated with poorer long-term outcomes following surgery for colorectal cancer (Richards et al. 2011). However, the magnitude of the postoperative systemic inflammatory response was not considered. More recently, it is now recognised that the magnitude of the systemic inflammatory response following surgery for colorectal cancer is associated with the extent of postoperative complications (Singh et al. 2014a, Platt et al. 2012, Selby et al. 2014, McSorley Chapter 3). The present study shows that both the pre and postoperative systemic inflammatory responses are associated with oncologic outcomes independent of tumour stage and postoperative complications.

The exact mechanisms underlying these relationships are unclear. However, the presence of an innate immune driven systemic inflammatory response can suppress cytotoxic immunity and promote the development of postoperative complications and tumour progression (Roxburgh et al. 2013, Roxburgh et al. 2016, McAllister and Weinberg 2014). If this were proven to be the case it would therefore be rational to consider the postoperative systemic inflammatory response a target for therapeutic intervention. Clearly, such therapeutic intervention would also test the above hypothesis since it would be anticipated that a reduction in the postoperative systemic inflammatory response would not only result in a reduction in the severity of postoperative complications but also improve long-term outcomes, not only in colorectal cancer surgery, but in surgery for all solid tumours. It remains to be determined whether the modulation of the postoperative systemic inflammatory response may reduce the frequency and/or severity of postoperative complications or improve long-term outcomes following surgery for colorectal cancer.

A main limitation of the present study was the relatively short follow up period. This may be in part responsible for the seemingly large treatment effect size of adjuvant therapy, disproportionate to that recognised within the established literature. The retrospective nature of the study leads to missing data and the possibility of missing patients. Not all patients had CRP measured on each postoperative day, with almost 20% of included patients not having a recorded postoperative day 4 CRP. In addition, a relatively small number of Clavien Dindo grade 3-4 complications occurred. The significant difference in frequency of severe complication between colonic and rectal resection led to the separate analysis of patients undergoing colonic resection. Nevertheless, comparative analysis showed similar significant relationships with survival when compared to the whole cohort.

In summary, the results of the present study report that the magnitude of the postoperative systemic inflammatory response was associated with oncologic outcome following surgery for colorectal cancer, independent of postoperative complications or disease stage.

4.5 Tables and Footnotes:

Table 4-1: Postoperative complications by type and severity

Complication			n	%
No complication			239	63
Any complication			138	37
Complication type				
Infective	All infective complications		94	25
	SSI	wound infection	43	11.5
		anastomotic leak	16	4
		intra-abdominal abscess	6	2
	RSI	pneumonia	23	6
		septicaemia	2	0.5
		UTI	4	1
Non-infective	All non-infective complications		44	12
	wound	seroma	2	0.5
		dehiscence	4	1
	surgical site	haemorrhage	1	0.25
	cardiac	MI	4	1
		arrhythmia	9	2.5
	vascular	VTE	3	0.75
		CVA	2	0.5
	urinary	renal failure	4	1
		acute urinary retention	3	0.75
	gastrointestinal	diarrhoea (non-infective)	4	1
		ileus	8	2.25
Complication severity				
	Clavien Dindo Grade	0	239	63
		1	36	10
		2	72	20
		3	18	4
		4	8	2
		5	4	1

SSI surgical site infection, RSI remote site infection, UTI urinary tract infection, MI myocardial infarction, VTE venous thromboembolism, CVA cerebrovascular accident

Table 4-2: Patient characteristics by severity of complication following surgery for colorectal cancer

Characteristic	All	Clavien Dindo complication grade				
		0a	1-2b	3-4c	5d	P
N (%)	377 (100)	239 (63)	108 (30)	26 (7)	4 (1)	-
Age (<65/65-74/>74)	122/149/106	82/96/61	31/44/33	9/7/10	0/2/2	0.451
Sex (male/female)	208/169	116/123	74/34	15/11	3/1	0.005
BMI (<20/20-25/26-30/>30)	16/112/114/90	12/69/75/55	3/32/31/28	1/8/8/6	0/3/0/1	0.833
ASA score (1/2/3/4)	48/169/145/14	36/112/83/7	9/45/48/6	3/11/12/0	0/1/2/1	0.014
Smoking (never/ex/current)	159/150/61	114/89/31	37/46/23	8/11/7	0/4/0	0.015
Preop mGPS (0/1/2)	284/37/56	180/23/36	82/9/17	18/5/3	4/0/0	0.636
Site (colon/rectum)	239/138	160/79	63/45	16/10	0/4	0.024
TNM stage (0/I/II/III)	10/80/159/128	8/54/101/76	1/20/43/44	0/5/14/7	1/1/1/1	0.120
Neoadjuvant treatment (no/yes)	299/65	191/40	84/19	21/5	3/1	0.970
Approach (open/laparoscopic)	266/110	162/77	83/24	18/8	3/1	0.323
Surgery >4h (yes/no)	83/247	51/154	22/76	9/16	1/1	0.456
Stoma (yes/no)	115/262	65/174	39/69	8/18	1/1	0.087
POD 2 CRP >150mg/L (yes/no)	205/162	114/117	72/35	16/9	3/1	0.004
POD 3 CRP >150mg/L (yes/no)	187/169	100/124	67/38	19/5	1/2	<0.001
POD 4 CRP >150mg/L (yes/no)	126/200	58/137	51/51	16/10	1/2	<0.001
Adjuvant treatment (no/yes)	269/108	171/68	73/35	21/5	4/0	0.323

mGPS preoperative modified Glasgow Prognostic score (0 = CRP<10mg/L, 1 = CRP≥10mg/L and albumin ≥35g/L, 2 = CRP≥10mg/L and albumin <35g/L). POD postoperative day. a) 0 = no complication, b) 1-2 = complication requiring minor intervention, c) 3-4 = complication requiring significant intervention, d) 5 = death

Table 4-3: Impact of complication severity on survival following surgery for colorectal cancer

Survival	Variable	Univariate HR (95% CI)	P	Multivariate HR (95% CI)	P
DSS	Age	1.54 (1.08-2.21)	0.018	-	0.225
	Sex	0.77 (0.45-1.32)	0.344	-	-
	BMI	0.88 (0.62-1.23)	0.446	-	-
	ASA score	1.69 (1.16-2.46)	0.007	1.52 (1.01-2.28)	0.044
	Smoking	1.00 (0.69-1.46)	0.984	-	-
	mGPS	1.67 (1.23-2.26)	0.001	1.49 (1.08-2.07)	0.016
	Rectal	1.00 (0.57-1.74)	0.998	-	-
	TNM stage	2.50 (1.63-3.85)	<0.001	2.46 (1.52-3.96)	<0.001
	Neoadjuvant treatment	1.23 (0.63-2.39)	0.548	-	-
	POD 2 CRP >150mg/L	1.62 (0.91-2.89)	0.101	-	-
	POD 3 CRP >150mg/L	1.84 (1.01-3.35)	0.047	-	-
	POD 4 CRP >150mg/L	2.53 (1.43-4.48)	0.001	2.00 (1.17-3.59)	0.020
	Infective complications	2.02 (1.16-3.52)	0.013	-	0.211
	Clavien Dindo grade	1.66 (1.13-2.43)	0.009	1.51 (0.98-2.33)	0.061
	Adjuvant treatment	0.78 (0.42-1.46)	0.432	-	-
OS	Age	1.83 (1.36-2.48)	<0.001	1.35 (0.97-1.87)	0.074
	Sex	1.06 (0.68-1.64)	0.799	-	-
	BMI	0.85 (0.65-1.12)	0.242	-	-
	ASA score	1.92 (1.41-2.61)	<0.001	1.49 (1.05-2.10)	0.024
	Smoking	1.20 (0.89-1.61)	0.238	-	-
	mGPS	1.52 (1.18-1.96)	0.001	-	0.170
	Rectal	0.78 (0.49-1.25)	0.308	-	-
	TNM stage	1.70 (1.25-2.31)	0.001	2.12 (1.45-3.41)	<0.001
	Neoadjuvant treatment	0.97 (0.54-1.73)	0.914	-	-
	POD 2 CRP >150mg/L	1.99 (1.22-3.26)	0.006	-	-
	POD 3 CRP >150mg/L	1.76 (1.08-2.85)	0.022	-	-
	POD 4 CRP >150mg/L	2.02 (1.27-3.20)	0.003	2.14 (1.34-3.41)	0.001
	Infective complications	1.40 (0.87-2.25)	0.170	-	-
	Clavien Dindo grade	1.30 (0.93-1.81)	0.127	-	-
	Adjuvant treatment	0.64 (0.37-1.09)	0.098	0.33 (0.17-0.64)	0.001

HR Hazard Ratio, CI Confidence Interval, DSS disease specific survival, OS overall survival, mGPS modified Glasgow Prognostic Score, POD postoperative day

Table 4-4: Patient characteristics by severity of complication following surgery for colonic cancer

Characteristic	All	Clavien Dindo complication grade				
		0a	1-2b	3-4c	5d	P
N (%)	239	160	63	16	0	-
Age (<65/65-74/>74)	66/88/85	48/59/53	14/24/25	4/5/7	0/0/0	0.724
Sex (male/female)	127/112	77/83	42/21	8/8	0/0/0	0.111
BMI (<20/20-25/26-30/>30)	11/64/68/60	9/41/50/38	1/19/12/19	1/4/6/3	0/0/0/0	0.430
ASA score (1/2/3/4)	24/99/105/11	20/70/63/7	2/23/34/4	2/6/8/0	0/0/0/0	0.227
Smoking (never/ex/current)	103/91/40	79/54/23	20/30/12	4/7/5	0/0/0	0.047
Preop mGPS (0/1/2)	170/28/41	115/18/27	46/6/11	9/4/3	0/0/0	0.513
TNM stage (0/I/II/III)	0/50/112/77	0/33/73/54	0/14/29/20	0/3/10/3	0/0/0/0	0.734
Approach (open/laparoscopic)	83/156	57/103	20/43	6/10	0/0	0.836
Surgery >4h (yes/no)	28/179	17/118	7/50	4/11	0/0	0.303
Stoma (yes/no)	14/158	7/113	6/37	1/8	0/0	0.277
POD 2 CRP >150mg/L (yes/no)	129/105	78/78	43/19	8/8	0/0	0.032
POD 3 CRP >150mg/L (yes/no)	121/105	69/81	41/20	11/4	0/0	0.002
POD 4 CRP >150mg/L (yes/no)	81/117	41/84	31/26	9/7	0/0	0.005
Adjuvant treatment (no/yes)	69/170	48/112	18/45	3/13	0/0	0.638

mGPS preoperative modified Glasgow Prognostic score (0 = CRP<10mg/L, 1 = CRP≥10mg/L and albumin ≥35g/L, 2 = CRP≥10mg/L and albumin <35g/L). POD postoperative day. a) 0 = no complication, b) 1-2 = complication requiring minor intervention, c) 3-4 = complication requiring significant intervention, d) 5 = death

Table 4-5: Impact of complication severity on survival following surgery for colonic cancer

Survival	Variable	Univariate HR (95% CI)	P	Multivariate HR (95% CI)	P
DSS					
	Age	1.52 (0.96-2.41)	0.073	-	0.316
	Sex	0.72 (0.37-1.44)	0.356	-	-
	BMI	0.69 (0.44-1.09)	0.109	-	-
	ASA score	1.63 (1.00-2.67)	0.051	1.70 (0.99-2.93)	0.057
	Smoking	0.94 (0.58-1.52)	0.792	-	-
	mGPS	1.95 (1.34-2.82)	<0.001	1.81 (1.20-2.72)	0.005
	TNM stage	2.27 (1.32-3.90)	0.003	2.28 (1.23-4.21)	0.009
	POD 2 CRP >150mg/L	1.69 (0.82-3.48)	0.157	-	-
	POD 3 CRP >150mg/L	1.97 (0.89-4.36)	0.094	-	-
	POD 4 CRP >150mg/L	2.78 (1.31-5.91)	0.008	2.42 (1.13-5.18)	0.023
	Infective complications	1.81 (0.86-3.82)	0.117	-	-
	Clavien Dindo grade	1.34 (1.01-1.78)	0.043	-	0.164
	Adjuvant treatment	0.77 (0.35-1.70)	0.516	-	-
OS					
	Age	1.78 (1.23-2.57)	0.002	1.43 (0.94-2.15)	0.092
	Sex	1.04 (0.61-1.78)	0.873	-	-
	BMI	0.75 (0.53-1.06)	0.100	-	-
	ASA score	1.98 (1.34-2.93)	0.001	1.99 (1.28-3.10)	0.002
	Smoking	1.19 (0.83-1.70)	0.354	-	-
	TNM stage	1.53 (1.04-2.25)	0.030	-	0.114
	mGPS	1.66 (1.23-2.23)	0.001	1.53 (1.11-2.10)	0.010
	POD 2 CRP >150mg/L	2.18 (1.20-3.96)	0.010	-	-
	POD 3 CRP >150mg/L	1.88 (1.03-3.42)	0.040	-	-
	POD 4 CRP >150mg/L	2.33 (1.31-4.17)	0.004	2.32 (1.29-4.20)	0.005
	Infective complications	1.03 (0.53-2.00)	0.920	-	-
	Clavien Dindo grade	1.08 (0.84-1.39)	0.548	-	-
	Adjuvant treatment	0.67 (0.35-1.27)	0.205	-	-

HR Hazard Ratio, CI Confidence Interval, DSS disease specific survival, OS overall survival, mGPS modified Glasgow Prognostic Score, POD postoperative day

5 The relationship between CT derived measures of body composition, tumour and host characteristics in male and female patients with primary operable colorectal cancer: implications for a systemic inflammation based framework for cancer cachexia.

5.1 Introduction

With disease progression in colorectal cancer there is an increased incidence of progressive involuntary weight loss, poor food intake, loss of lean tissue, poor functional status, poorer quality of life, and ultimately, survival (Fearon et al. 2011, Aapro et al. 2014, Malietzis et al. 2016c). Measuring simple weight loss is problematic since many patients in the developed world will be overweight but with significant loss of lean tissue (Richards et al. 2012b, Douglas et al. 2014). Indeed, methods such as CT scanning have shown that there are body compositional changes in the absence of overt weight loss (Martin et al. 2013).

In particular, the disproportionate loss of lean tissue has been associated with chemotherapy toxicity (Antoun et al. 2010, Prado et al. 2007, Prado et al. 2009, Prado et al. 2011), increased risk of post-operative complications (Peng et al. 2011), poorer outcome, and poorer survival (Prado et al. 2008). Recently, based on such CT analyses, the terms visceral obesity, myopenia, myopenic obesity, and myosteatosis have been defined in the literature (Malietzis et al. 2016c, Martin et al. 2013, Prado et al. 2008, Doyle et al. 2013).

It has been recently proposed that a systemic inflammatory response, as evidenced by the Glasgow Prognostic Score (GPS), given its association with loss of lean tissue (McMillan 2009) and its established prognostic value (McMillan 2013), would form a method of simply and objectively identifying patients with different cachexia states (Bye et al. 2016). Indeed, systemic inflammation, as evidence by C-reactive protein (CRP), neutrophil lymphocyte ratio (NLR) and the GPS, is associated with the depletion of skeletal muscle in cancer patients (Reisinger et al. 2015), with a consequent effect on quality of life (Laird et al. 2016). However, it was not clear whether this association was independent of other potential confounders, in particular, sex.

In addition, it is increasingly recognised that postoperative complications have a significant impact on long-term oncologic outcomes following surgery for colorectal cancer (Artinyan et al. 2015). The magnitude of the postoperative systemic inflammatory response is associated with the development of, and severity of, complications following surgery for colorectal cancer (McSorley Chapter 3). Indeed, threshold values of CRP have been established in the postoperative period which are associated with the development of complications (McDermott et al. 2015). There is some evidence that BMI might influence the magnitude of the postoperative systemic inflammatory response after surgery for colorectal cancer (Ramanathan 2016). In addition, body composition has been reported to

be associated with postoperative complications following colorectal surgery (Lieffers et al. 2012). However, there is no evidence directly linking CT derived measures of body composition, the postoperative systemic inflammatory response, and complications.

Therefore, the aim of the present observational study was to examine the relationship between BMI, CT derived measures of body composition**,** the systemic inflammatory response both before and after surgery, and postoperative complications in male and female patients with primary operable colorectal cancer.

5.2 Patients and Methods

5.2.1 Patients

Consecutive patients who underwent elective, potentially curative resection for colorectal cancer between March 2008 and May 2013 at a single centre were identified from a prospectively maintained database. Those patients with a preoperative CT scan and a recorded height were included. Patients who had undergone emergency surgery, palliative surgery, or with metastatic disease were not considered for inclusion.

Patients were classified according to Body Mass Index (BMI) as underweight (BMI <18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25.0–29.9) or obese (BMI >30). ASA score was recorded. All tumours were staged according to TNM 5th edition.

On each postoperative day patients were clinically assessed and had blood samples, including serum CRP, obtained as standard until discharged.

The study was approved by the West of Scotland Research Ethics Committee, Glasgow.

5.2.2 Methods

CT images were obtained at the level of the third lumbar vertebra as previously described (Richards et al. 2012b). Each image was analysed using a free-ware program (NIH Image J version 1.47, http://rsbweb.nih.gov/ij/) shown to provide reliable measurements.

Region of interest (ROI) measurements (cm^2) were made of visceral fat (VFA), subcutaneous fat (SFA) (Figure 5-1), and skeletal muscle areas (SMA) (Figure 5-2) using standard Hounsfield Unit (HU) ranges (adipose tissue -190 to -30, and skeletal muscle -29 to +150). These were then normalised for height^2 to create indices; total fat index (TFI, cm^2/m^2), subcutaneous fat index (SFI, cm^2/m^2), visceral fat index (VFI, cm^2/m^2), and skeletal muscle index (SMI, cm^2/m^2). Skeletal muscle radiodensity (SMD, HU) was measured from the same ROI used to calculate SMA, as its mean HU. Visceral obesity was defined as VFA >160cm^2 for male patients and >80cm^2 for female patients (Doyle et al. 2013). Myopenia was defined as SMI for male patients of <52.4cm^2/m^2 and <38.5cm^2/m^2 for female patients (Prado et al. 2008). Myopenic obesity was defined as the presence of myopenia and BMI>30kg/m^2 (Malietzis et al. 2016c). Myosteatosis was

defined by SMD <41HU in patients with BMI <25kg/m^2 and <33HU in patients with BMI >25kg/m^2 (Martin et al. 2013).

Measurements were made by one individual (DB) blind to clinicopathological and demographic data. Another individual (SM) performed an independent measurement of 40 patient images to assess inter-rater reliability using intra-class correlation coefficients (ICCC) (TFA ICCC= 0.999, SFA ICCC=0.997, VFA ICCC=0.996, SMA ICCC=0.995, SMD ICCC=0.996).

Serum concentrations of CRP (mg/L) and albumin (g/L) were measured using an autoanalyzer (Architect; Abbot Diagnostics, Maidenhead, UK). The preoperative GPS was calculated from CRP and albumin as previously described (McMillan 2013). The more recent mGPS was not used as greater evidence exists validating GPS with regards to measures of body composition and cachexia. The neutrophil lymphocyte ratio (NLR) was calculated for each patient for whom preoperative neutrophil and lymphocyte counts were available, values >3 were considered raised (Malietzis et al. 2016b).

Exceeding the established CRP threshold of 150 mg/L on postoperative days 3 or 4 was recorded (McDermott et al. 2015). Postoperative complications were recorded and categorised by severity using the Clavien Dindo scale (Dindo et al. 2004). Infective complications were categorised as described previously (Platt et al. 2012).

5.2.3 Statistical analysis

Body composition indices were presented as median and range, and compared using Mann-Whitney or Kruskal-Wallis tests. Categorical variables were analysed using χ^2 test for linear-by-linear association, or χ^2 test for 2 by 2 tables.

Missing data were excluded from analysis on a variable by variable basis. Two sided p values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS software (Version 21.0. SPSS Inc., Chicago, IL, USA).

5.3 Results

5.3.1 Patients

377 patients were eligible for inclusion over the study period, however 55 were excluded due to either missing anthropometric data or unavailable preoperative CT images, giving n=322 (Table 5-1). In both females and males, the majority of patients were over 65 years old (68% and 66% respectively), were overweight or obese (63% and 61% respectively), had some comorbid disease (87% and 89% respectively), and had node negative disease (64% in each). There were no significant differences in clinicopathological characteristics between the sexes.

There was no significant difference in BMI between the sexes (Table 5-1). Female patients had a significantly higher median SFI (92 vs. 60 cm^2/m^2, p<0.001), lower median VFI (58 vs. 74 cm^2/m^2, p<0.001), and lower SMI (41 vs. 49 cm^2/m^2, p<0.001) when compared to male patients. In addition, a significantly lower proportion of female patients were considered myopenic (34% vs. 61%, p<0.001).

There were a total of 112 (35%) postoperative complications of which 77 were infective, 86 were Clavien Dindo grade 1-2, and 26 were Clavien Dindo grade 3-5. There was a significant association between male sex and higher incidence of any postoperative complication (42 % vs. 26%, p=0.003), infective complication (29% vs. 18%, p=0.018), and Clavien Dindo grade (p=0.005). Due to these profound differences in body composition and postoperative outcomes, subsequent analysis was carried out separately in male and female patients.

5.3.2 Females

There was a significant association (Table 5-2) between BMI defined obesity and exceeding the established CRP threshold of 150mg/L on postoperative days 3 (p=0.030), and 4 (p=0.024). There was a significant association between visceral obesity and ASA score (p=0.015), exceeding the established CRP threshold of 150mg/L on postoperative days 3 (p=0.003), and 4 (p=0.020), any postoperative complication (p=0.017), infective complications (p=0.005), and Clavien Dindo grade (p=0.032). There was a significant association between myopenia and age (p<0.001), and a non-signficant trend (p=0.054) toward an increasing proportion of myopenic female patients with increasing GPS. Myopenic obesity was not significantly associated with any clinicopathological or systemic

inflammatory response variable. Myosteatosis was significantly associated with increasing age ($p<0.001$), increasing ASA score ($p<0.001$), increasing GPS ($p=0.019$), NLR ($p=0.007$), and exceeding the established CRP threshold of 150mg/L on postoperative day 4 ($p=0.046$).

5.3.3 Males

There was a significant inverse association (Table 5-3) between BMI defined obesity and increasing age ($p=0.003$), and GPS ($p=0.001$). There was a significant association between visceral obesity and GPS ($p=0.007$) with a trend toward a higher proportion of visceral obesity in higher TNM stage disease ($p=0.050$). There was a significant association between myopenia and increasing age ($p<0.001$), GPS ($p<0.001$), and NLR ($p=0.043$). Myopenic obesity was not significantly associated with any clinicopathological or systemic inflammatory response variable. There was a significant association between myosteatosis and increasing age ($p<0.001$), and GPS ($p=0.004$).

5.4 Discussion

In the present study, there were clear differences in CT body composition indices and their relationship with clinicopathological characteristics, the magnitude of the postoperative systemic inflammatory response, and postoperative complications between females and males.

Myosteatosis was consistently associated with patient characteristics and measures of the preoperative systemic inflammatory response in both sexes. Recently Malietzis and colleagues reported a significant inverse relationship between NLR, myopenia, and myosteatosis in patients with operable colorectal cancer (Malietzis et al. 2016b, Malietzis et al. 2016c). As in the present study, there were significant differences in CT derived measures of body composition between the sexes. However, this observation was not commented on and sex specific analysis was not carried out. These results would suggest that not only the quantity but also the quality of skeletal muscle is influenced by the preoperative systemic inflammatory response. The mechanism by which a systemic inflammatory response appears to promote a greater catabolic state in males is not clear. The present results are also consistent with longitudinal studies (Malietzis et al. 2016a), including historical work (McMillan et al. 1998), and the recent work of Wallengren and colleagues who reported that, patients with advanced cancer and a CRP>10mg/L had less muscle mass and lost muscle mass at an accelerated rate during cancer progression (Wallengren et al. 2015). However, it remains to be determined whether there is a sex specific effect on these longitudinal relationships.

Taken together, it is clear that measures of systemic inflammation are associated with a lower quantity and quality of skeletal muscle, and is consistent with the concept that the systemic inflammatory response is a major driver of the loss of lean tissue. These results have a number of important implications for the classification, monitoring and treatment of cachexia. For example, these results point to a revised systemic inflammation based framework for the assessment of cancer cachexia. Further longitudinal and interventional studies will be required to confirm the importance of the present observations.

A comparison of the predictive value of such body composition analysis in the development of postoperative infective complications in both males and females in a large cohort of patients with colorectal cancer has been called for (Reisinger et al. 2015). With regard to the postoperative systemic inflammatory response, and complications following

elective surgery for colorectal cancer, the present study again reports clear differences between the sexes. In female patients, increasing BMI was associated with an exaggerated postoperative systemic inflammatory response. This was also the case with CT derived visceral obesity which, in addition, was associated with a greater number and severity of postoperative complications. Neither BMI, or any CT derived measure of body composition, was associated with the postoperative systemic inflammatory response or complications in male patients.

There is some existing evidence that BMI, a crude measure of body composition, is associated with the magnitude of the postoperative systemic inflammatory response following surgery for colorectal cancer (Ramanathan 2016). The present study adds to this evidence but suggests a sex specific difference. It may be that obesity leads to increased postoperative complications through direct mechanical problems such as the requirement for longer and deeper wounds at laparotomy, difficulty mobilising in the postoperative period, and problems surrounding glycaemic control. However, fat, in particular visceral fat, is well understood to be a potent pro-inflammatory tissue, and it may be that the sex specific difference in fat distribution reported in the present study has a role to play (Schrager et al. 2007).

Limitations of the present study include its retrospective nature and that only patients with an available CT scan were included. Also, that other methods of body composition and assessments of physical function were not included. However, it does highlight the importance of sex in the relationship between body composition, the systemic inflammatory response, and outcome in patients with primary operable colorectal cancer.

The results of the present study suggest that BMI and visceral obesity are associated with the magnitude of the postoperative systemic inflammatory response and complications in female patients following surgery for colorectal cancer. This factor will need to be accounted for in future work examining the magnitude of the postoperative systemic inflammatory response and outcomes following surgery for colorectal cancer.

5.5 Tables and Footnotes

Table 5-1: Association between sex, clinicopathological characteristics, systemic inflammation, CT derived measures of body composition and postoperative outcomes following elective surgery for colorectal cancer

Characteristic		Female n= 148(%)	Male n=174 (%)	P
Clinicopathological				
Age	<65	47 (32)	59 (34)	0.327
	65-74	55 (37)	72 (41)	
	>74	46 (31)	43 (25)	
ASA score	1	19 (13)	19 (11)	0.334
	2	71 (48)	80 (46)	
	3	54 (37)	69 (40)	
	4	3 (2)	6 (3)	
TNM stage	0	3 (2)	4 (2)	0.695
	1	30 (20)	39 (22)	
	2	61 (41)	69 (40)	
	3	54 (37)	62 (36)	
Tumour site	Colon			
	Rectum			
Neoadjuvant	No			
	Yes			
Systemic inflammation				
GPS	0	87 (59)	103 (59)	0.824
	1 (CRP)	15 (10)	15 (9)	
	1 (albumin)	25 (17)	32 (18)	
	2	21 (14)	24 (14)	
NLR	≤3	88 (59)	93 (54)	0.312
	>3	60 (41)	80 (46)	
Body composition				
BMI (kg/m^2)	Underweight (<20)	9 (7)	4 (2)	0.506
	Normal (20-25)	41 (30)	60 (37)	
	Overweight (26-30)	43 (31)	61 (37)	
	Obese (>30)	44 (32)	39 (24)	
TFI (median, range, cm^2/m$^{2)}$		149 (18-443)	134 (30-437)	0.126
SFI (median, range, cm^2/m^2)		92 (12-270)	60 (22-275)	<0.001
VFI (median, range, cm^2/m^2)		58 (4-189)	74 (8-195)	<0.001
SMI (median, range, cm^2/m^2)		41 (16-74)	49 (26-77)	<0.001
SMD (median, range, HU)		35 (5-56)	34 (9-68)	0.712
Outcomes				
POD 3 CRP (mg/L)	≤150	76 (54)	79 (49)	0.359
	>150	65 (46)	84 (51)	
POD 4 CRP (mg/L)	≤150	77 (64)	95 (61)	0.706
	>150	43 (36)	60 (39)	
Any complication	No	109 (74)	101 (58)	0.003
	Yes	39 (26)	73 (42)	
Infective complication	No	122 (82)	123 (71)	0.018
	Yes	26 (18)	51 (29)	
Clavien Dindo grade	0	108 (73)	98 (57)	0.005
	1-2	30 (20)	56 (33)	
	3-5	9 (7)	17 (10)	

BMI body mass index, *ASA* American Society of Anaesthesiology, *CRP* C-reactive protein, *GPS* Glasgow Prognostic Score, *mGPS* modified Glasgow Prognostic Score, *NLR* neutrophil lymphocyte ratio, HU Hounsfield units, *TFI* total fat index, *SFI* subcutaneous fat index, *VFI* visceral fat index, *SMI* skeletal muscle index, *SMD* skeletal muscle density, *POD* postoperative day

Table 5-2: Relationship between CT derived measures of body composition, clinicopathological characteristics, markers of systemic inflammation, and postoperative outcomes in female patients

Characteristic		BMI obesity no/yes (n)	P	Visceral obesity no/yes (n)	P	Myopenia no/yes (n)	P	Myopenic obesity no/yes (n)	P	Myosteatosis no/yes (n)	P
Clinicopathological											
Age	<65	27/20	0.295	12/35	0.953	41/6	<0.001	46/1	0.138	33/14	<0.001
	65-74	44/11		12/43		32/23		53/2		26/29	
	>74	31/15		12/43		24/22		42/4		11/35	
ASA Score	1	17/2	0.060	10/9	0.015	11/8	0.202	19/0	0.568	17/2	<0.001
	2	49/22		16/55		45/26		67/4		36/35	
	3	34/20		9/45		37/17		51/3		17/37	
	4	2/1		1/2		3/0		3/0		0/3	
TNM stage	0	3/0	0.755	0/3	0.294	1/2	0.697	3/0	0.298	2/1	0.759
	1	22/8		9/21		22/8		30/0		16/14	
	2	38/23		18/43		40/21		57/4		22/39	
	3	39/15		9/45		34/20		51/3		30/24	
Systemic inflammation											
GPS	0	61/26	0.668	19/68	0.959	63/24	0.054	83/4	0.839	49/38	0.019
	1 (CRP)	15/10		4/11		9/6		13/2		8/17	
	1 (albumin)	9/6		9/16		14/11		24/1		7/8	
	2	17/4		4/17		11/10		21/0		6/15	
NLR	≤3	64/24	0.278	24/64	0.336	62/26	0.159	86/2	0.120	50/38	0.007
	>3	38/22		12/48		35/25		55/5		20/40	
Outcomes											
POD 3 CRP (mg/L)	<150	58/18	0.030	27/49	0.003	48/28	0.374	74/2	0.248	40/40	0.414
	>150	38/27		9/56		46/19		60/5		30/41	
POD 4 CRP (mg/L)	>150	59/18	0.024	22/55	0.020	47/30	0.239	75/2	0.348	44/40	0.046
	<150	24/19		4/39		31/12		40/3		16/32	
Any complication	No	79/30	0.158	32/77	0.017	73/36	0.560	104/5	1.000	55/54	0.262
	Yes	23/16		4/35		24/15		37/2		15/24	
Infective complication	No	88/34	0.100	35/87	0.005	81/41	0.654	116/6	1.000	61/61	0.196
	Yes	14/12		1/25		16/10		25/1		9/17	
Clavien Dindo grade	0	77/30	0.241	31/76	0.032	72/35	0.448	102/5	0.646	53/54	0.344
	1-2	17/13		3/27		19/11		29/1		11/9	
	3-5	6/3		1/8		5/4		8/1		4/5	

BMI body mass index, *ASA* American Society of Anaesthesiology, *CRP* C-reactive protein, *GPS* Glasgow Prognostic Score, *mGPS* modified Glasgow Prognostic Score, *NLR* neutrophil lymphocyte ratio, *HU* Hounsfield units, *TFI* total fat index, *SFI* subcutaneous fat index, *VFI* visceral fat index, *SMI* skeletal muscle index, *SMD* skeletal muscle density, *POD* postoperative day, * Visceral obesity; VFA = males >160cm^2, females >80cm^2 , [£] Myopenia; SMI = Males <52.4cm^2/m^2, Females <38.5cm^2/m^2, [$] Myopenic obesity; myopenia and BMI >30kg/m^2, [¥] Myosteatosis; BMI <25kg/m^2 and SMD <41HU, or BMI >25kg/m^2 and SMD <33HU

Table 5-3: Relationship between CT derived measures of body composition, clinicopathological characteristics, markers of systemic inflammation, and postoperative outcomes in male patients

Characteristic		BMI obesity no/yes (n)	P	Visceral obesity no/yes (n)	P	Myopenia no/yes (n)	P	Myopenic obesity no/yes (n)	P	Myosteatosis no/yes (n)	P
Clinicopathological											
Age	<65	39/19	0.003	21/38	0.492	36/23	<0.001	56/3	0.968	37/21	<0.001
	65-74	47/25		17/55		28/44		65/7		24/48	
	>74	41/2		19/24		3/40		41/2		4/39	
ASA Score	1	17/2	0.771	6/13	0.547	9/10	0.403	19/0	0.909	10/9	0.132
	2	53/27		24/56		31/49		72/8		31/49	
	3	51/17		25/44		25/44		65/4		22/46	
	4	6/0		2/4		2/4		6/0		2/4	
TNM stage	0	3/1	0.879	4/0	0.050	2/2	0.816	4/0	0.705	2/2	0.413
	1	27/12		12/27		17/22		35/4		18/21	
	2	53/16		26/43		20/49		65/4		22/47	
	3	44/17		15/47		28/34		58/4		23/38	
Systemic inflammation											
GPS	0	65/38	0.001	26/77	0.007	55/48	<0.001	95/8	0.947	48/55	0.004
	1 (CRP)	28/3		14/18		4/11		31/1		5/10	
	1 (albumin)	12/3		3/12		8/24		14/1		8/23	
	2	22/2		14/10		0/24		22/2		4/20	
NLR	≤3	62/30	0.055	22/71	0.006	42/51	0.043	84/9	0.146	40/52	0.116
	>3	65/15		35/45		24/56		77/3		25/55	
Outcomes											
POD 3 CRP (mg/L)	<150	59/20	0.859	29/50	0.508	30/49	1.000	75/4	0.537	32/47	0.518
	>150	60/23		26/58		32/52		77/7		29/54	
POD 4 CRP (mg/L)	>150	70/25	1.000	30/65	0.860	38/57	1.000	89/6	1.000	36/59	0.864
	<150	44/15		18/42		24/36		56/4		21/38	
Any complication	No	75/26	0.862	32/69	0.746	38/63	0.875	94/7	1.000	40/61	0.529
	Yes	52/20		25/48		29/44		68/5		25/47	
Infective complication	No	92/31	0.570	40/83	1.000	44/79	0.305	115/8	0.749	43/80	0.301
	Yes	35/15		17/34		23/28		47/4		22/28	
Clavien Dindo grade	0	73/25	0.523	32/66	0.903	37/61	0.789	91/7	0.798	39/59	0.240
	1-2	40/15		19/37		23/33		53/3		21/34	
	3-5	12/6		6/12		7/11		16/2		4/14	

BMI body mass index, *ASA* American Society of Anaesthesiology, *CRP* C-reactive protein, *GPS* Glasgow Prognostic Score, *mGPS* modified Glasgow Prognostic Score, *NLR* neutrophil lymphocyte ratio, *HU* Hounsfield units, *TFI* total fat index, *SFI* subcutaneous fat index, *VFI* visceral fat index, *SMI* skeletal muscle index, *SMD* skeletal muscle density, *POD* postoperative day, * Visceral obesity; VFA = males >160cm^2, females >80cm^2, [£] Myopenia; SMI = Males <52.4cm^2/m^2, Females <38.5cm^2/m^2, [$] Myopenic obesity; myopenia and BMI >30kg/m^2 , [¥] Myosteatosis; BMI <25kg/m^2 and SMD <41HU, or BMI >25kg/m^2 and SMD <33HU

5.6 Figures and Legends

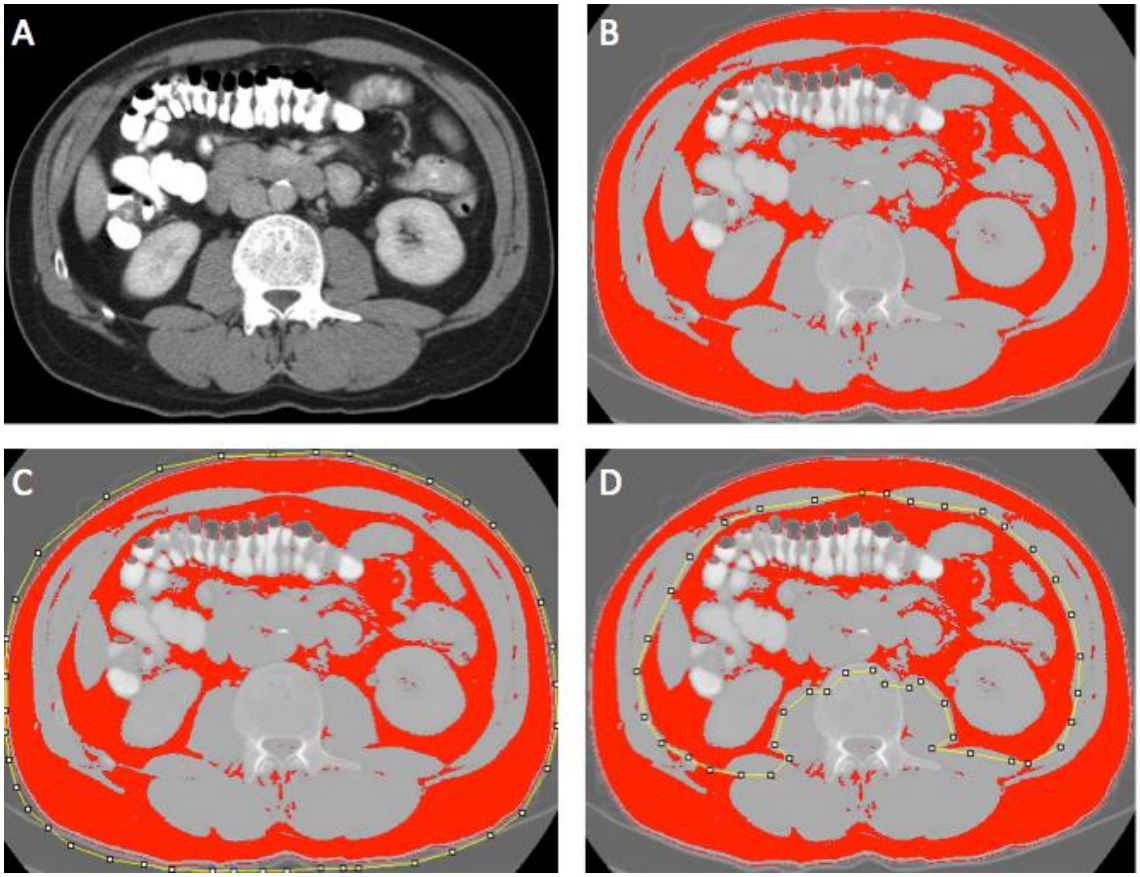

Figure 5-1: Example of selection of CT body composition fat areas using ImageJ software: (A) mid-L3 vertebra axial slice from preoperative portal venous CT, (B) threshold selection of adipose tissue using automatic selection of pixels of radiodensity ranging -190 to -30 Hounsfield Units (HU), (C) region of interest selection for total fat area (TFA, cm^2), (D) ROI selection for visceral fat area (VFA, cm^2)

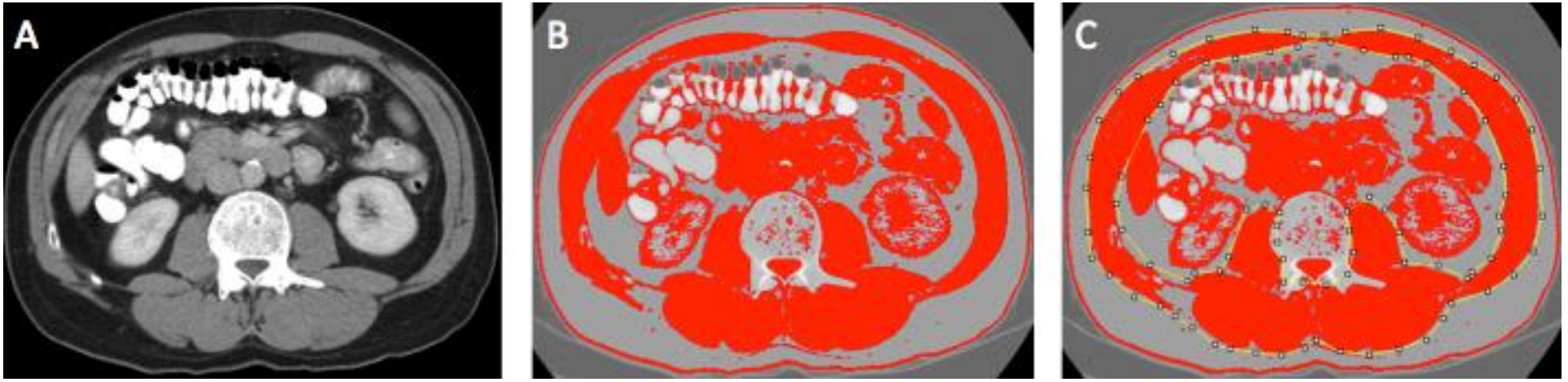

Figure 5-2: Example of selection of CT body composition skeletal muscle area using ImageJ software: (A) mid-L3 vertebra axial slice from preoperative portal venous phase CT, (B) threshold selection of skeletal muscle tissue using automatic selection of pixels of radiodensity ranging -29 to 150 Hounsfield Units (HU), (C) region of interest (ROI) selection for skeletal muscle area (SMA, cm^2)

6 The relationship between cardiopulmonary exercise test variables, the postoperative systemic inflammatory response, and complications following surgery for colorectal cancer

6.1 Introduction

Colorectal cancer is a leading cause of death in the developed world (Cancer Research UK). Surgery continues to form the mainstay of treatment in the majority of cases, however there is a significant associated degree of morbidity and mortality (Ghaferi et al. 2011). Long-term survival is primarily dictated by tumour differentiation and stage at presentation, however it is increasingly recognised that postoperative complications have a significant impact on long-term oncologic outcomes (Khuri et al. 2005, Law et al. 2007, Mirnezami et al. 2011).

Cardiopulmonary exercise testing (CPET/CPX) has been developed as a method of assessing patients' ability to meet the increased oxygen demand of major surgery (Older et al. 1993). It represents a dynamic, non-invasive assessment of a patient's cardiovascular and pulmonary reserve (Smith et al. 2009). Two key measurements relating to oxygen delivery can be derived via CPET: oxygen consumption at the anaerobic threshold (VO_2 at AT) which represents the point at which anaerobic metabolism is required in addition to aerobic metabolism to meet tissue energy demand, and oxygen consumption at peak exercise (VO_2 at peak). Patients with VO_2 at AT <11ml/min/kg or VO2 at peak <19ml/min/kg are at significant risk of postoperative cardiovascular death and also of surgical complications following major abdominal surgery (Older et al. 1999). Very similar thresholds have also been found to predict the development of postoperative complications in surgery for oesophagogastric cancer (Moyes et al. 2013), rectal cancer (West et al. 2014a) and colon cancer (West et al. 2014b).

The magnitude of the postoperative systemic inflammatory response is associated with infective complications, and complications of greater severity, following surgery for colorectal cancer (Platt et al. 2012, McSorley Chapter 3). Indeed, threshold values of the acute phase reactant, C-reactive protein (CRP) have been established in the postoperative period which are associated with the development of postoperative complications and the need for investigation (Adamina et al. 2015, McDermott et al. 2015). The exact mechanism by which poor VO_2 at AT and VO_2 at peak exercise are linked to the development of postoperative complications is incompletely understood. It may be that poor cardiopulmonary exercise tolerance leads to the development of postoperative complications due to an exaggerated postoperative systemic inflammatory response.

Therefore, the aim of the present pilot study was to investigate the relationship between CPET measurements, the preoperative systemic inflammatory response as measured by mGPS, the postoperative systemic inflammatory response as evidenced by CRP, and complications following surgery for colorectal cancer.

6.2 Patients and Methods

6.2.1 Patients

This observational pilot study included patients who had undergone CPET prior to elective surgery for histologically confirmed colorectal cancer in a single centre between September 2008 and April 2017.

All patients received prophylactic antibiotics and venous thromboprophylaxis prior to the induction of anaesthesia as per hospital policy. Further postoperative investigation and intervention was at the discretion of the patient's surgical team.

6.2.2 Methods

Clinicopathological data were collected prospectively in a database and anonymised. Recorded information included patient demographics, American Society of Anesthesiology score (ASA), body mass index (BMI), smoking status, tumour site, TNM stage (TNM, AJCC), surgical approach, preoperative and postoperative serum CRP and albumin measurements. Data regarding the nature, severity, and management of complications was retrospectively categorised using the Clavien Dindo scale (Dindo et al. 2004). Any uncertainties were addressed by review of electronic and/or physical case notes. The study was approved by the West of Scotland Research Ethics Committee, Glasgow.

Serum concentrations of CRP (mg/L) were measured using an autoanalyzer (Architect; Abbot Diagnostics, Maidenhead, UK) with a lower detectable limit of 0.2 mg/L as was serum albumin (normal range 35-50g/L). The preoperative modified Glasgow Prognostic Score (mGPS) was calculated from preoperative serum CRP and albumin (McMillan 2013).

Cardiopulmonary exercise testing was performed in a single respiratory function laboratory using a ZAN 600 (nSpire Health, Hertford, UK) and Ergoselect bicycle ergometer (Ergoline, Bitz, Germany). A doctor and resuscitation equipment were present during all tests. Several variables were recorded including electrocardiography, blood pressure, oxygen uptake, and carbon dioxide output from analysis of inspiratory and expiratory gases. Patients were exposed to an incremental physical exercise protocol to their maximally tolerated level which was determined by exhaustion, symptomatic

breathlessness, or pain. The measured variables along with the exercise protocol allowed VO_2 at AT and at peak exercise to be quantified.

6.2.3 Statistical Analysis

In addition to being analysed as continuous variables, patients were grouped according to the previously described thresholds of VO_2 at AT (<11 or >11 ml/min/kg) and at peak exercise (<19 or >19 ml/min/kg). Categorical data were compared using the Chi-square test or Fisher's exact test where appropriate. Continuous data were presented as median and range and were compared using the Mann-Whitney U test or Kruskal-Wallis test in multiple groups. Postoperative CRP concentrations were displayed graphically by postoperative day as median and 95% confidence interval. Correlation between VO_2 at AT and VO_2 at peak exercise and the peak postoperative CRP concentration was assessed using Spearman's correlation coefficients. Two sided p values <0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS version 22 for Windows (Chicago, IL, USA).

6.3 Results

6.3.1 Patients

38 patients completed CPET prior to elective surgery for colorectal cancer at Glasgow Royal Infirmary between 2008 and 2017 (Table 6-1). The majority were male (30, 79%), over 65 years old (30, 79%), with colonic cancer (23, 61%) and node negative disease (24, 63%). 14 patients (37%) had open surgery and 24 (63%) had a laparoscopic resection. Prior to surgery, 3 patients with locally advanced or margin threatening rectal cancer underwent neoadjuvant chemoradiotherapy (nCRT). There were no cases of pathological complete response.

6.3.2 Complications

Of the 38 patients, 15 (39%) experienced complications (Table 6-1). No patients died within 30 days of surgery or during the same admission. Of the patients with complications, 10 were infective and 5 were non-infective. When classified using the Clavien Dindo scale, 12 were grade 1-2 (i.e. required minor intervention) and 3 were grade 3-4 (i.e. necessitated major intervention).

6.3.3 Associations between CPET variables, co-morbidity and mGPS

There was a significant positive correlation (r_s=0.628, p<0.001) between VO_2 at anaerobic threshold (AT) and VO_2 at peak exercise (Figure 6-1). An increasing burden of co-morbidity, as measured by ASA score (Figure 6-2), was significantly associated with progressively lower VO_2 at peak exercise (median 22 vs. 19 vs. 15 vs. 12 ml/kg/min, p=0.014) but not VO_2 at AT (p=0.058).

When VO_2 at AT was compared as a continuous variable amongst patients grouped by preoperative mGPS 0, 1, and 2 (Figure 6-3), there was no significant association (p=0.147). However, when VO_2 at peak exercise was compared as a continuous variable amongst patients grouped by mGPS 0, 1, and 2 (Figure 6-3), higher mGPS was significantly associated with progressively lower VO_2 at peak exercise (median 18 vs. 16 vs. 14 ml/kg/min respectively, p=0.039).

There was a non-significant linear trend toward greater preoperative systemic inflammation in patients with a higher ASA score (p=0.058).

6.3.4 VO_2 at anaerobic threshold and the postoperative SIR

14 patients (37%) had VO_2 at AT >11ml/min/kg and 24 patients (63%) had VO_2 at AT <11ml/min/kg (Table 6-1). When the two groups were compared there was a significant association between VO_2 at AT and ASA score (p=0.041). There was no significant association between VO_2 at AT and other preoperative characteristics including patient age, sex, BMI, smoking status, tumour site, TNM stage, preoperative mGPS, or neoadjuvant treatment (Table 6-1).

There were no significant associations between VO_2 at AT and postoperative complications, the established CRP thresholds on postoperative days 3 or 4 (Table 1), or the postoperative CRP trend (Figure 6-2). When both VO_2 at AT and peak postoperative CRP (day 4) concentrations were compared as continuous variables (Figure 6-5), there was no significant correlation (p=0.885).

6.3.5 VO_2 at peak exercise and the postoperative SIR

13 patients (34%) had VO_2 at peak exercise >19ml/min/kg and 25 patients (66%) had VO_2 at peak exercise <19ml/min/kg (Table 6-1). When the two groups were compared (Table 1) there was a significant association between VO_2 at peak exercise and ASA score (p=0.004). A significantly higher proportion of patients with VO_2 at peak exercise <19ml/min/kg had an mGPS of 1-2 (41% vs. 8%, p=0.036). A significantly lower proportion of patients with VO_2 at peak exercise <19ml/min/kg underwent nCRT (0% vs. 23%, p=0.034). With regard to intraoperative variables (Table 6-1), a significantly higher proportion of patients with VO_2 at peak exercise <19ml/min/kg underwent laparoscopic surgery (84% vs. 23%, p<0.001).

There was no significant association between VO_2 at peak exercise and postoperative complications, established CRP thresholds on postoperative days 3 or 4 (Table 6-1), or the postoperative CRP trend (Figure 6-4). When VO_2 at peak exercise and peak postoperative CRP (day 3) concentrations were compared as continuous variables (Figure 6-5), there was no significant correlation (p=0.898).

6.4 Discussion

The present pilot study confirms the relationship between CPET derived measures of exercise tolerance and co-morbidity as measured by ASA score in patients prior to surgery for colorectal cancer. Moreover, the present results show for the first time an inverse relationship between the VO_2 at peak exercise and the preoperative systemic inflammatory response. There was no significant association with the magnitude of the postoperative systemic inflammatory respons, however, given the small numbers of patients examined, these relationships warrant further investigation.

The neuroendocrine, metabolic, and immune responses to surgical trauma lead to an increase in oxygen requirement from baseline usually supplied by increasing tissue oxygen extraction and cardiac output in the postoperative period, with the aim of increasing oxygen delivery (Shoemaker et al. 1979). However, not all patients are able to utilise these mechanisms sufficiently to prevent the accrual of an "oxygen debt", when oxygen delivery is outstripped by tissue oxygen requirement (Waxman et al. 1981). CPET thus uses graded exercise to quantify a given patient's anaerobic threshold and other measures including VO_2 at peak exercise and MET. These CPET variables are associated with postoperative outcomes following abdominal and colorectal surgery (Older et al. 1999, West et al. 2014a, West et al. 2014b).

In the present study, there was a significant association between poorer VO_2 at peak exercise and an increasing burden of co-morbidity as defined by ASA score. Although the relationship between VO_2 at the anaerobic threshold and ASA score did not reach significance, there was a strong inverse trend. This may simply relate to the small numbers of included patients. However, it may also reflect the differences in the two CPET derived variables and be explained by how ASA score is assigned. ASA score is assigned both by the presence of co-morbidity and by overall physical limitation caused by these co-morbidities. Although such co-morbidities will likely reduce a patient's anaerobic threshold, it may be that the physical limitation denoted by their ASA score is better encapsulated by their maximal exercise ability and thus VO_2 at peak exercise.

It was of interest that a significant association was found between VO_2 at peak exercise and the preoperative mGPS at the univariate level. It remains unclear whether this relationship is explained by the association between preoperative systemic inflammation and co-morbid state, or other effects. Indeed, the preoperative systemic inflammatory

response has previously been shown to be directly associated with preoperative co-morbidity in patients undergoing surgery for colorectal cancer (Richards et al. 2010), and it may be this which links mGPS to reduced peak exercise tolerance. This finding was not confirmed by the results of the present study. However, the trend to association between mGPS and ASA score was likely non-significant due to patient numbers. Alternatively, systemic inflammation has a key causal role in the development of the cancer cachexia syndrome, with loss of skeletal muscle quantity and quality, and resultant loss of physical function in patients with cancer (McSorley et al. 2017). It may be that systemic inflammation exerts its influence on exercise tolerance through this mechanism.

The degree of oxidative stress placed on the patient during surgery has been found to be associated with the production of pro-inflammatory cytokines (Rixen et al. 2000). It has been postulated that oxidative stress and resultant tissue hypoxia, especially in the gut, drives a significant proportion of the postoperative systemic inflammatory response (Mainous et al. 1995). Indeed, it is well recognised that tissue hypoxia can lead to activation and augmentation of the innate immune system via hypoxia-inducible factor 1α (HIF-1α) (Peyssonnaux et al. 2005, Nizet et al .2009).

Although previous studies in colorectal surgery have reported an association between patients with VO_2 at AT <11ml/min/kg and VO_2 at peak exercise <19ml/min/kg and the development of postoperative complications (West et al. 2014[a], West et al. 2014[b]), this was not confirmed in the present study. This is most likely due to the small number of patients in the present study. Postoperative complications, whether categorised by their type or severity, are associated with poorer long-term oncologic outcomes following surgery for colorectal cancer (McSorley, Introduction). The magnitude of the postoperative systemic inflammatory response, as evidenced by CRP, is increasingly understood to be associated with the development of postoperative complications following surgery for colorectal cancer (Singh et al. 2014). Indeed, a recent comprehensive review suggests that CRP concentrations >150mg/L on postoperative days 3-5 are associated with the development of postoperative complications and should prompt investigation by the surgical team (McDermott et al. 2015). Furthermore, studies in surgery for oesophageal and gastric cancer suggest that the magnitude of the postoperative systemic inflammatory response is itself a prognostic factor (Matsuda et al. 2015, Saito et al. 2015).

The main limitation of the present study is the small number of included patients. Preoperative CPET is not routinely used as an evaluation of fitness for colorectal surgery

in our unit at present. These small numbers lead to limited ability to make confident statements about the association between CPET, postoperative CRP, and complications. Indeed, there were significant differences in the proportion of patients undergoing open or laparoscopic surgery when divided into groups by CPET variables. Although laparoscopic surgery has been shown to reduce the magnitude of the postoperative systemic inflammatory response, small numbers prevented any further, meaningful subgroup analysis (Watt et al. 2015).

In conclusion, the present pilot study reports a possible association between preoperative CPET derived measures of exercise tolerance and the preoperative systemic inflammatory response in patients undergoing surgery for colorectal cancer. The mGPS may be a surrogate for overall "fitness" in these patients, or may be more directly related to poorer exercise testing results through effects on skeletal muscle quality and quantity. No association was found between CPET derived measures and the magnitude of the postoperative systemic inflammatory response, however small numbers and the presence of important confounders mean that further work in a larger cohort of patients is warranted.

6.5 Tables and Footnotes

Table 6-1: Patient characteristics and postoperative C-reactive protein concentrations grouped by VO_2 at the anaerobic threshold and peak exercise

Characteristic	Cardiopulmonary exercise test variable					
	VO_2 at AT <11ml/kg/min (n)	VO_2 at AT >11ml/kg/min (n)	P	VO_2 at peak <19ml/kg/min (n)	VO_2 at peak >19ml/kg/min (n)	P
Preoperative						
Age (<65/65-74/>74)	5/8/11	3/7/4	0.488	4/9/12	4/6/3	0.130
Sex (male/female)	19/5	11/3	1.000	19/6	11/2	0.689
ASA score (1/2/3/4)	0/11/12/1	2/8/4/0	0.041	0/10/14/1	2/9/2/0	0.004
BMI (<20/20-25/26-30/>30, kg/m^2)	1/4/7/12	1/4/5/4	0.206	1/4/7/13	1/4/5/3	0.106
Smoker (never/ex/current)	11/9/4	6/6/2	0.981	10/12/3	10/12/3	0.912
Site (colon/rectum)	16/8	7/7	0.492	17/8	6/7	0.295
TNM stage (I/II/III/IV)	2/12/9/0	3/7/3/1	0.510	3/13/9/0	2/6/3/1	0.969
Preop mGPS (0/1-2)	14/8	11/2	0.259	13/9	12/1	0.036
Neoadjuvant (yes/no)	1/23	2/12	0.542	0/25	3/10	0.034
Intraoperative						
Approach (open/laparoscopic)	6/18	8/6	0.081	4/21	10/3	<0.001
Stoma (yes/no)	10/13	6/8	1.000	11/13	5/8	0.666
Transfusion (yes/no)	1/20	0.10	1.000	1/20	0/10	1.000
Surgery > 4h (yes/no)	14/10	6/8	0.503	16/9	4/9	0.087
Postoperative						
Any complication (yes/no)	9/15	6/8	1.000	10/15	5/8	1.000
Clavien Dindo grade 3-5(yes/no)	8/16	2/12	0.268	2/23	1/12	1.000
Length of stay (median,range,days)	8 (3-19)	8 (5-15)	0.790	8 (3-15)	9 (5-19)	0.169
POD 3 CRP >150mg/L (yes/no)	11/12	8/4	0.476	12/12	7/4	0.493
POD 4 CRP >150mg/L (yes/no)	5/12	5/9	0.709	6/13	4/8	0.919

ASA American Society of Anesthesiology, *BMI* Body Mass Index, *AT* anaerobic threshold, *mGPS* modified Glasgow Prognostic Score, *POD* postoperative day, *CRP* C-reactive protein

6.6 Figures and Legends

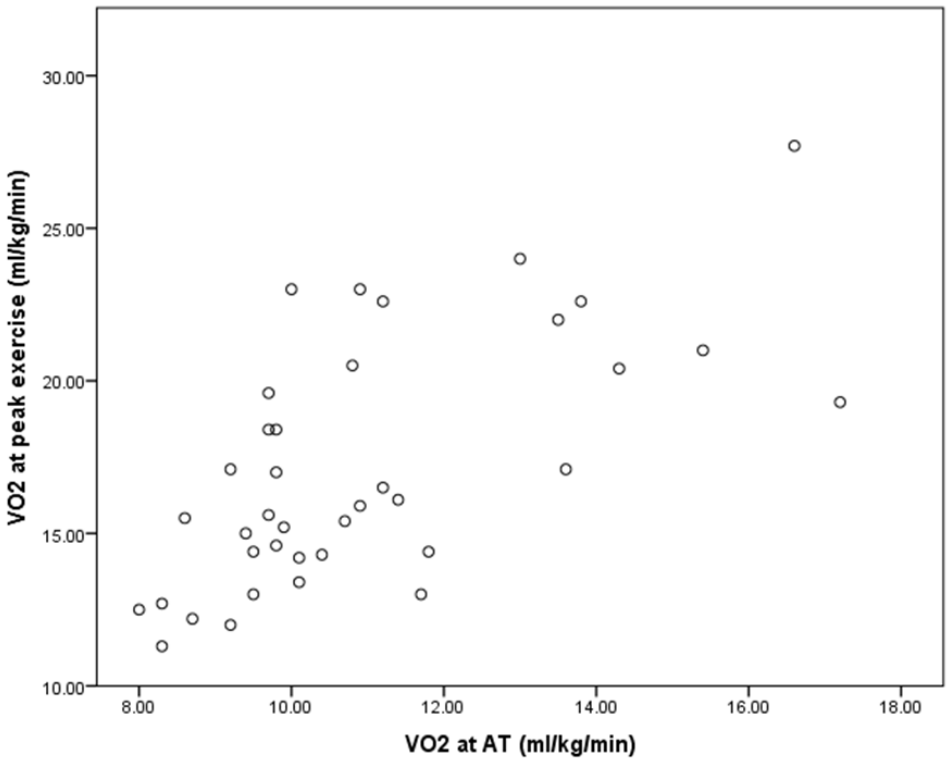

Figure 6-1: Scatter plot of VO_2 at anaerobic threshold (ml/kg/min) and VO_2 at peak exercise (ml/kg/min)

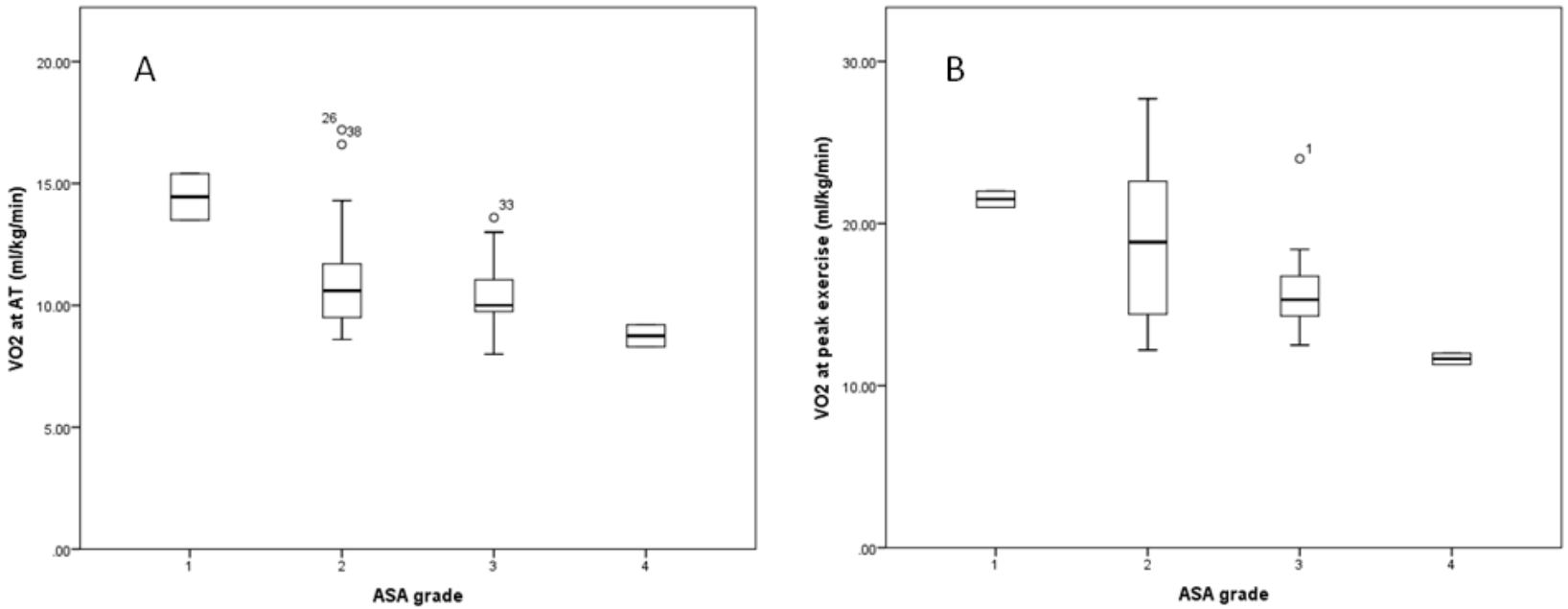

Figure 6-2: Box plots of (A) VO_2 at anaerobic threshold (ml/kg/min) and (B) VO_2 at peak exercise (ml/kg/min) grouped by American Society of Anesthesiology (ASA) score

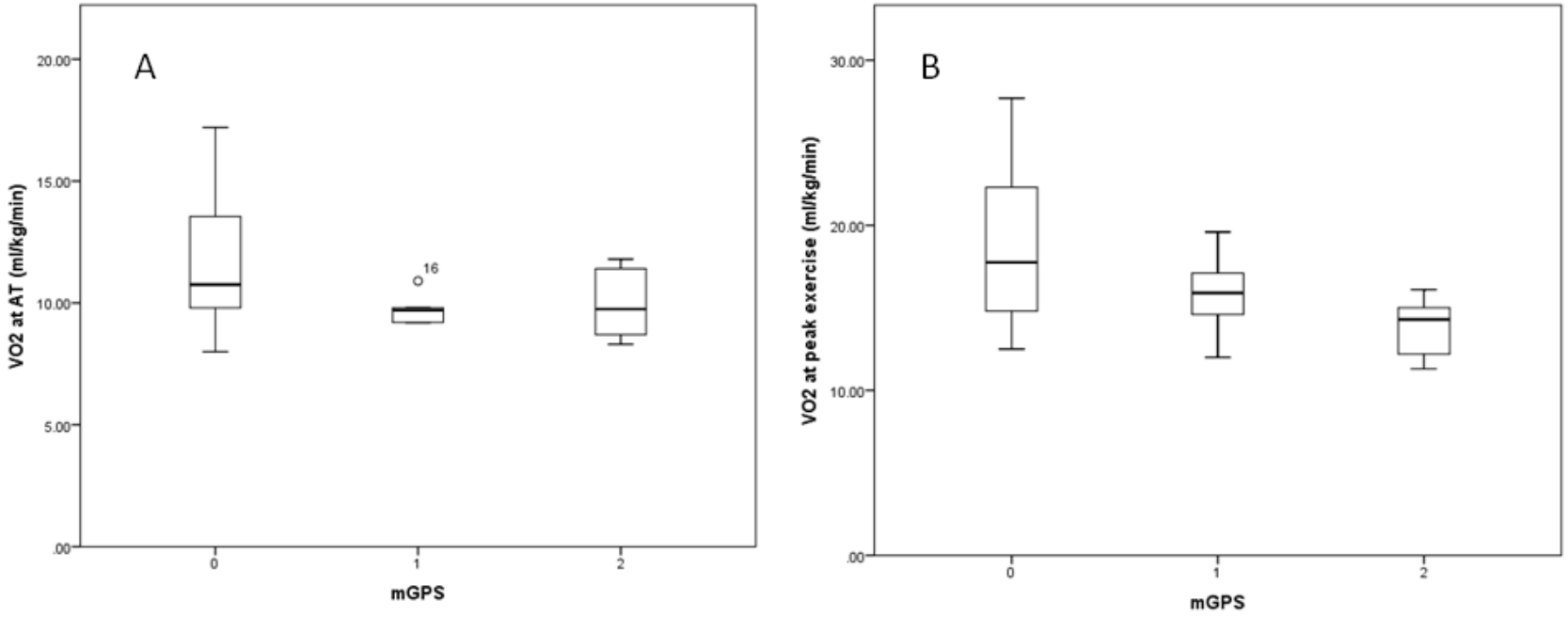

Figure 6-3: Box plots of (A) VO_2 at anaerobic threshold (ml/kg/min) and (B) VO_2 at peak exercise (ml/kg/min) grouped by modified Glasgow Prognostic Score (mGPS)

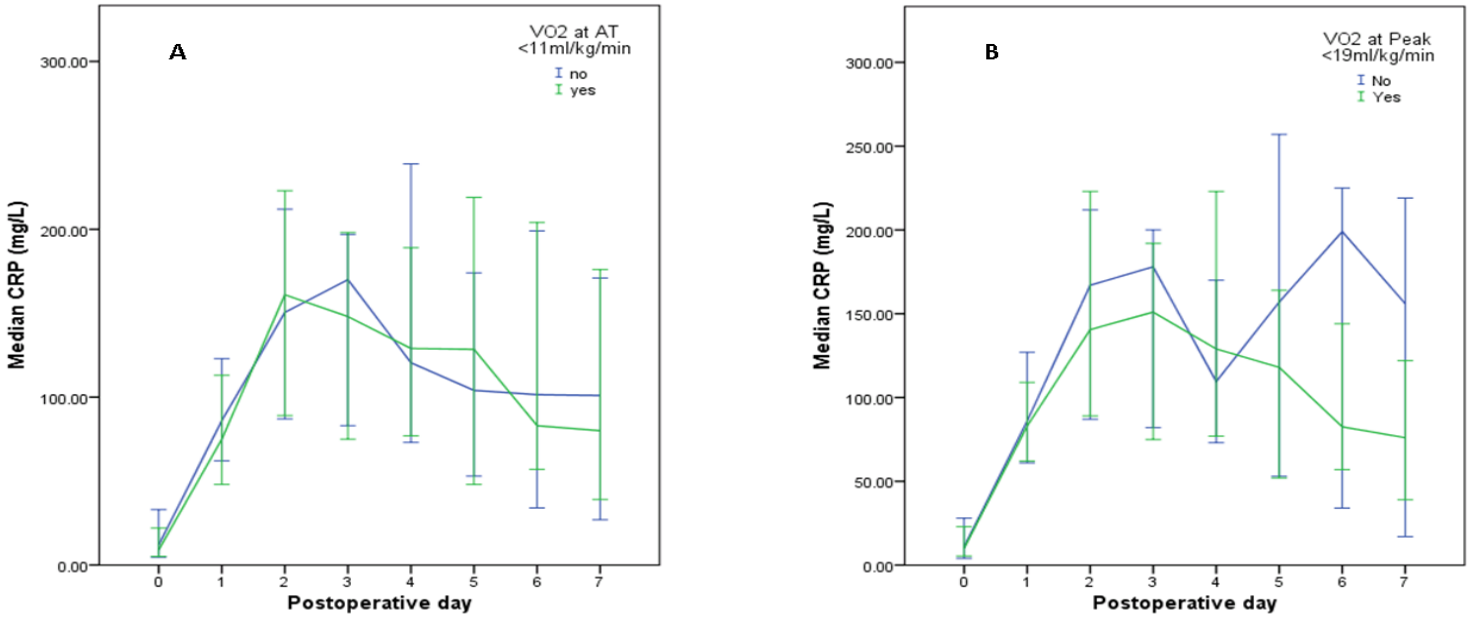

Figure 6-4: Median postoperative C-reactive protein (CRP) concentrations (mg/L) in patients grouped by (A) VO_2 at the anaerobic threshold (ml/kg/min) and (B) VO_2 at peak exercise

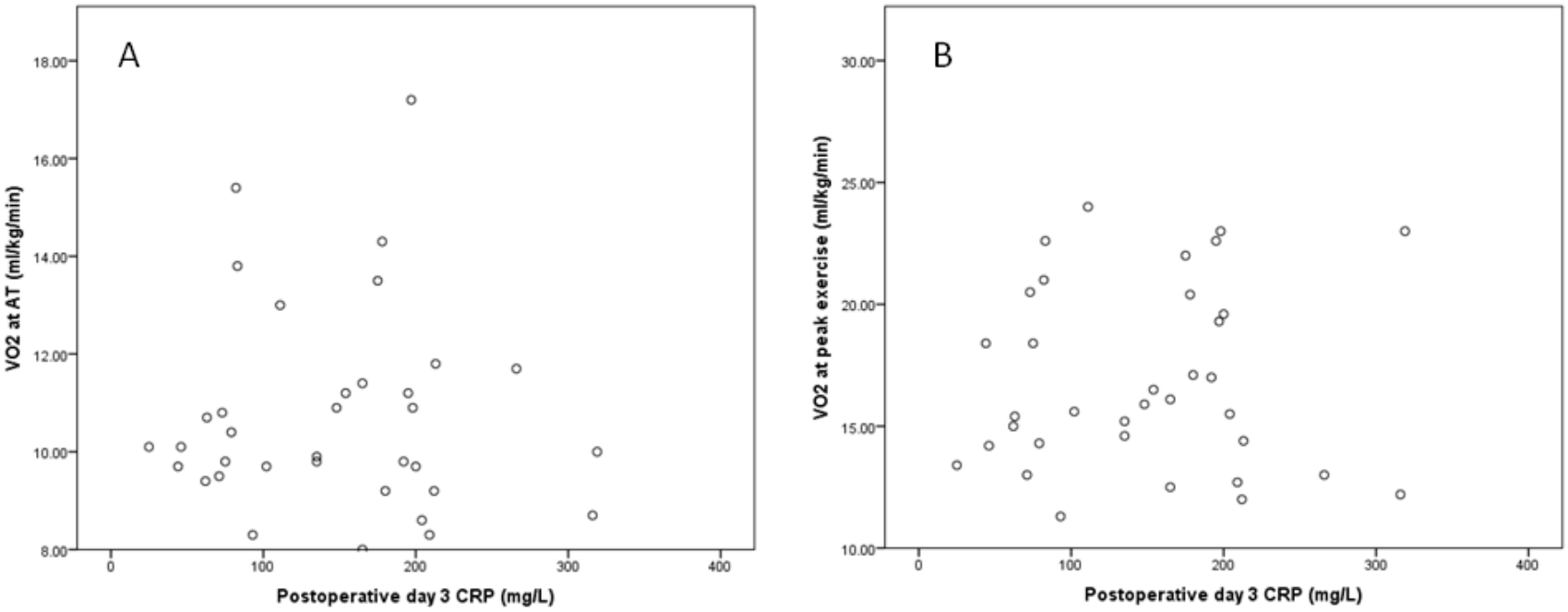

Figure 6-5: Scatter plot of postoperative day 3 C-reactive protein (CRP) concentrations (mg/L) and (A) VO_2 at the anaerobic threshold (ml/kg/min) and (B) VO_2 at peak exercise (ml/kg/min)

7 The relationship between systemic inflammation and stoma formation following anterior resection for rectal cancer: a cross-sectional study

7.1 Introduction

Rectal cancer is one of the most prevalent cancers diagnosed in the western world (CRUK 2014). Anterior resection with total mesorectal excision (TME) is the preferred surgical technique to preserve the anal sphincter and avoid a permanent colostomy where abdominoperineal resection is not required (Abraham et al. 2005). However, anterior resection is associated with increased risk of anastomotic leakage, a major complication of this type of rectal surgery, when compared to resection of colorectal cancer in other locations (Matthiesen et al. 2004). Furthermore, anastomotic leakage has been indicated to be associated with increased risk of local recurrence and decreased short and long term survival of patients who have undergone potentially curative resection (Mirnezami et al. 2011, Artinyan et al. 2015).

Recent evidence suggests that the postoperative systemic inflammatory response, measured by C-reactive protein (CRP), is associated with both short and long term outcomes in colorectal cancer patients (Adamina et al. 2015, McSorley Chapter 4). A recent comprehensive review has suggested that CRP concentrations exceeding 150mg/L on postoperative days 3 to 5 should alert clinicians to the possible development of postoperative complications, including anastomotic leakage, precluding early discharge (McDermott et al. 2015).

Several studies have suggested that construction of a defunctioning stoma in patients who are undergoing anterior resection reduces the incidence of postoperative complications, including anastomotic leakage, and reoperation (Huser et al 2008, Tan et al. 2009, Montedori et al. 2010). Although it has traditionally been thought that this reduction in anastomotic leak rate is due to diversion of the faecal stream, it may be that the formation of a stoma attenuates the magnitude of the postoperative systemic inflammatory response and that it is through this mechanism by which they reduce the rate of postoperative complications.

Therefore, the aim of the present study was to investigate the relationship between defunctioning stoma formation, stoma reversal, the magnitude of the postoperative systemic inflammatory response, and complications in rectal cancer patients who have undergone anterior resection.

7.2 Patients and Methods

7.2.1 Patients

Patients with histologically proven rectal cancer who underwent anterior resection, between February 2008 and April 2015 at a single centre were included in the study. Patients who underwent emergency surgery, palliative procedures, or who had existing inflammatory conditions were excluded. Neoadjuvant treatment was offered to patients with histologically proven, locally advanced (T3-T4, borderline operable or inoperable) rectal tumours following discussion at a multi-disciplinary colorectal oncology meeting.

All patients received prophylactic antibiotics and venous thromboprophylaxis prior to the induction of anaesthesia as per hospital policy. All patients had a primary anastomosis formed and the decision to form a proximal defunctioning stoma, with temporary intent, was at the discretion of the operating surgeon. Patients had routine preoperative blood sampling including a full blood count (FBC), serum CRP, and albumin concentration.

On each postoperative day, patients were clinically assessed and had blood samples, including serum CRP, obtained routinely until discharged. Further postoperative investigation and intervention was at the discretion of the patient's surgical team, who were not blinded to blood results. This study was approved by the West of Scotland Research Ethics Committee.

7.2.2 Methods

Data was collected prospectively in a database, anonymised, and subsequently analysed retrospectively. Recorded information included patient demographics, clinicopathological data, operative data, postoperative data, and date of stoma reversal if applicable. Data regarding the nature of the operation with regard to its categorisation and extent were taken form the operation note. The height of the resected lesion and anastomosis was not routinely recorded.

Serum concentrations of CRP (mg/L) were measured using an autoanalyzer (Architect; Abbot Diagnostics, Maidenhead, UK) with a lower detectable limit of 0.2 mg/L, as was serum albumin (normal range 35-50g/L). The preoperative modified Glasgow Prognostic Score (mGPS) was calculated in patients for whom serum CRP and albumin concentrations

were available (McMillan 2013). Exceeding the established postoperative CRP threshold of 150mg/L on postoperative days 3 or 4 was recorded (McDermott et al. 2015).

Postoperative complications were recorded up to and including the first follow up clinic, usually six weeks after discharge from hospital. Infective complications were categorised as described elsewhere and summarised here briefly (Platt et al. 2012). Wound (superficial surgical site) infection was defined as the presence of pus either spontaneously discharging from the wound or requiring drainage. Deep surgical site infection was defined as surgical or image-guided drainage of intra-abdominal pus. Anastomotic leak was defined as radiologically verified fistula to bowel anastomosis or diagnosed at laparotomy. Pneumonia was defined by fever above 38.5^{o}C and consolidatory chest X-ray findings requiring antibiotic treatment. Septicaemia was defined by the presence of sepsis combined with positive blood culture. Urinary tract infection (UTI) was only included if complicated by septicaemia and confirmed with positive urine culture. Complications were also classified by severity using the Clavien Dindo grade (Dindo et al. 2004).

7.2.3 Statistical Analysis

Categorical data were compared using the Chi square test. Continuous data were non-normal so were displayed as medians and ranges, and were compared using the Mann-Whitney U test. Significant differences were found in the rate of defunctioning stoma formation dependent on whether a laparoscopic or open surgical approach was used, and so a post hoc subgroup analysis was performed in those patients who underwent open surgery. Binary logistic regression of factors associated with permanent stoma was performed using a backward conditional model with removal of terms with $p>0.05$ at each step. Statistical analyses were performed using IBM SPSS version 22 for Windows (Chicago, IL, USA). Two sided p values <0.05 were considered statistically significant. Missing data were excluded from analysis.

7.3 Results

7.3.1 Patients

After exclusion of those patients who underwent emergency or palliative surgery, or with existing inflammatory disease, 869 resections for colorectal cancer were performed during the study period, with 251 patients undergoing surgery for rectal cancer, of which 167 patients underwent anterior resection and were included in the study. The majority were male (102, 61%), over 65 years old (93, 56%), and underwent open surgery (109, 65%). 36 patients (22%) underwent neoadjuvant chemoradiotherapy. 7 patients (4%) had metastatic disease at the time of surgery, all located in the liver, of which 4 underwent synchronous resection, and 3 underwent staged liver resection following anterior resection. 79 patients (47%) developed a postoperative complication of which 73 were infective. There were 12 reported anastomotic leaks (7%). There were 3 deaths (2%) within the immediate postoperative period. Of the 79 patients who developed a postoperative complication, 61 were Clavien Dindo grade 1-2 and 18 were Clavien Dindo grade 3-5. 100 (60%) patients who underwent anterior resection had a defunctioning stoma formed.

7.3.2 Variables associated with stoma formation

Defunctioning stoma formation (Table 7-1) was significantly associated with male sex (69% vs. 50%, p=0.017), neoadjuvant chemoradiotherapy (30% vs 9%, p=0.001), and open surgery (71% vs. 55%, p=0.040). There was no significant association between stoma formation and other patient factors including age, BMI, smoking status, ASA score, or TNM staging. No significant association was found between stoma formation and preoperative mGPS. There was no significant association between stoma formation and CRP on postoperative days 3 or 4. There was no significant difference in the incidence or severity of postoperative complication, or in the rate of anastomotic leak between either group.

7.3.3 Variables associated with stoma formation in patients undergoing open surgery

Within the patients who underwent open surgery, there was significant association (Table 7-2) between stoma formation and neoadjuvant chemoradiotherapy (34% vs 14%, p=0.029). There was no significant association between stoma formation and other patient factors including age, BMI, smoking status, ASA score, TNM staging, or operation type.

There was no significant difference in CRP between the patient groups with and without stoma on postoperative days 3 or 4 (Figure 7-1). There was no significant association between stoma formation and the incidence or severity of postoperative complications.

7.3.4 Variables associated with permanent stoma in patients undergoing open surgery

Of the 71 patients who had open surgery and a defunctioning stoma formed, 53 (75%) had their stoma reversed (Table 7-3). The median time from anterior resection to stoma reversal was 8 months (range 1-23). Permanent stoma was significantly associated with increasing age (p=0.011), higher CRP on postoperative days 3 (212mg/L vs 144mg/L, p=0.048) and 4 (179mg/L vs 128mg/L, p=0.044), the proportion of patients exceeding the established CRP threshold of 150mg/L on postoperative day 4 (67% vs 37%, p=0.039), a higher incidence of postoperative complications (76% vs 47%, p=0.035), anastomotic leakage (24% vs 2%, p=0.003), and higher Clavien Dindo grade (p=0.036). However, there was no significant association between permanent stoma and BMI, smoking status, ASA score, TNM staging, or neoadjuvant chemoradiotherapy. At binary logistic regression of those factors found to be significantly associated with permanent stoma, increasing age (OR 3.46, 95% CI 1.46-8.12, p=0.005), and Clavien Dindo grade (OR 3.00, 95% CI 1.14-7.84, p=0.025) remained significantly independently associated.

7.4 Discussion

The results of the present study suggest that temporary defunctioning stoma formation is not associated with the magnitude of the postoperative systemic inflammatory response, or complications in patients who have undergone anterior resection for rectal cancer. However, they do suggest that increasing age, inflammation, and a complicated postoperative course increases the likelihood of having a permanent stoma.

In keeping with some earlier published reports, the present study reports that males and patients who have undergone neoadjuvant chemoradiotherapy are more likely to have a defunctioning stoma at anterior resection (Marusch et al. 2002, Gastinger et al. 2005). In addition, the present study is also in agreement with a single study which demonstrated that stoma formation is not associated with body mass index (Karahasanoglu et al. 2011). The present study also reports that stoma formation is not associated with ASA score, TNM staging and age group which is in keeping with other published work (Gastinger et al. 2005).

To the author's knowledge, there has been no prior study examining the association between stoma formation and preoperative systemic inflammatory status. There is limited evidence which examines the association between stoma formation the postoperative systemic inflammatory response: a single study, which investigated CRP on the first and third postoperative day which reported a significant difference in CRP on postoperative day 3 (Ma et al. 2013). In contrast, the present study reported no association between CRP levels on postoperative days 3 or 4 between patient groups with and without stoma. The anastomotic leak rate in the present study was around half that (8%) of Ma and colleagues' study (16%) which may in part explain this difference.

The present study demonstrates no association between stoma formation and postoperative complications when all included patients were considered. However, the present study reports a trend towards reduced incidence of anastomotic leakage in patients with stoma, although it did not reach statistical significance due to cohort size. As surgical approach is a significant confounder with regard to the postoperative systemic inflammatory response, and was associated with the incidence of stoma formation in the present study, subgroup analysis was performed.

It was of interest that there was no significant association between stoma formation and patient factors such as BMI, ASA score, or smoking status. There was, however, a significant association between stoma formation and neoadjuvant treatment, although recent evidence suggests no reduction in postoperative complication, unplanned reoperation, or mortality in patients who have a stoma formed following neoadjuvant treatment (Messaris et al. 2015). It may be that perceived differences in rectal dissection in patients who have had neoadjuvant treatment prompts some surgeons to create more temporary defunctioning stomas in this patient group.

The present study is in line with a few published studies, reporting that permanent stoma is associated with older patients (age<65) (Lee et al. 2015) and higher incidence of postoperative complications, including anastomotic leakage (Dulk et al. 2007, Floodeen et al. 2013, Kim et al. 2016). The present study also reports that permanent stoma is associated with higher CRP on postoperative days 3 and 4, and a higher proportion of patients who breached the CRP threshold on postoperative day 4. Given the greater anastomotic leak rate and higher Clavien Dindo grade, this may simply reflect that patients experiencing significant complications are less likely to have subsequent stoma reversal, which would be in keeping with the result of the binary logistic regression analysis. However, to the author's knowledge, there have not been any previous studies that have examined the relationship between postoperative systemic inflammatory response and permanent stoma.

The main limitation of the present study is the relatively small number of patients undergoing anterior resection as a proportion of all patients operated on for colorectal cancer during the period. However, this group was chosen, rather than the inclusion of resections at other locations, due the relatively high rate of stoma formation and to allow direct comparison. The fact that data regarding lesion and anastomosis height was not recorded and that such a low proportion of patients had minimally invasive surgery following nCRT may lead to selection bias. Furthermore, the retrospective nature of the study means that not all patients had CRP measured in the pre- and postoperative periods studied. Finally, the high rate of both temporary stoma (60%), and of subsequent permanent stoma in that subgroup (25%), might suggest that more of the included patients should have been considered for permanent colostomy following an elective low Hartmann's procedure from the outset. The risk factors for permanent stoma; age and co-morbidity, were those which might prompt the surgical team to pursue such a course of action at the outset.

In conclusion, the present study reports a lack of association between stoma formation and postoperative systemic inflammatory response in patients who have undergone anterior resection for rectal cancer. However, both the systemic inflammatory response and postoperative complications were associated with permanent stoma.

7.5 Tables and Footnotes

Table 7-1: Relationship between temporary defunctioning stoma formation and clinicopathological variables in patients undergoing elective anterior resection of rectal cancer (n=167)

Characteristic	All	Stoma		P
		No	Yes	
Sex (male/female)	102/65	33/34	69/31	0.017
Age (<65/65-74/>74)	74/69/24	27/31/9	47/38/15	0.566
BMI (<20/20-25/26-30/>30, kg/m^2)	4/59/47/31	1/22/21/10	3/37/26/21	0.965
ASA score (1/2/3/4)	44/71/40/2	13/29/19/0	31/42/21/2	0.235
Smoking (no/ex/current)	277/66/23	32/27/8	45/39/15	0.839
Preoperative mGPS (0/1/2)	135/14/9	51/8/4	84/6/5	0.356
Neoadjuvant chemoradiotherapy (yes/no)	36/131	6/61	30/70	0.001
Operative (laparoscopic/open)	58/107	29/36	29/71	0.040
TNM stage (0/1/2/3/4)	4/40/56/58/7	0/19/26/18/2	4/21/30/40/5	0.141
POD 3 CRP (median,range,mg/L)	147 (2-386)	143(21-354)	149(2-386)	0.464
POD 4 CRP (median,range,mg/L)	128 (2-425)	133(20-425)	124(2-408)	0.495
POD 3 CRP >150mg/L (yes/no)	70/80	25/34	45/46	0.396
POD 4 CRP >150mg/L (yes/no)	55/84	19/31	36/53	0.777
Any postoperative complication (yes/no)	79/82	29/35	50/47	0.439
Anastomotic leakage (yes/no)	12/149	7/57	5/92	0.172
Clavien Dindo Classification (0/1-2/3-5)	82/61/18	35/21/8	47/40/10	0.784
Adjuvant therapy (yes/no)	41/126	16/51	25/75	0.704

ASA American Society of Anaesthesiology, *BMI* Body Mass Index, *CRP* C-reactive protein, *mGPS* modified Glasgow Prognostic Score

Table 7-2: Relationship between temporary defunctioning stoma formation and clinicopathological variables in patients undergoing elective, open anterior resection for rectal cancer (n=107)

Characteristic	All	Stoma		P
		No	Yes	
Sex (male/female)	63/44	18/18	45/26	0.184
Age (<65/65-74/>74)	47/44/16	15/17/4	32/27/12	0.580
BMI (<20/20-25/26-30/>30, kg/m^2)	3/36/26/25	0/11/11/7	3/25/15/18	0.707
ASA score (1/2/3/4)	29/46/26/1	6/18/10/0	23/28/16/1	0.309
Smoking (no/ex/current)	49/42/15	19/13/4	30/29/11	0.597
Preoperative mGPS (0/1/2)	89/7/8	26/4/4	63/3/4	0.175
Neoadjuvant chemoradiotherapy (yes/no)	29/78	5/31	24/47	0.029
TNM stage (0/1/2/3/4)	3/23/31/43/6	0/7/13/13/2	3/16/18/30/4	0.589
POD 3 CRP (median,range,mg/L)	152 (37-386)	148(37-354)	153(40-386)	0.829
POD 4 CRP (median,range,mg/L)	134 (2-408)	136(20-369)	133(2-408)	0.752
POD 3 CRP >150mg/L (yes/no)	51/47	16/18	35/29	0.472
POD 4 CRP >150mg/L (yes/no)	39/57	10/20	29/37	0.327
Any postoperative complication (yes/no)	57/49	19/17	38/32	0.883
Anastomotic leakage (yes/no)	8/98	3/33	5/65	0.826
Clavien Dindo Classification (0/1-2/3-5)	49/45/12	17/15/4	32/30/8	0.785
Adjuvant therapy (yes/no)	27/80	10/26	17/54	0.813

ASA American Society of Anaesthesiology, *BMI* Body Mass Index, *CRP* C-reactive protein, *mGPS* modified Glasgow Prognostic Score

Table 7-3: Relationship between permanent stoma and clinicopathological variables in patients following stoma formation during elective, open anterior resection for rectal cancer (n=71)

Characteristic	All	Permanent Stoma		P
		No	Yes	
Sex (male/female)	45/26	34/19	11/7	0.817
Age (<65/65-74/>74)	32/27/12	29/18/6	3/9/6	0.011
BMI (<20/20-25/26-30/>30, kg/m^2)	3/26/16/19	2/19/12/15	1/7/4/4	0.606
ASA score (1/2/3/4)	23/28/16/1	18/20/12/1	5/8/4/0	0.884
Smoking (no/ex/current)	30/29/11	23/19/10	7/10/1	0.241
Preoperative mGPS (0/1/2)	63/3/4	46/3/3	17/0/1	0.579
Neoadjuvant chemoradiotherapy (yes/no)	24/47	19/34	5/13	0.532
TNM stage (0/1/2/3/4)	3/16/17/30/4	2/13/13/22/3	1/3/4/8/1	0.974
POD 3 CRP (median,range,mg/L)	152(37-386)	144(40-386)	212(55-333)	0.048
POD 4 CRP (median,range,mg/L)	134(2-408)	128(2-388)	179(33-408)	0.039
POD 3 CRP >150mg/L (yes/no)	35/29	24/25	11/4	0.097
POD 4 CRP >150mg/L (yes/no)	29/37	19/32	10/5	0.044
Any postoperative complication (yes/no)	38/32	25/28	13/4	0.035
Anastomotic leakage (yes/no)	5/65	1/52	4/13	0.003
Clavien Dindo Classification (0/1-2/3-5)	32/30/8	28/22/3	4/8/5	0.036
Adjuvant therapy (yes/no)	17/54	14/39	3/15	0.510

ASA American Society of Anaesthesiology, *BMI* Body Mass Index, *CRP* C-reactive protein, *mGPS* modified Glasgow Prognostic Score

7.6 Figures and Legends

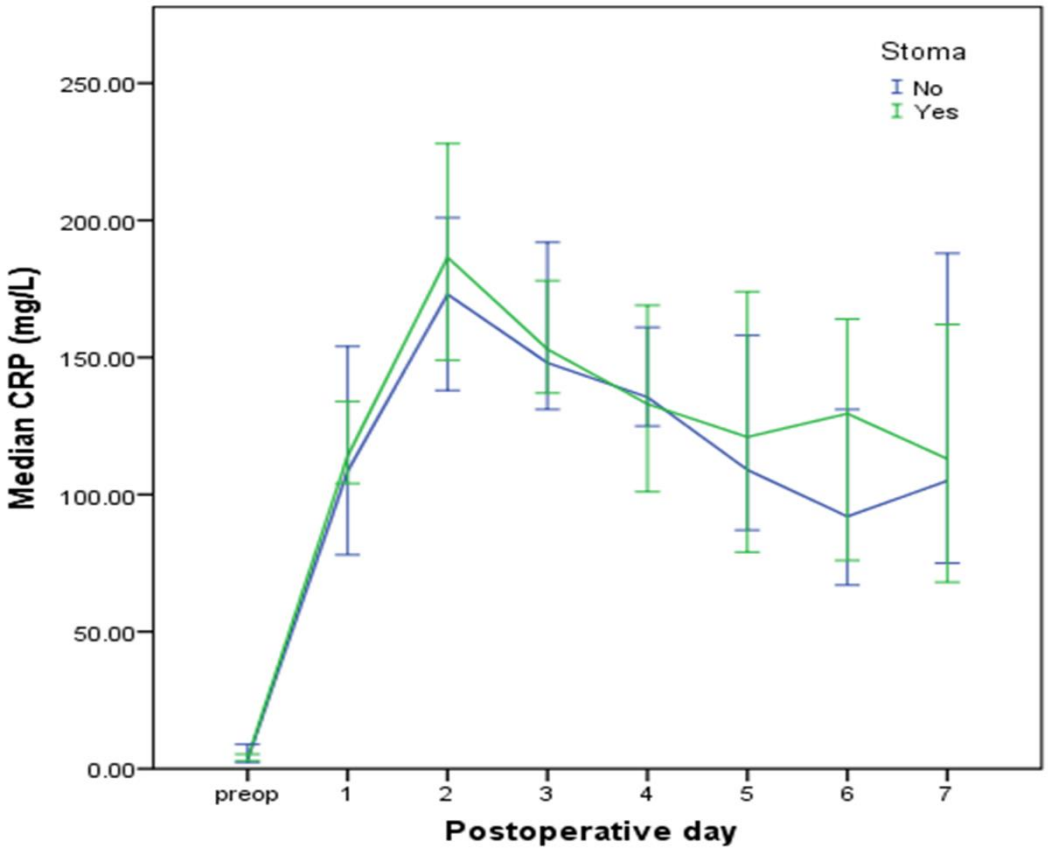

Figure 7-1: Impact of stoma formation on the postoperative systemic inflammatory response following elective, open anterior resection for rectal cancer

8 The impact of operation duration on postoperative complications and the systemic inflammatory response following surgery for colorectal cancer

8.1 Introduction

As discussed in earlier chapters, postoperative serum C-reactive protein (CRP) has been found to be an objective marker of the magnitude of surgical injury and the postoperative systemic inflammatory, or "stress", response (Watt et al. 2015c). In the context of surgery for colorectal cancer, established threshold postoperative CRP concentrations are associated with the development of postoperative complications (McDermott et al. 2015). Furthermore, laparoscopic colorectal surgery has been found to be associated with lower postoperative serum CRP concentrations when compared to open surgery, suggesting a lesser degree of surgical trauma (Veenhoff et al. 2012, Ramanathan et al. 2015b, Watt et al. 2015c).

Several recent studies have reported that increasing operative duration has a negative impact on short term outcomes following both laparoscopic and open colorectal surgery in terms of increasing postoperative complication rates (Evans et al. 2012, Owen et al. 2013, Bailey et al. 2014), readmission rates (Kelly et al. 2013), and length of stay (Harrison et al. 2014). Studies, in patients undergoing aortic and spinal surgery, report that increasing operative time is associated with a greater postoperative systemic inflammatory response, and in particular, higher postoperative serum concentrations of CRP and IL 6 (Norman et al. 1997, Chung et al. 2011). This finding suggests that longer operations lead to greater surgical trauma and/or complications which increase the postoperative systemic inflammatory response. This is of interest given the observed associations between the magnitude of the postoperative systemic inflammatory response and postoperative complications, and with long term outcomes following surgery for colorectal cancer.

To the authors' knowledge no similar studies have examined the impact of operation duration on the postoperative systemic inflammatory response following surgery for colorectal cancer. Therefore, the aim of the present observational study was to examine the impact of operative time on postoperative complications and the systemic inflammatory response following both open and laparoscopic surgery for colorectal cancer.

8.2 Patients and Methods

8.2.1 Patients

This observational study included patients who underwent elective, potentially curative resection for histologically confirmed colorectal cancer at two centres between March 2010 and May 2013. Patients who underwent emergency surgery, with metastatic disease, or who had existing inflammatory conditions, e.g. inflammatory bowel disease and the systemic vasculitides, were excluded. All patients received prophylactic antibiotics and venous thromboprophylaxis prior to the induction of anaesthesia as per hospital policy. On each postoperative day patients were clinically assessed and had blood samples, including serum CRP, obtained as standard until discharged. Further postoperative investigation and intervention was at the discretion of the patient's surgical team.

8.2.2 Methods

Data was collected prospectively in a database, anonymised, and was subsequently analysed. Recorded information included patient demographics, tumour site, TNM stage (TNM, AJCC), surgical approach, complications, and postoperative serum CRP measurements. Data regarding the nature, severity, and management of complications was categorised using the Clavien Dindo scale (Dindo et al. 2004). Data regarding operation duration was collected retrospectively from the operating room management software (Opera, v4.0, CHCA, Canada). The duration of the operation in minutes was defined as the time from first incision to placement of the wound dressing. Time in the anaesthetic room and/or theatre recovery was not included. Serum concentrations of CRP (mg/L) were measured using an autoanalyzer (Architect; Abbot Diagnostics, Maidenhead, UK) with a lower detectable limit of 0.2 mg/L. Any uncertainties were addressed by review of electronic and/or physical case notes. This study was approved by the West of Scotland Research Ethics Committee as part of surgical audit.

8.2.3 Statistical Analysis

Categorical data regarding patient characteristics were compared using the Chi square test. Data regarding postoperative CRP were not normally distributed and are presented as medians and ranges. Medians of continuous variables were compared using the Mann-Whitney U test. Correlation between operation duration and CRP concentrations on postoperative days 3 and 4 were assessed using Spearman's correlation coefficients and

scatter plots with CRP measured on a logarithmic scale. In all tests, a two sided p value <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS version 22 for Windows (Chicago, IL, USA).

8.3 Results

In total, 341 patients were included in the study. The majority were male (185, 54%), over 65 years old (231, 68%), with colonic (241, 71%) and node negative disease (230, 67%). 188 patients (55%) underwent open surgery and 153 (45%) underwent laparoscopic surgery. Patients who underwent laparoscopic surgery had a longer median operation duration (220 mins vs. 150 mins, $p<0.001$) and lower median serum CRP on the second (124 mg/L vs. 174 mg/L, $p<0.001$), third (122 mg/L vs. 171 mg/L, $p<0.001$), and fourth (101 mg/L vs. 138 mg/L, $p=0.013$) postoperative days when compared to those who underwent open surgery.

Of the total 341 patients (Table 8-1), the median operation duration was 180 mins (range 42-500). There was a significant association between surgery lasting longer than 180 mins and increasing age ($p=0.016$), male sex ($p=0.041$), rectal cancer ($p<0.001$), ASA score ($p=0.011$), preoperative mGPS ($p=0.001$), and neoadjuvant chemoradiotherapy ($p=0.001$). Surgery lasting longer than 180 mins was significantly associated with stoma formation (36% vs. 22%, $p=0.024$) and Clavien Dindo grade 3-5 complications (16% vs. 5%, $p=0.001$). There was no significant correlation (Figure 8-1) between the operation duration and CRP on postoperative day 3 ($rs=0.009$), or 4 ($rs=-0.040$). Furthermore, there was no significant association between operation duration and the established thresholds for postoperative CRP.

Of the 188 patients who underwent open surgery (Table 8-2), the median operation duration was 150 mins (range 42-500). 100 (53%) experienced a complication, of which 71 (38%) were infective type and 21 (11%) were Clavien Dindo grade 3-5 severity. There was a significant association between surgery lasting longer than 150 mins and surgery for rectal cancer ($p<0.001$) and neoadjuvant chemoradiotherapy ($p=0.005$). Surgery lasting longer than 150 mins was significantly associated with stoma formation (43% vs. 24%, $p=0.022$) and any postoperative complication (61% vs. 44%, $p=0.001$). There was no significant correlation (Figure 8-2) between the operation duration and CRP on postoperative day 3 ($r^s=0.121$), or 4 ($r^s=0.043$). Furthermore, there was no significant association between operation duration and the established thresholds for postoperative CRP.

Of the 122 patients who underwent open surgery for colonic cancer (Table 8-3), the median operation duration was 140 mins (range 42-476). 63 (52%) experienced a

complication, of which 44 (36%) were infective type and 14 (11%) were Clavien Dindo grade 3-5 severity. There were no significant associations between surgery lasting longer than 140 mins and any preoperative clinicopathological characteristics. Surgery lasting longer than 140 mins was not significantly associated with stoma formation or postoperative complications. There was no significant correlation (Figure 8-3) between the operation duration and CRP on postoperative day 3 (r^s=0.192), or 4 (r^s=0.054). Furthermore, there was no significant association between operation duration and the established thresholds for postoperative CRP.

8.4 Discussion

The results of the present study report no association between operative time and postoperative CRP, suggesting that the duration of an operation does not necessarily correlate with the degree of the surgical injury. Furthermore, after adjusting for variables associated with the postoperative systemic inflammatory response and complications, including surgical approach and tumour location, there was no association with postoperative complications.

In keeping with earlier published reports, the present study found that those who underwent laparoscopic surgery for colorectal cancer had a longer operation (Grailey et al. 2012) and lower postoperative serum CRP (Karanika et al. 2013) when compared to those undergoing open surgery. In the present study, surgery for a rectal cancer, and neoadjuvant treatment, were associated with longer operative time in both the open and laparoscopic groups. Previous studies have reported longer operative duration in patients who have undergone surgery for rectal cancer following neoadjuvant therapy (Cheung et al. 2009), but this has not been universally replicated (Rosati et al. 2007, Akiyoshi et al. 2009).

Both IL6 and CRP concentrations in the postoperative period are thought to accurately represent the magnitude of the postoperative systemic inflammatory response and reflect the degree of surgical trauma (Watt et al. 2015c). The use of laparoscopic surgical techniques is well recognised to be associated with less surgical trauma and attenuation of the postoperative systemic inflammatory response when compared to more traditional open surgical techniques (Watt et al. 2015c). However, the reasons for this remain poorly understood. Some suggestions include the smaller overall abdominal wound size, the use of warm CO_2 insufflation, and the no-touch techniques employed during most minimally invasive surgery (Krikri et al. 2013). Alternatively, it may be that selection of patients suitable for laparoscopic surgery in such clinical studies leads to biased reporting.

This is of clinical interest due to the association between the magnitude of the postoperative systemic inflammatory response and outcomes following surgery for colorectal cancer (Adamina et al. 2015). Exceeding established postoperative CRP thresholds has been shown to be associated with both postoperative complication severity (McSorley Chapter 3) and cancer specific survival (McSorley Chapter 4). The results of the present study suggest that a longer operation does not necessarily reflect a greater

degree of surgical trauma, and that the surgical approach is of far more importance with regard to the postoperative systemic inflammatory response.

The main limitation of the present study was the relatively small number of patients included, especially following subgroup analysis to control for the most significant cofounders: surgical approach and rectal disease. This, however, was based on previous evidence demonstrating that laparoscopic procedures have a significantly longer operative time (Grailey et al. 2012) but lower postoperative serum CRP than open procedures (Veenhof et al. 2012, Ramanathan et al. 2015b, Watt et al. 2015c). In addition, due to the retrospective nature of the study, there was a high proportion of missing data (almost 40%) with regard to BMI and stoma formation recording. Given that BMI in particular is thought to relate to postoperative systemic inflammation this may well lead to significant bias. Furthermore, although the use of the Opera theatre management software allowed for relatively straightforward data collection, the time recording for the start and end of each operation is user dependent and therefore prone to error.

The present study demonstrates minimal impact of operation duration on the postoperative systemic inflammatory response following either open or laparoscopic surgery for colorectal cancer. This suggests that the duration of the operation itself is not associated with the degree of surgical trauma, especially in comparison to the surgical approach used. Given the lower postoperative CRP concentrations in those undergoing laparoscopic procedures, it may be that open surgery, along with other, as yet unidentified, intraoperative variables, may contribute to the postoperative systemic inflammatory response more significantly.

8.5 Tables and Footnotes

Table 8-1: Impact of operation duration on postoperative complications and systemic inflammation after elective surgery for colorectal cancer

Characteristic	All	Operation duration (mins)		
		<180	>180	P
Age (<65/65-74/>74)	110/119/112	50/53/69	60/66/43	0.016
Sex (male/female)	193/148	88/84	105/64	0.041
TNM Stage (0/I/II/III)	7/80/143/111	1/35/82/54	6/45/61/57	0.255
Site (colon/rectum)	241/100	142/30	99/70	<0.001
ASA score (1/2/3/4)	38/136/119/11	14/63/68/7	24/73/51/4	0.011
BMI (<20/20-25/25-30/>30) kg/m2	11/61/81/77	3/34/34/37	8/27/47/40	0.978
mGPS (0/1/2)	241/25/57	110/10/41	131/15/16	0.001
Neoadjuvant treatment (yes/no)	40/289	10/158	30/131	0.001
Approach (open/laparoscopic)	188/153	122/50	66/103	<0.001
Stoma (yes/no)	71/171	25/88	46/83	0.024
Any complication (yes/no)	153/188	73/99	80/89	0.385
Infective complication (yes/no)	111/230	52/120	59/110	0.419
Clavien Dindo ≥3 complication (yes/no)	36/305	9/163	27/142	0.001
POD3 CRP >150 mg/L (yes/no)	156/157	74/79	82/78	0.652
POD4 CRP >150 mg/L (yes/no)	118/162	56/81	62/81	0.717

POD: postoperative day, *CRP*: c-reactive protein, *ASA* American Society of Anesthesiology, *BMI* body mass index, *mGPS* modified Glasgow Prognostic Score

Table 8-2: Impact of operation duration on postoperative complications and systemic inflammation after elective open surgery for colorectal cancer

Characteristic	All	Operation duration (mins)		
		<150	>150	P
Age (<65/65-74/>74)	59/62/67	29/26/34	30/36/33	0.829
Sex (male/female)	103/85	48/41	55/44	0.884
TNM Stage (0/I/II/III)	3/37/84/64	1/16/41/31	2/21/43/33	0.561
Site (colon/rectum)	122/66	72/17	50/49	<0.001
ASA score (1/2/3/4)	19/65/74/10	9/27/37/5	10/38/37/5	0.524
BMI (<20/20-25/25-30/>30) kg/m^2	7/41/44/43	2/19/13/23	5/22/31/20	0.332
mGPS (0/1/2)	126/12/45	54/5/26	72/7/19	0.214
Neoadjuvant treatment (yes/no)	30/152	7/80	23/72	0.005
Stoma (yes/no)	51/94	15/47	36/47	0.022
Any complication (yes/no)	100/88	39/50	61/38	0.019
Infective complication (yes/no)	71/117	29/60	42/57	0.178
Clavien Dindo ≥3 complication (yes/no)	21/167	6/83	15/84	0.068
POD3 CRP >150 mg/L (yes/no)	105/76	44/40	61/36	0.153
POD4 CRP >150 mg/L (yes/no)	75/95	31/44	44/51	0.537

POD: postoperative day, *CRP*: c-reactive protein, *ASA* American Society of Anesthesiology, *BMI* body mass index, *mGPS* modified Glasgow Prognostic Score

Table 8-3: Impact of operation duration on postoperative complications and systemic inflammation following elective, open surgery for colonic cancer

Characteristic	All	Operation duration (mins)		
		<140	>140	P
Age (<65/65-74/>74)	36/35/51	21/17/23	15/18/28	0.235
Sex (male/female)	63/59	31/30	32/29	1.000
TNM Stage (I/II/III)	24/60/38	11/33/17	13/27/21	0.798
ASA score (1/2/3/4)	10/39/49/8	6/17/26/3	4/22/23/5	0.805
BMI (<20/20-25/25-30/>30) kg/m^2	6/22/23/24	1/10/10/14	5/12/13/10	0.109
mGPS (0/1/2)	72/10/35	32/5/20	40/5/15	0.219
Stoma (yes/no)	8/77	3/36	5/41	0.721
Any complication (yes/no)	63/59	29/32	34/27	0.469
Infective complication (yes/no)	44/78	20/41	24/37	0.572
Clavien Dindo ≥3 complication (yes/no)	14/108	5/56	9/52	0.395
POD3 CRP >150 mg/L (yes/no)	73/42	32/25	41/17	0.124
POD4 CRP >150 mg/L (yes/no)	51/56	20/29	31/27	0.244

POD: postoperative day, *CRP*: c-reactive protein, *ASA* American Society of Anesthesiology, *BMI* body mass index, *mGPS* modified Glasgow Prognostic Score

8.6 Figures and Legends

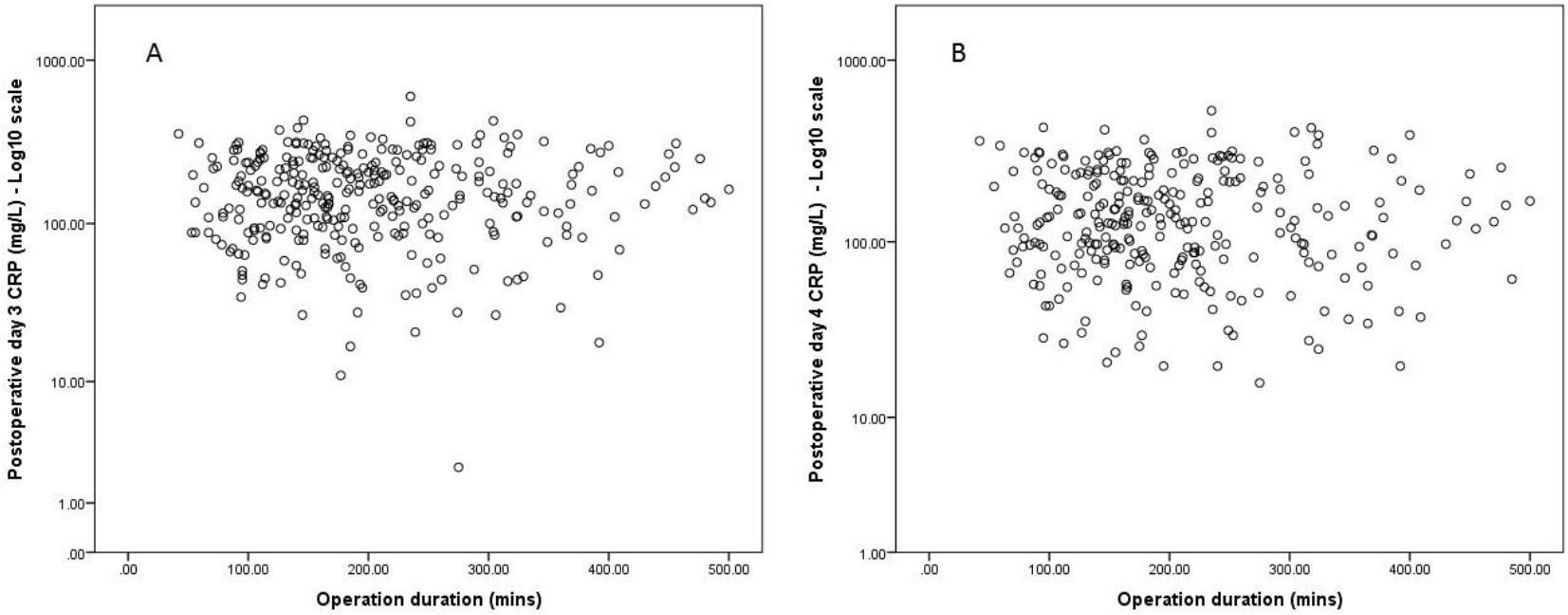

Figure 8-1: Scatter plots of operation duration (mins) and postoperative C-reactive protein concentration (mg/L) on (A) postoperative day 3 and (B) day 4, following elective surgery for colorectal cancer

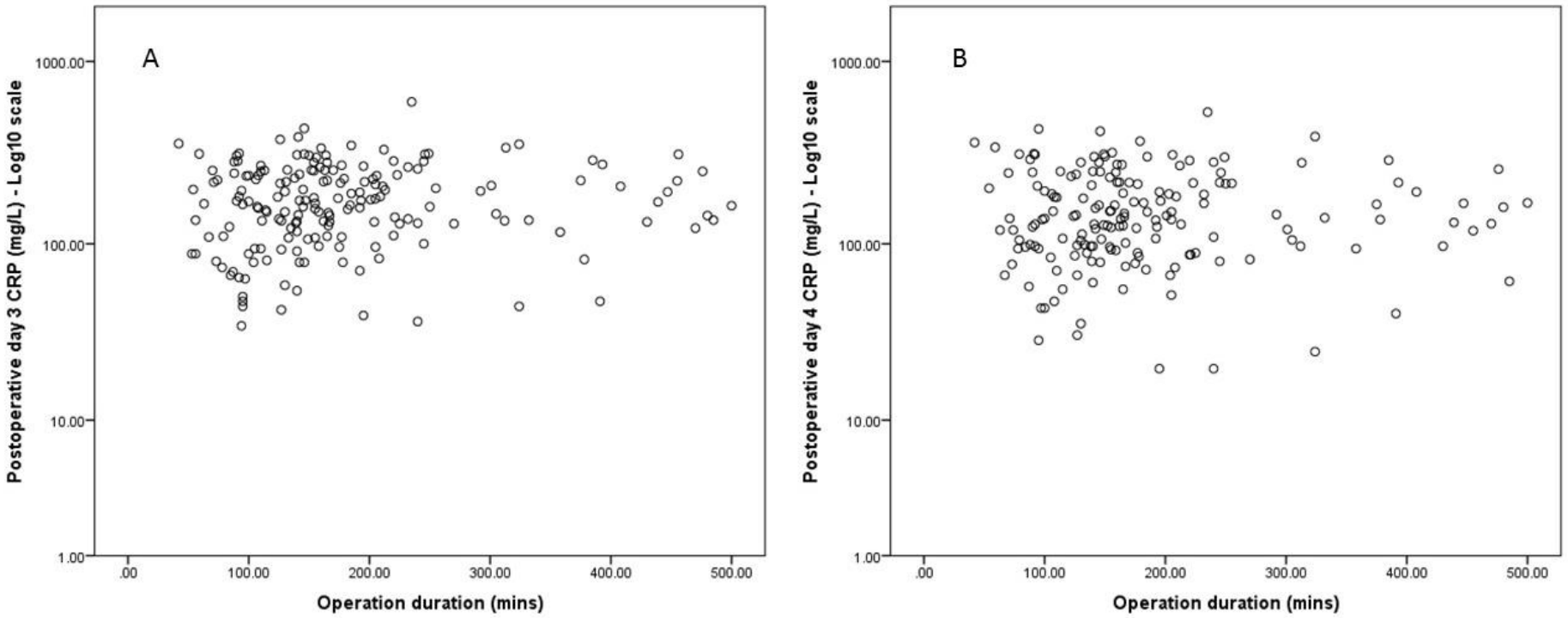

Figure 8-2: Scatter plots of operation duration (mins) and postoperative CRP concentrations (mg/L) on (A) postoperative day 3 and (B) day 4, following elective open surgery for colorectal cancer

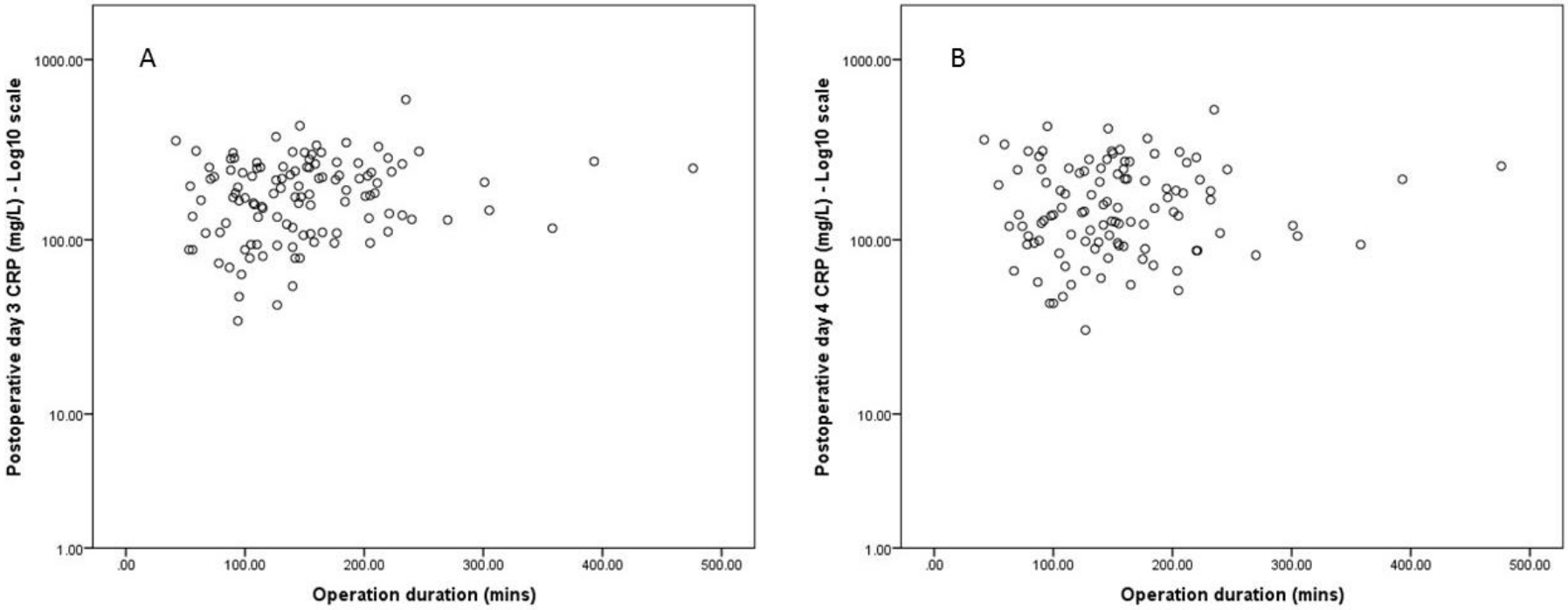

Figure 8-3: Scatter plots of operation duration (mins) and postoperative CRP concentrations (mg/L) on (A) postoperative day 3 and (B) day 4, following elective open surgery for colonic cancer

9 Anaemia and preoperative systemic inflammation are independently associated with perioperative blood transfusion in patients undergoing surgery for colorectal cancer

9.1 Introduction

A significant proportion of patients undergoing surgery for colorectal cancer will require allogeneic blood transfusion in the perioperative period, most due to iron deficiency anaemia (Acheson et al. 2012). Blood products are a scarce healthcare resource. In addition, perioperative blood transfusion has been reported to be associated with the development of infective postoperative complications and anastomotic leak following surgery for colorectal cancer (McDermott et al. 2015). Furthermore, there is some evidence that perioperative blood transfusion is associated with disease recurrence following surgery for colorectal cancer, and that this effect is even greater in the presence of infective complications (Mynster et al. 2000, Amato et al. 2006). Although the preoperative anaemia associated with colorectal cancers has traditionally been attributed to frank or occult gastrointestinal blood loss, there is increasing concern that other mechanisms may be additionally responsible. One of these is the host systemic inflammatory response to cancer.

The presence of a preoperative systemic inflammatory response, as measured by the modified Glasgow Prognostic Score, has been widely reported to be associated with both postoperative complications (Moyes et al. 2009) and poorer long term oncologic outcomes independent of stage, following surgery for colorectal cancer (McMillan et al. 2013, Park et al 2016). It is therefore of interest that the presence of systemic inflammation, as measured by serum C-reactive protein (CRP) and albumin, is also associated with significant perturbation of common serum measures of iron status (McSorley et al. 2016a). Indeed, this state of functional iron deficiency, or anaemia of chronic inflammation, is of particular importance in the context of colorectal cancer surgery. Whereas true iron deficient anaemia secondary to blood loss is likely to respond to preoperative iron replacement therapy, functional iron deficiency secondary to systemic inflammation will not (Kelly et al. 2017). Although there have been recent calls to examine the impact of systemic inflammation on the treatment of preoperative anaemia (McSorley et al. 2016b), little data exists as to the prevalence of this kind of anaemia and its effect on the need for blood transfusion within the colorectal cancer surgery patient population.

The hypothesis of the present study is that preoperative systemic inflammation has a significant impact on both preoperative anaemia and rates of perioperative blood

transfusion in patients undergoing surgery for colorectal cancer. Therefore, the aim of the present study was to explore these relationships in this cohort of patients.

9.2 Patients and Methods

9.2.1 Patients

Patients with histologically proven colorectal cancer, who underwent elective open surgery with curative intent between December 1998 and November 2007 at a single centre were included in the study. Patients who underwent emergency surgery, palliative procedures, with metastatic disease or who had existing inflammatory conditions were excluded. All patients received prophylactic antibiotics and venous thromboprophylaxis prior to the induction of anaesthesia as per hospital policy. Patients had routine preoperative blood sampling and measurement of haemoglobin concentration, serum CRP, and albumin. This study was approved as part of surgical audit by the West of Scotland Research Ethics Committee.

9.2.2 Methods

Data was collected prospectively in a database, anonymised, and subsequently analysed. Recorded information included patient demographics, tumour site, TNM stage (TNM, AJCC), American Society of Anaesthesiologists score (ASA), preoperative haemoglobin concentration (Hb g/dL), and postoperative complications. The proportion of patients exceeding the established CRP threshold 150mg/L on postoperative days 3 and 4 was recorded (McDermott et al. 2015).

Serum concentrations of CRP (mg/L) were measured using an autoanalyzer (Architect; Abbot Diagnostics, Maidenhead, UK) with a lower detectable limit of 0.2 mg/L as was serum albumin (normal range 35-50g/L). The preoperative modified Glasgow Prognostic Score (mGPS), which was associated with cancer specific survival independent of disease stage was calculated in patients for whom preoperative serum CRP and albumin were available (McMillan 2013). Using local laboratory reference ranges, anaemia was defined as Hb <13.0g/dl in males and <11.5g/dl in females. Severe anaemia was defined as Hb <11.0g/dl in males and <10.0g/dl in females.

Information concerning transfusion history and the number of units of packed red cells (PRCs) transfused was acquired retrospectively from a prospective haematology computer database at Glasgow Royal Infirmary. Perioperative transfusion was defined as a blood

transfusion occurring within 30 days before or after surgery. The indication for the blood transfusion, its timing within the perioperative window, and the haemoglobin threshold used to decide on transfusing were not documented. There was no perioperative blood transfusion protocol in place during the study period.

Infective complications were categorised as described elsewhere and summarised here briefly (Platt et al. 2012). Superficial surgical site infection was defined as the presence of pus either spontaneously discharging from the wound or requiring drainage. Deep surgical site infection was defined as surgical or image-guided drainage of intra-abdominal pus. Anastomotic leak was defined as radiologically verified fistula to bowel anastomosis or diagnosed at laparotomy. Pneumonia was defined by fever above 38.5^{o}C and consolidatory chest X-ray findings requiring antibiotic treatment. Septicaemia was defined by the presence of sepsis combined with positive blood culture. Urinary tract infection was only included if complicated by septicaemia and confirmed with positive urine culture.

9.2.3 Statistical Analysis

Categorical data regarding patient characteristics were compared using the Chi square test. Continuous data relating to preoperative Hb and postoperative CRP were non-normal and displayed as medians and ranges. These continuous data were compared using the Mann-Whitney U test. Missing data were not included in analysis. Binary logistic regression of variables associated with perioperative blood transfusion was performed. Those variables associated with perioperative blood transfusion at a significance level of $p < 0.1$ at univariate analysis were included in multivariate binary logistic regression using a backward conditional model. Statistical analyses were performed using IBM SPSS version 22 for Windows (Chicago, IL, USA). Two sided p values <0.05 were considered statistically significant.

9.3 Results

9.3.1 Patients

In total, 371 patients were included in the study (Table 9-1). All patients underwent elective, open surgery. The majority were male (195, 53%), over 65 years old (249, 67%), with colonic (229, 62%) and node negative disease (219, 59%). After correcting for sex, 179 patients (48%) had no evidence of preoperative anaemia, 110 (30%) had mild preoperative anaemia, and 73 (20%) had severe preoperative anaemia. 85 patients (23%) developed a postoperative complication, of which 71 (19%) were infective complications. 18 patients (5%) developed a postoperative anastomotic leak. There were 7 (2%) deaths in the postoperative period.

9.3.2 Perioperative blood transfusion

115 patients (31%) required a blood transfusion in the perioperative period, of which 51 were preoperative. There was a significant association between preoperative median Hb in males (11.3 vs 13.1 g/dL, $p<0.001$) and females (10.5 vs. 12.3 g/dL, $p<0.001$) and the need for perioperative blood transfusion. After correcting for sex, there was a significant association between any perioperative blood transfusion and the severity of preoperative anaemia ($p<0.001$). There was a significant association between any perioperative blood transfusion and preoperative mGPS ($p<0.001$). Of those receiving a blood transfusion in the perioperative period, 75 (20%) received 1-2 units of packed red cells (PRCs), 25 (7%) received 3-4 units, and 15 (4%) received more than 4 units. There was a significant association between the number of units of PRCs transfused and both the degree of the preoperative anaemia ($p<0.001$) and the preoperative mGPS ($p<0.001$).

9.3.3 Preoperative and intraoperative factors associated with perioperative blood transfusion

At univariate analysis, age ($p=0.066$), ASA score ($p=0.065$), preoperative anaemia ($p<0.001$), and preoperative mGPS ($p<0.001$) were associated with perioperative blood transfusion at a significance level of $p<0.1$ (Table 9-1). At multivariate analysis, preoperative anaemia (OR 2.65, 95% CI 1.87-3.75, $p<0.001$) and preoperative mGPS (OR

1.88, 95% CI 1.29-2.73, p<0.001) remained independently associated with perioperative blood transfusion.

When patients were grouped by preoperative mGPS 0, or mGPS 1-2 (Table 9-2), only the degree of preoperative anaemia, corrected for sex, was associated with perioperative blood transfusion (both p<0.001).

When the same analysis was carried out in patients who underwent surgery for colonic cancer (Table 9-3), the degree of preoperative anaemia was significantly associated with perioperative blood transfusion in those patients with preoperative mGPS 1-2 (p<0.001), but not mGPS 0 (p=0.125)

9.3.4 Postoperative outcomes associated with perioperative blood transfusion

At univariate analysis, anastomotic leak (p=0.027), and 30 day mortality (p=0.039) were significantly associated with perioperative blood transfusion (p=0.065), (Table 9-1). At multivariate analysis, both anastomotic leak (OR 2.82, 95% CI 1.07-7.42, p=0.036), and 30 day mortality (OR 5.39, 95% CI 1.01-28.63, p=0.048) remained independently associated with perioperative blood transfusion.

When patients were grouped by preoperative mGPS 0 or mGPS 1-2 (Table 9-2), anastomotic leak was significantly associated with perioperative blood transfusion in patients with mGPS 0 (p=0.039), but not mGPS 1-2 (p=0.719). In addition, median length of stay was significantly longer in patients receiving a perioperative blood transfusion in both those with mGPS 0 (12 vs 10 days, p=0.004) and mGPS 1-2 (13 vs 11 days, p=0.020).

Similar results were found when the same analysis was performed in patients who underwent surgery for colonic cancer (Table 9-3). Anastomotic leak was significantly associated with perioperative blood transfusion in patients with mGPS 0 (p=0.034), but not mGPS 1-2 (p=0.322). Median length of stay was significantly longer in patients receiving a perioperative blood transfusion in both those with mGPS 0 (11 vs 9 days, p=0.014) and mGPS 1-2 (13 vs 10 days, p=0.015).

There was no association between the postoperative systemic inflammatory response and blood transfusion in the whole cohort, or at subgroup analysis of those patients without preoperative systemic inflammation, or colonic cancer only.

9.3.5 Preoperative anaemia, systemic inflammation and perioperative blood transfusion

Rates of perioperative blood transfusion (Table 9-4) varied from 17% in patients without anaemia to 62% in those with severe anaemia ($p<0.001$), and from 24% in patients with mGPS 0 to 42% in patients with mGPS 1-2 ($p<0.001$). When combined, rates of perioperative blood transfusion varied from 16% in patients without anaemia and mGPS 0, to 78% in patients with severe anaemia and mGPS 1-2 ($p<0.001$).

9.4 Discussion

The results of the present study report associations between preoperative anaemia, systemic inflammation, and perioperative blood transfusion in patients undergoing elective surgery for stage I-III colorectal cancer. Therefore, the apparent requirement for perioperative blood transfusion, based primarily on preoperative anaemia, may be exacerbated by the presence of a preoperative systemic inflammatory response. There was no significant association between perioperative blood transfusion and the magnitude of the postoperative systemic inflammatory response. However, in keeping with prior studies, perioperative blood transfusion was associated with anastomotic leak, although this relationship was strongest in patients without preoperative systemic inflammation.

The aetiology of preoperative anaemia, and thus the likelihood of receiving a blood transfusion in surgery for colorectal cancer, is increasingly complex (Edgren et al. 2009). There has been ongoing assumption that anaemia in patients with colorectal cancer relates primarily to occult gastrointestinal blood loss, and treatment with preoperative oral or parenteral administration of iron preparations has been proposed (Beale et al. 2005). However, the recognition that the presence of systemic inflammation can lead to a state of functional iron deficiency (also known as the anaemia of chronic disease or anaemia of inflammation) questions the above assumption (Thomas et al. 2013). In the systemic inflammatory state, iron stores are sufficient but iron is sequestered by the reticuloendothelial system, a process driven by the effect of circulating interleukin 6 on the hepcidin mediated iron transport protein ferroportin (vonDrygalski et al. 2013).

This perturbation has long been recognised (Fraser et al. 1989, Galloway et al. 2000). However, it is only recently that the magnitude of the effect has been well described in large numbers of patient observations (Duncan et al. 2012). There have been two main approaches to the confounding effect of the systemic inflammatory response on the measurement of iron status. The first is to develop other measurements of iron status that are not affected by systemic inflammation. The second is to adjust measurement of iron status and anaemia using measures of systemic inflammation (Thurnham et al. 2011).

In the Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) publications, this second approach has been carried out using C-reactive protein (CRP) and α-1-acid glycoprotein (AGP), two positive acute phase proteins of

varying half-life (Namaste et al. 2017, Rohner et al. 2017, Mei et al. 2017). They reported significant differences in the prevalence of depleted iron stores based on serum ferritin criteria (Namaste et al. 2017). When serum ferritin was examined in women of reproductive age there was a significant difference in the proportion of patients meeting criteria for iron deficiency (<15 μg/L) in the lowest and highest decile of both CRP (29% and 6% respectively) and AGP (26% and 8% respectively). In addition, when women of reproductive age were grouped by phase of inflammation using the combination of CRP and AGP, there was as significant difference in the mean lowest (34.9 μg/L, 95% CI 25.7-47.4, in "reference" group [CRP ≤5mg/L and AGP ≤1g/L]) and highest ferritin concentration (59.2 μg/L, 95% CI 48.5-72.2 in "early convalescence" group [CRP >5mg/L and AGP >1g/L]). Furthermore, the authors show that measures of iron status are altered below currently clinically relevant threshold values for both CRP and AGP and so propose that the use of a regression based correction factor should provide a more accurate assessment of true iron status in the context of systemic inflammation (Namaste et al. 2017). However, AGP is not routinely available as a measure of systemic inflammation in the clinical setting. In the BRINDA project paper, the authors propose the continued and expanded use of AGP as a measure of the phase and magnitude of systemic inflammation. However, as they themselves note, "…CRP is the more routinely measured and should continue to be measured along with AGP…", in part as it is not routinely used in clinical practice (Namaste et al. 2017). In addition, the authors also discuss, in an earlier publication, the problem associated with the calculation of regression based correction factors caused by serum micronutrient concentrations that do not necessarily "move in synchrony" with the CRP and AGP defined phases of inflammation (Thurnham et al. 2016).

Perhaps a better approach would be to use the combination of CRP and albumin, since both are independently associated with measures of iron status and are routinely available. Clinically, this has recently been confirmed in a recent observational study in a large patient cohort (n=16,552), whereby the presence of systemic inflammation, as measured by CRP and albumin, had a profound association with all commonly used serum measures of iron status (McSorley et al. 2016a). Patients were stratified by the magnitude of the systemic inflammatory response using both CRP and albumin as follows: group 1: CRP <10mg/L and albumin >35g/L, group 2: CRP11-80mg/L and albumin 25-35mg/L, and group 3: CRP >80mg/L and albumin <25g/L. When serum ferritin was compared amongst the three groups the median concentration was 77, 173, and 445 μg/L respectively

(p<0.001). Furthermore, there was a significant difference in the proportion of patients meeting criteria for iron deficiency (<15 μg/L, 13%, 3% and 0% respectively, p=0.001) or iron excess (M>300 μg/L F>50 μg/L, 21%, 38% and 75% respectively, p<0.001). When transferrin saturation was compared amongst the three groups there was a significant difference in the proportion of patients meeting criteria for iron deficiency (TSAT <10%, 15%, 39% and 53% respectively, p<0.001) or iron excess (TSAT M>55% F>50%, 7%, 5% and 5% respectively, p<0.001).

Therefore, it may be speculated that only those patients with preoperative anaemia in the absence of systemic inflammation, around 24% of patients in the present study, will derive benefit from preoperative iron supplementation. Those patients who are both anaemic and systemically inflamed in the preoperative period, around 26% of patients in the present study, are unlikely to respond to preoperative iron supplementation and are more likely to require perioperative blood transfusion. Furthermore, in this significant proportion of patients who have functional rather than true iron deficiency, iron supplementation may be harmful by promoting infective complications. If this were to prove to be the case it may be further speculated that anaemia in the presence of systemic inflammation may be corrected by the use of effective anti-inflammatory medication prior to surgery. These speculations remain to be tested in the context of a randomised clinical trial (McSorley et al. 2016b). However, it is clear that such work is of considerable importance as it has the potential to profoundly change clinical practice.

Indeed, the present work is consistent with a series of observations in the literature. For example, a meta-analysis of previously published studies investigating the use of preoperative parenteral iron supplementation in patients with iron deficiency anaemia, across a variety of surgical specialities, reported a significant increase in preoperative haemoglobin and a reduction in the requirement for perioperative blood transfusion (Litton et al. 2013). Somewhat concerningly, they also reported that those patients given parenteral iron preoperatively were more likely to have an infective complication following surgery. Furthermore, a recent randomised controlled trial of preoperative parenteral iron supplementation in patients with apparent iron deficiency anaemia undergoing major abdominal surgery reported similar results in terms of both a reduction in the requirement for perioperative blood transfusion, and an increase in risk of postoperative infective complications in the treatment arm (Froessler et al. 2016). Froessler and colleagues reported no significant difference in median CRP concentration

between the intervention and control group either preoperatively (7.2 mg/L vs. 7.7 mg/L, p=0.99) or 4 weeks postoperative (5.8 mg/L vs. 11.0 mg/L, p=0.18). However, the upper ranges of measured CRP concentration in both groups at both time points was above 10 mg/L, a value above which the measures of iron status reported by Froessler and colleagues, ferritin and transferrin saturation, have been reported to be significantly affected by the systemic inflammatory response (McSorley et al. 2016b). Furthermore, Froessler and colleagues did not describe the proportion of patients in each group with CRP >10mg/L at each time point, making interpretation of the difference in the degree of systemic inflammation between the two groups difficult. Indeed, this may in part explain the significant differences in serum ferritin and transferrin saturation between the two groups prior to randomization and may introduce bias in terms of the difference in haemoglobin concentration between the two time points.

Further trials of the use of perioperative parenteral iron therapy with the aim of reducing perioperative blood transfusion requirement should clearly define the preoperative systemic inflammatory status of participants. In fact, we should go further, and it is the authors' opinion that further trials should use preoperative CRP as an exclusion criteria, given that iron replacement therapy is unlikely to be as efficacious in this group of patients, and that their inclusion may introduce bias as well as being ethically dubious. Patients undergoing surgery who have a preoperative systemic inflammatory response, whether due to cancer or other reasons, can perhaps be offered alternative interventions. In addition, it is of interest that the current study also suggests that preoperative systemic inflammation may be associated with perioperative blood transfusion independent of preoperative anaemia. This may be due to greater intraoperative blood loss, slower recovery from surgery, suppression of erythropoiesis in the postoperative period, or indeed it may be multifactorial in nature. Although the reasons for such a finding remain unclear, if confirmed, it would add to the importance of targeting the preoperative systemic inflammatory response in these patients.

The main limitation of the present study was that it was conducted in a historic cohort of patients. This was due to the lack of availability of transfusion data in more recent cohorts at the time of writing. The retrospective nature of the analysis lead to missing data. A significant proportion of patients with no evidence of preoperative anaemia underwent perioperative blood transfusion. Moreover, the present study was not able to determine what the indications for blood transfusion were, other than preoperative anaemia, since

they were not reliably recorded. In addition, a high proportion of patients were anaemic (50%), and required blood transfusion (30%), which is higher than in more modern practice although some recent data from the same centre finds rates of anaemia to be 40% and perioperative blood transfusion rates to remain high at 20% (McSorley unpublished data). Finally, that all included patients underwent open surgery may be considered a limitation given the current move toward minimally invasive surgery. However, open surgery continues to form a major part of UK surgical practice in patients undergoing resection for colorectal cancer, and reduces the potential for confounding with regard to blood loss and blood transfusion introduced with other less invasive surgical modalities.

In conclusion, the present study reports a significant association between preoperative systemic inflammation and perioperative blood transfusion in patients undergoing elective surgery for colorectal cancer. It may be that systemic inflammation has this effect through both anaemia and through other, as yet, unidentified mechanisms. Studies investigating the preoperative treatment of anaemia with iron should consider preoperative systemic inflammation as a limiting factor in treatment efficacy.

9.5 Tables and Footnotes

Table 9-1: Univariate and multivariate binary logistic regression of factors associated with any perioperative blood transfusion

Characteristic	Univariate (OR, 95% CI)	P	Multivariate (OR, 95% CI)	P
Factors affecting transfusion				
Age	1.29 (0.98-1.69)	0.066	-	0.164
Sex	0.84 (0.54-1.31)	0.439	-	-
ASA score	1.36 (0.98-1.88)	0.065	-	0.945
Tumour site	0.72 (0.46-1.15)	0.165	-	-
TNM stage	1.15 (0.84-1.58)	0.377	-	-
Venous invasion	0.87 (0.56-1.36)	0.550	-	-
Neoadjuvant treatment	1.8 (0.36-3.25)	0.891	-	-
<12 lymph nodes sampled	0.92 (0.58-1.46)	0.920	-	-
Preop Anaemia	2.69 (1.99-3.63)	<0.001	2.65 (1.87-3.75)	<0.001
Preop mGPS	1.98 (1.45-2.71)	<0.001	1.88 (1.29-2.73)	<0.001
Outcomes affected by transfusion				
POD 3 CRP >150mg/L	1.03 (0.65-1.65)	0.892	-	-
POD 4 CRP >150mg/L	0.99 (0.52-1.87)	0.967	-	-
Any complication	1.20 (0.72-2.02)	0.479	-	-
Infective complication	1.48 (0.86-2.54)	0.156	-	-
Anastomotic leak	2.95 (1.13-7.69)	0.027	2.82 (1.07-7.42)	0.036
Thirty day mortality	5.73 (1.10-30.01)	0.039	5.39 (1.01-28.63)	0.048

mGPS modified Glasgow Prognostic score, *POD* postoperative day, *CRP* C-reactive protein, *Anaemia* (none/mild/severe): males (>13/<13/<11, g/dL), females (>11.5/<11.5/<10, g/dL).

Table 9-2: Clinicopathological characteristics of patients undergoing elective open surgery for colorectal cancer receiving any perioperative blood transfusion

Characteristics	mGPS 0		p	mGPS 1-2		p
	No transfusion (n=170)	Transfused (n=54)		No transfusion (n=84)	Transfused (n=60)	
Clinicopathological						
Age (<65 / 65-74 / ≥75)	59/62/49	18/16/20	0.448	31/23/30	14/20/26	0.134
Sex (male / female)	99/71	29/25	0.558	37/47	27/33	0.910
ASA score (1/2/3/4)	20/65/47/7	2/17/19/1	0.158	11/23/31/4	3/22/26/3	0.349
Tumour Site (colon / rectum)	89/81	28/26	0.949	61/23	49/11	0.208
TNM stage (I/II/III)	36/66/68	9/21/24	0.4487	10/37/37	2/36/22	0.910
Venous invasion (yes/no)	76/90	28/25	0.371	43/41	22/38	0.084
<12 lymph nodes sampled (yes/no)	67/99	16/37	0.184	22/62	23/37	0.121
Margin involved (yes/no)	13/153	6/47	0.432	10/74	6/54	0.720
Neoadjuvant treatment (yes/no)	6/137	2/42	0.920	4/65	3/52	1.000
Haematological						
Preop anaemia (none/mild/severe)£	107/37/19	21/19/14	<0.001	40/34/9	10/18/31	<0.001
Postoperative SIR						
POD 3 CRP >150mg/L (yes/no)	65/92	21/29	0.940	37/36	25/27	0.774
POD 4 CRP >150mg/L (yes/no)	21/111	5/38	0.625	15/51	11/40	0.881
Short term outcomes						
Any complication (yes/no)	34/136	12/42	0.725	22/62	16/44	0.949
Infective complication (yes/no)	25/145	12/42	0.195	19/65	14/46	0.920
Anastomotic leak (yes/no)	4/166	5/49	0.039	4/80	4/56	0.719
Thirty day mortality (yes/no)	2/164	1/52	0.566	0/84	3/57	0.070
Length of stay (median, days)	10	12	0.004	11	13	0.020
Adjuvant treatment (yes/no)	34/131	15/39	0.272	19/65	12/48	0.838

ASA American Society of Anesthesiology. *Hb* Haemoglobin. *CRP* C-reactive protein. *PRCs* Packed red cells. *POD* postoperative day. *mGPS* modified Glasgow Prognostic score, *poGPS* postoperative Glasgow Prognostic Score, *SIR* systemic inflammatory response, £ Preoperative anaemia (none/mild/severe): males (>13/<13/<11, g/dL), females (>11.5/<11.5/<10, g/dL).

Table 9-3: Clinicopathological characteristics of patients undergoing elective open surgery for colonic cancer receiving any perioperative blood transfusion

Characteristics	mGPS 0		p	mGPS 1-2		p
	No transfusion (n=89)	Transfused (n=28)		No transfusion (n=61)	Transfused (n=49)	
Clinicopathological						
Age (<65 / 65-74 / ≥75)	29/33/27	8/10/10	0.587	23/18/20	9/17/23	0.034
Sex (male / female)	51/38	11/17	0.096	28/33	20/29	0.593
ASA score (1/2/3/4)	9/32/26/6	1/10/11/0	0.758	11/16/24/1	3/18/22/3	0.108
TNM stage (I/II/III)	20/37/32	4/13/11	0.474	5/29/27	2/28/19	0.905
Venous invasion (yes/no)	34/52	14/13	0.274	35/26	16/33	0.010
<12 lymph nodes sampled (yes/no)	34/52	8/19	0.493	16/45	18/31	0.300
Margin involved (yes/no)	9/77	2/25	1.000	8/53	3/46	0.340
Haematological						
Preop anaemia (none/mild/severe)£	53/21/11	12/11/5	0.125	24/29/8	8/15/25	<0.001
Postoperative SIR						
POD 3 CRP >150mg/L (yes/no)	35/48	15/9	0.104	23/28	19/23	0.989
POD 4 CRP >150mg/L (yes/no)	8/59	4/16	0.460	10/37	9/33	0.986
Short term outcomes						
Any complication (yes/no)	18/71	7/21	0.603	15/46	12/37	0.990
Infective complication (yes/no)	13/76	7/21	0.250	12/49	10/39	0.924
Anastomotic leak (yes/no)	3/86	4/24	0.034	1/60	3/46	0.322
Thirty day mortality (yes/no)	2/84	0/27	1.000	0/61	2/47	0.196
Length of stay (median, days)	9	11	0.014	10	13	0.015
Adjuvant treatment (yes/no)	18/68	5/23	1.000	14/47	8/41	0.475

ASA American Society of Anesthesiology. *Hb* Haemoglobin. *CRP* C-reactive protein. *PRCs* Packed red cells. *POD* postoperative day. *mGPS* modified Glasgow Prognostic score, *poGPS* postoperative Glasgow Prognostic Score, *SIR* systemic inflammatory response, £ Preoperative anaemia (none/mild/severe): males (>13/<13/<11, g/dL), females (>11.5/<11.5/<10, g/dL).

Table 9-4: The relationship between preoperative anaemia, modified Glasgow Prognostic Score, and any perioperative blood transfusion in patients undergoing elective surgery for colorectal cancer

Anaemia	All		mGPS=0		mGPS=1-2		P
	n	Transfused n(%)	n	Transfused n(%)	n	Transfused n(%)	
All	368	114 (31)	224	54 (24)	144	60 (42)	<0.001
None	178	31 (17)	128	21 (16)	50	10 (20)	0.570
Moderate	108	37 (34)	56	19 (34)	52	18 (35)	0.940
Severe	73	45 (62)	33	14 (42)	40	31 (78)	0.002
P	<0.001		<0.001		<0.001		<0.001

Anaemia (none/mild/severe): males (>13/<13/<11, g/dL), females (>11.5/<11.5/<10, g/dL), *mGPS* modified Glasgow Prognostic Score

10 The relationship between neoadjuvant chemoradiotherapy, the postoperative systemic inflammatory response, and adverse outcomes following surgery for rectal cancer: a propensity score matched analysis

10.1 Introduction

Neoadjuvant chemoradiotherapy (nCRT) prior to surgical resection has become a standard of care for management of locally advanced rectal cancer (Sauer et al. 2004). nCRT confers oncological benefits, such as downstaging of the tumour to allow clear circumferential margins at resection (Kim et al. 2006), and reduction of local recurrence (Bosset et al. 2006).

Although nCRT has been shown to improve outcomes in rectal cancer, there is significant variability in the degree of response to treatment (Kim et al. 2014). It is now evident that the presence of a systemic inflammatory response, evaluated using the modified Glasgow Prognostic Score (mGPS), is associated with poor long-term outcomes in resectable colorectal cancer (McMillan et al. 2013). The presence of systemic inflammation prior to nCRT has been reported to be associated with poorer overall, and disease free, survival in patients with locally advanced rectal cancer (Carruthers et al. 2012). Furthermore, a recent study of patients receiving nCRT prior to surgical resection of rectal cancer in the West of Scotland reported that the presence of a pre-treatment systemic inflammatory response was associated with a lower likelihood of complete pathological response (Dreyer et al. 2017).

It is now well established that the magnitude of the postoperative systemic inflammatory response, measured by C-reactive protein (CRP), is associated with short-term outcomes following colorectal surgery (Singh et al. 2014, Adamina et al. 2015). These postoperative complications (e.g. anastomotic leakage) have been indicated to be associated with increased local recurrence and reduced long term survival following surgery for colorectal cancer (Artinyan et al. 2014). A recent comprehensive review suggested that exceeding CRP concentrations of 150mg/L on postoperative days 3 to 5 following colorectal surgery should alert clinicians to the possible development of complications (McDermott et al. 2015). Furthermore, there is some evidence to suggest that the postoperative systemic inflammatory response is associated with long-term oncologic outcomes following surgery for colorectal cancer, independent of complications (McSorley Chapter 4).

Although there is evidence linking the pretreatment systemic inflammatory response to oncologic outcomes following nCRT for rectal cancer, to the authors' knowledge, no studies have examined the impact of nCRT on the magnitude of the postoperative systemic inflammatory response. Therefore, the aim of the present study was to investigate the

relationship between nCRT, the postoperative systemic inflammatory response, and postoperative outcomes in patients undergoing elective surgery for rectal cancer.

10.2 Patients and Methods

10.2.1 Patients

Patients with histologically proven rectal cancer who underwent elective surgery between February 2008 and April 2015 at a single centre were included in the study. Patients who underwent emergency surgery, palliative procedures, or who had existing inflammatory conditions were excluded.

Preoperative nCRT was offered to patients with histologically proven, locally advanced, circumferential margin (CRM) threatening rectal tumours following discussion at a multi-disciplinary colorectal oncology meeting. The nCRT protocol was of 45Gy given over 5 weeks in 25 daily fractions alongside oral fluorouracil (5-FU) and the addition of folinic acid on days 1 to 5 and 29 to 33.

All patients received prophylactic antibiotics and venous thromboprophylaxis prior to the induction of anaesthesia as per hospital policy. Patients had routine preoperative and daily postoperative blood sampling including a full blood count (FBC), serum CRP and albumin concentration. Further postoperative investigation and intervention was at the discretion of the patient's surgical team who were not blinded to blood test results. This study was approved as part of surgical audit by the West of Scotland Research Ethics Committee.

10.2.2 Methods

Data was collected prospectively in a database, anonymised, and subsequently analysed. Prospectively recorded information included patient demographics including operation, body mass index (BMI), American Society of Anesthesiology (ASA) score, smoking status, and pathological data including TNM stage (TNM, AJCC), CRM status, differentiation, and venous invasion.

Serum concentrations of CRP (mg/L) were measured using an autoanalyzer (Architect; Abbot Diagnostics, Maidenhead, UK) with a lower detectable limit of 0.2 mg/L, as was serum albumin (normal range 35-50g/L). The preoperative modified Glasgow Prognostic Score (mGPS) was calculated in patients for whom serum CRP and albumin concentrations were available (McMillan 2013). Exceeding the established CRP threshold of 150 mg/L on postoperative days 3 or 4 was recorded (McDermott et al. 2015).

Infective complications were categorised as described elsewhere and summarised here briefly (Platt et al. 2012). Superficial surgical site infection was defined as the presence of pus either spontaneously discharging from the wound or requiring drainage. Deep surgical site infection was defined as surgical or image-guided drainage of intra-abdominal pus. Anastomotic leak was defined as radiologically verified fistula to bowel anastomosis or diagnosed at laparotomy. Pneumonia was defined by fever above 38.5^{o}C and consolidatory chest X-ray findings requiring antibiotic treatment. Septicaemia was defined by the presence of sepsis combined with positive blood culture. Urinary tract infection (UTI) was only included if complicated by septicaemia and confirmed with positive urine culture. Additionally, postoperative complications were categorised by their severity using the Clavien Dindo scale (Dindo et al. 2004).

10.2.3 Statistical Analysis

Categorical data were compared using the Chi square test or Fisher's exact test in analyses with small numbers. Continuous data were non-normal so were displayed as medians and ranges. These continuous data were compared using the Mann-Whitney U test.

Multivariate logistic regression was used to generate a propensity score for each patient, predicting the probability of having received nCRT or not, based on the following variables thought to be associated with the postoperative systemic inflammatory response or complications: age, sex, BMI, smoking status, ASA score, mGPS, TNM stage, surgical approach (open or laparoscopic), operation type (anterior or abdominoperineal resection), stoma formation, and the use of epidural anaesthesia. Patients who received preoperative nCRT were then matched 1:1 with a patient who did not, using the closest propensity score on the logit scale (calliper <0.05, order of match selection randomised, without replacement). Categorical data were compared using McNemar's test. The appropriateness of the propensity score matching was assessed visually by frequency of propensity scores in each group before and after matching. In addition, the propensity scores were included as a linear covariate alongside preoperative nCRT in multivariate binary logistic regression models for exceeding the postoperative day 3 CRP threshold and postoperative complications. Finally, the propensity scores were used to stratify the patients by quintiles from which an average treatment effect was calculated for both the postoperative day 3 CRP threshold and postoperative complications as an OR and 95% CI.

In all tests, a two sided p value <0.05 was considered statistically significant. Propensity scoring, matching, and all statistical analyses were performed using IBM SPSS version 21 for Windows (Chicago, IL, USA).

10.3 Results

10.3.1 Patients

In total, 251 patients were included in the study (Table 10-1). The majority were male (155, 62%), over 65 years old (142, 57%), and had node negative disease (165, 66%). 85 patients (33%) underwent preoperative nCRT. 163 patients (65%) underwent open surgery, 75 patients (30%) underwent laparoscopic surgery, and 13 patients (5%) underwent transanal surgery. 173 patients (69%) underwent anterior resection (AR) and 62 patients (25%) underwent abdominoperineal resection (APR). 111 patients (44%) developed a postoperative complication of which 75 (30%) were infective and 24 (10%) were Clavien Dindo grade 3-5. There were 5 deaths (2%) within the immediate postoperative period.

10.3.2 The relationship between nCRT and perioperative factors in the unmatched cohort

A significantly higher proportion of patients who underwent nCRT (Table 10-1) went on to APR (51% vs. 12%, $p<0.001$) and had open surgery (80% vs. 63%, $p=0.004$). Of the patients who underwent nCRT, 11 (13%) achieved complete pathological response. A significantly higher proportion of those who underwent nCRT subsequently had macroscopically involved circumferential margins (9% vs. 0.6%, $p=0.003$). A significantly lower proportion of patients who underwent nCRT had histopathologically detectable venous invasion (45% vs. 61%, $p=0.027$). A significantly higher proportion of those patients who underwent nCRT had a NLR >5 (39% vs. 12%, $p<0.001$) and a mGPS of 2 (14% vs. 6%, $p=0.035$) prior to surgery. There was no significant association between nCRT and the postoperative systemic inflammatory response or postoperative complications.

10.3.3 The relationship between nCRT and perioperative factors in the propensity score matched cohort

Propensity scores could not be assigned to 124 patients due to missing covariate data, leaving 127 patients with propensity scores, of which 75 had received nCRT and 52 had not. 104 patients (52 from each group) were matched based on their propensity score, with a subsequent improvement in the balance of the distribution of propensity scores in each group (Figure 10-1). In the propensity score matched cohort, there was no significant

association between nCRT and either the postoperative systemic inflammatory response (Figure 10-2) or complications following surgery for rectal cancer (Table 10-2).

10.3.4 Sensitivity analyses using propensity scores

A similarly non-significant association was found when the impact of nCRT on exceeding the postoperative day 3 CRP threshold (Table 10-3), was analysed in the unadjusted cohort (OR 0.90, 95% CI 0.51-1.58), in the propensity score matched cohort (OR 0.64, 95% CI 0.28-1.45), through propensity score regression (OR 0.80, 95% CI 0.38-1.71), and propensity score stratification (OR 0.80, 95% CI 0.38-1.72). The same analysis of the impact of nCRT on postoperative complications (Table 10-3) found a similarly non-significant relationship in the unmatched cohort (OR 0.84, 95% CI 0.49-1.44), the propensity score matched cohort (OR 0.85, 95% CI 0.39-1.86), through propensity regression (OR 0.86, 95% CI 0.41-1.81), and propensity stratification (OR 0.86, 95% CI 0.41-1.81).

10.4 Discussion

The present study reports no significant association between nCRT and either the magnitude of the postoperative systemic inflammatory response, or short term postoperative outcomes, following surgery for rectal cancer.

Although the present paper reports that a higher proportion of patients who underwent nCRT were found to have a preoperative systemic inflammatory response, had undergone an abdominoperineal resection, using open surgical techniques, this did not impact on either the postoperative systemic inflammatory response, or short term postoperative outcomes, when compared to patients who did not undergo nCRT. In addition, this remained the case after accounting for confounding variables related to the postoperative systemic inflammatory response and complications, using propensity score matching.

Previous studies in patients undergoing nCRT prior to surgery for rectal cancer have reported that the presence of a systemic inflammatory response prior to treatment is associated with poorer tumour response to chemoradiotherapy and poorer oncologic outcome (Shen et al. 2014). Higher baseline NLR has been reported to be a negative predictor of pathological response and disease free survival (Carruthers et al. 2012, Krauthamer et al. 2013). Both CRP, and subsequently mGPS, have been reported to be significantly associated with poorer pathological response and poorer survival following nCRT for rectal cancer (Toiyama et al. 2013, Kim et al. 2014, Dreyer et al. 2017). Other characteristics such as age, gender, tumour site and body mass index (BMI) have been shown to have limited influence (Mikaela et al. 2014, Kim et al. 2014).

The main limitation of the present study was the small number of patients included, in particular the number of patients who underwent nCRT. In addition, the retrospective nature of the study lead to some missing data, particularly with regard to the administration of perioperative dexamethasone, and the proportion of patients having CRP measured on postoperative day 4. Significant differences between the groups in terms of variables associated with the postoperative systemic inflammatory response, and complications, lead to propensity score matching being used. This achieved improved balance in terms of demographic and operative confounders but resulted in the exclusion of a significant proportion of patients. Additional models were trialled as some imbalance remained, for example in the proportion of patients receiving preoperative dexamethasone in each group,

however additional variables, and missing covariate data reduced the sample size such that type II error would have become very likely. However, it was reassuring that the overall treatment effect and its magnitude were similar amongst the unmatched cohort, the matched cohort, and when other propensity analyses were used.

In conclusion, the present study reports that nCRT is significantly associated with the presence of a preoperative systemic inflammatory response prior to surgery for rectal cancer. However, this finding did not extend to a significant association between nCRT and either the postoperative systemic inflammatory response or complications.

10.5 Tables and Footnotes

Table 10-1: Relationship between clinicopathological characteristics and neoadjuvant therapy in patients undergoing elective surgery for rectal cancer

Characteristic	All rectal (n=251)	Neoadjuvant		P
		No (n=166)	Yes (n=85)	
Demographics				
Sex (male/female)	155/96	105/61	50/35	0.496
Age (<65/65-74/>74)	107/106/37	68/67/31	39/39/6	0.057
BMI (<20/20-25/26-30/>30, kg/m^2)	7/88/70/41	4/51/48/33	3/37/22/8	0.078
Smoking (never/ex/current)	110/94/33	78/56/20	32/38/13	0.125
ASA score (1/2/3/4)	64/103/62/4	40/66/42/3	24/37/20/1	0.471
Operative variables				
Preoperative dexamethasone (yes/no)	97/78	59/50	38/28	0.754
Operation (AR/APR/Transanal)	173/62/13	134/20/11	39/42/1	<0.001
Approach (laparoscopic/open)	75/163	58/97	17/66	0.004
Operation >4h (yes/no)	117/90	72/58	45/32	0.772
Intraoperative transfusion (yes/no)	9/161	4/102	5/59	0.299
Stoma (yes/no)	156/71	84/64	72/7	<0.001
Postoperative pathology				
TNM stage (0/ I/ II/III/IV)	11/67/84/75/11	0/56/52/50/7	11/11/32/25/4	<0.001
CRM (R0/R1/R2)	200/28/8	134/21/1	68/7/7	0.003
Differentiation (well-mod/poor)	210/16	143/8	67/8	0.170
Venous invasion (yes/no)	130/105	94/61	36/44	0.027
Tumour perforation (yes/no)	2/228	1/149	1/79	1.000
Systemic inflammation				
Pre-operative mGPS (0/1/2)	198/19/20	131/16/9	67/3/11	0.033
POD 3 CRP >150mg/L (yes/no)	103/110	69/71	34/39	0.773
POD 4 CRP >150mg/L (yes/no)	76/126	53/74	23/52	0.134
Postoperative outcomes				
Any postoperative complication (yes/no)	111/130	75/85	36/45	0.721
Infective complication (yes/no)	75/166	51/109	24/57	0.722
Clavien Dindo 3-5 complication (yes/no)	24/217	18/142	6/75	0.347

AR anterior resection, *APR* abdominoperineal excision, *BMI* Body Mass Index, *CRM* circumferential margin, *CRP* C-reactive protein, *mGPS* modified Glasgow Prognostic Score, *POD* postoperative day, *nCRT* neoadjuvant chemoradiotherapy, *ASA* American Society of Anesthesiology

Table 10-2: Relationship between clinicopathological characteristics and neoadjuvant therapy in propensity score matched patients undergoing elective surgery for rectal cancer

Characteristic	All (n=104)	Neoadjuvant		P
		No (n=52)	Yes (n=52)	
Demographics				
Sex (male/female)	62/42	33/19	29/23	-
Age (<65/65-74/>74)	62/33/9	34/13/5	28/20/4	-
BMI (<20/20-25/26-30/>30, kg/m^2)	8/45/30/21	4/22/13/13	4/23/17/8	-
Smoking (never/ex/current)	45/41/18	24/18/10	21/23/8	-
ASA score (1/2/3/4)	34/42/27/1	17/21/13/1	17/21/14/0	-
Operative variables				
Preoperative dexamethasone (yes/no)	51/39	21/22	30/17	-
Operation (AR/APR)	69/35	35/17	34/18	-
Approach (laparoscopic/open)	25/79	11/41	14/38	-
Operation >4h (yes/no)	57/46	25/26	32/20	-
Intraoperative transfusion (yes/no)	5/83	1/41	4/42	-
Stoma (yes/no)	81/23	35/17	46/6	-
Postoperative pathology				
TNM stage (0/ I/ II/III/IV)	6/20/43/31/4	0/15/20/16/1	6/5/23/15/3	-
CRM (R0/R1/R2)	92/8/1	46/4/0	46/4/1	-
Differentiation (well-mod/poor)	11/88	3/48	8/40	-
Venous invasion (yes/no)	58/45	33/19	25/26	-
Tumour perforation (yes/no)	1/103	1/51	0/52	-
Systemic inflammation				
Pre-operative mGPS (0/1/2)	91/8/5	44/6/2	47/2/3	-
POD 3 CRP >150mg/L (yes/no)	43/51	25/24	18/27	0.523
POD 4 CRP >150mg/L (yes/no)	34/57	20/25	14/32	0.774
Postoperative outcomes				
Any postoperative complication (yes/no)	48/56	25/27	23/29	1.000
Infective complication (yes/no)	30/74	14/38	16/36	0.815
Clavien Dindo 3-5 complication (yes/no)	12/92	6/46	6/46	1.000

AR anterior resection, *APR* abdominoperineal excision, *BMI* Body Mass Index, *CRM* circumferential margin, *CRP* C-reactive protein, *mGPS* modified Glasgow Prognostic Score, *POD* postoperative day, *nCRT* neoadjuvant chemoradiotherapy, *ASA* American Society of Anesthesiology

Table 10-3: Odds ratios for exceeding the C-reactive protein threshold of 150mg/L on postoperative day 3, and postoperative complications, with respect to neoadjuvant therapy across the propensity score methods

Propensity Score Model	n	POD 3 CRP >150mg/L OR (95%CI)	Complication OR (95% CI)
Unadjusted	251	0.90 (0.51-1.58)	0.84 (0.49-1.44)
Regression adjustment	127	0.80 (0.38-1.71)	0.86 (0.41-1.81)
Stratification by quintiles (ATE)	127	0.80 (0.38-1.72)	0.86 (0.41-1.81)
Matched 1:1	104	0.64 (0.28-1.45)	0.85 (0.39-1.86)

POD postoperative day, *CRP* C-reactive protein, *OR* odds ratio, *CI* confidence interval, ATE average treatment effect

10.6 Figures and Legends

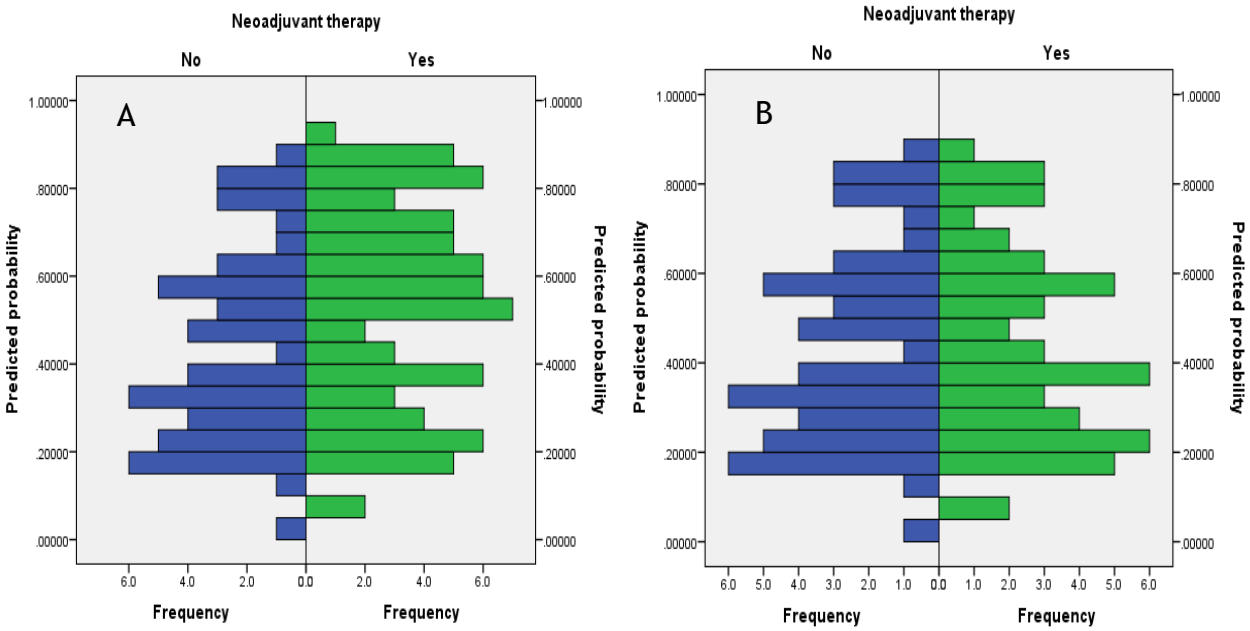

Figure 10-1: Distribution of propensity scores (A) before, and (B) after matching

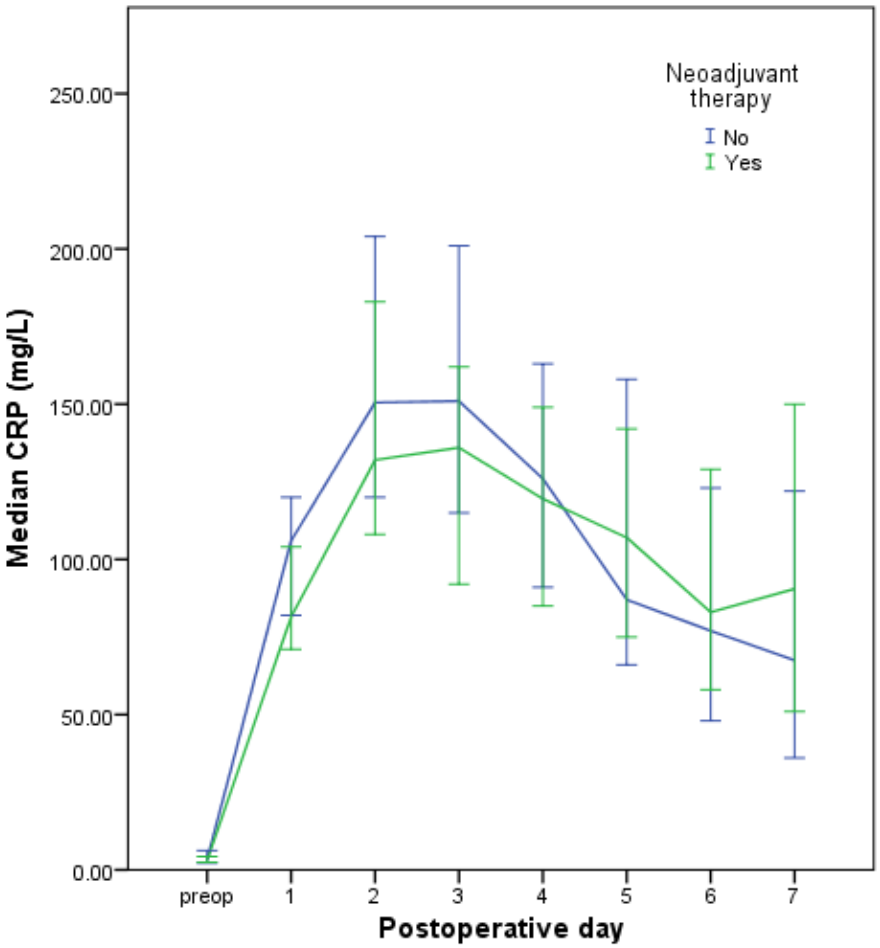

Figure 10-2: Postoperative C-reactive protein (CRP) concentrations grouped by neoadjuvant therapy (nCRT) following surgery for rectal cancer after propensity score matching (n=104)

11 Comparison of the magnitude of the postoperative systemic inflammatory response following elective surgery for colorectal cancer in the UK and Japan

11.1 Introduction

Despite continuing advances in care, colorectal cancer remains one of the leading causes of cancer death worldwide (Ferlay et al. 2013). Resection at surgery remains the primary treatment modality for cure, however it is associated with significant rates of postoperative complications (Ghaferi et al. 2011). It is now well appreciated that postoperative infective complications (Aritnyan et al. 2014) and anastomotic leak (Mirnezami et al. 2011) may lead to increased recurrence and poorer survival following surgery with curative intent, although the mechanism remains unclear (McSorley Introduction).

One hypothesis is that the innate immune response to surgery itself increases the risk of postoperative complication, and also of disease recurrence (Roxburgh et al. 2013). Indeed, the association between serum concentrations of C-reactive protein (CRP), a marker of the magnitude of the postoperative systemic inflammatory response (Watt et al. 2015), and postoperative complications is now well described (Adamina et al. 2015). A recent systematic review examining factors associated with anastomotic leak following colorectal surgery suggested that CRP concentrations of greater than 150mg/L on postoperative days 3 to 5 warrant at least delaying early discharge, and most likely further investigation (McDermott et al. 2015).

Several factors including laparoscopic surgery (Watt et al. 2015), BMI, and preoperative systemic inflammation (Watt et al. 2017a) have been reported to influence the magnitude of the postoperative systemic inflammatory response. One factor which may influence the magnitude of the postoperative systemic inflammatory response which has not been investigated thus far is ethnicity. Indeed, there is some evidence to suggest that, when compared to those from Europe, fewer patients with cancer from Japan are found to have preoperative systemic inflammation, although the negative prognostic impact is consistent across these ethnic groups (Park et al. 2017).

Therefore, the aim of the present study was to examine the relationship between the magnitude of the postoperative systemic inflammatory response and perioperative variables in patients undergoing elective surgery, with curative intent, in the UK and Japan.

11.2 Methods

11.2.1 Patients

Patients from two surgical units, at Glasgow Royal Infirmary (United Kingdom) and Dokkyo Medical University (Japan) were identified from prospectively collected and maintained databases of elective and emergency colorectal cancer resections. Consecutive patients who, on the basis of preoperative abdominal computed tomography and laparotomy findings were considered to have undergone potentially curative resection for colorectal adenocarcinoma between February 2008 and November 2015 at both centres were considered for inclusion. Patients with pre-existing inflammatory disease, metastatic disease, who underwent resection with palliative intent or local resection only, who underwent multivisceral resection, or had emergency surgery were excluded. The prospective databases contained demographic, clinicopathological, perioperative, systemic inflammation, and outcome variables.

11.2.2 Glasgow Royal Infirmary

Tumours were staged using the fifth edition of the TNM classification, with additional data taken from pathological reports issued following resection. All patients were discussed at a colorectal multi-disciplinary meeting involving surgeons, oncologists, radiologists, and pathologists with a colorectal cancer special interest before and after surgery. Neoadjuvant treatment (nCRT) was offered to patients with histologically proven, locally advanced (T3-T4, borderline operable or inoperable) rectal tumours following discussion at a multi-disciplinary colorectal oncology meeting. Complications were recorded at discharge and at first outpatient clinic follow up.

All patients received prophylactic antibiotics and venous thromboprophylaxis prior to the induction of anaesthesia as per hospital policy. All patients were cared for in line with a unit standardised perioperative care policy which included early postoperative mobilisation, early enteral nutrition, and the avoidance of routine nasogastric or peritoneal drainage.

11.2.3 Dokkyo Medical University

Patients were staged according to the seventh edition of the TNM classification with additional data taken from pathological reports issued following resection. Patients with

rectal disease were offered nCRT at the discretion of the treating surgical and oncology teams.

All patients received prophylactic antibiotics and venous thromboprophylaxis prior to the induction of anaesthesia. Postoperative care included the selective use of peritoneal drainage in patients with rectal disease, and selective use of parenteral nutrition

11.2.4 Methods

Patients had serum CRP and albumin measured preoperatively and on postoperative day 3. Serum concentrations of CRP (mg/L) were measured using an autoanalyzer, as was serum albumin (normal range 35-50g/L). Exceeding the established CRP threshold of 150 mg/L on postoperative day 3 was recorded (McDermott et al. 2015). The preoperative modified Glasgow Prognostic Score (mGPS) was calculated in patients for whom preoperative serum CRP and albumin were available (McMillan 2013). The study was approved by the West of Scotland Research Ethics Committee, Glasgow (UK cohort) and the local institutional review board (Japan cohort).

11.2.5 Statistical analysis

Categorical data were compared using the Chi square test. Continuous data were non-normal so were displayed as medians and ranges. These continuous data were compared using the Mann-Whitney U test.

Multivariate logistic regression was used to generate a propensity score for each patient, predicting the probability of having received surgery in either the UK or Japan, based on the following variables, age sex, TNM stage, along with variables thought to be associated with the postoperative systemic inflammatory response: BMI, ASA score, mGPS, tumour site, and surgical approach (open or laparoscopic). Patients who underwent surgery in the UK were then matched 1:1 with a patient who underwent surgery in Japan, using the closest propensity score on the logit scale (calliper <0.05, order of match selection randomised, without replacement). Categorical data were compared using McNemar's test. Medians of continuous data were compared using the related samples Wilcoxon sign rank test. The appropriateness of the propensity score matching was assessed visually by frequency of propensity scores in each group before and after matching. In addition, the propensity scores were included as a linear covariate alongside preoperative nCRT in multivariate binary logistic regression models for exceeding the postoperative day 3 CRP

threshold and postoperative complications. Finally, the propensity scores were used to stratify the patients by quintiles from which an average treatment effect was calculated for both the postoperative day 3 CRP threshold and postoperative complications as an OR and 95% CI.

In all tests, a two sided p value <0.05 was considered statistically significant. Propensity scoring, matching, and all statistical analyses were performed using IBM SPSS version 22 for Windows (Chicago, IL, USA).

11.2.6 Literature review

The results obtained stimulated a post hoc systematic literature review that examined reported values of CRP following open and laparoscopic surgery in Europe compared to China and Japan. A search was performed of PubMed from inception to 1st October 2016 using the search terms "c-reactive protein", "postoperative", "colorectal surgery". Abstracts were screened for relevance after which relevant full texts were appraised. Those studies which were pre-clinical, reviews, not in colorectal surgery, or did not report an average serum CRP value for patients undergoing laparoscopic or open surgery on postoperative days 2 or 3 were excluded. Weighted mean averages of CRP concentrations reported in studies comparing laparoscopic and open surgery in Europe and Asia were calculated. The statistical significance of the mean difference between groups was assessed using the Z test.

11.3 Results

11.3.1 Patients

In total 1,194 patients were included in the study (Figure 11-1), of which 636 underwent surgery in the UK centre and 558 underwent surgery in the Japanese centre (Table 11-1). A lower proportion of patients who underwent surgery in the UK were over 74 years old (27% vs. 32%, p=0.034), and male (57% vs. 63%, p=0.038), while a higher proportion were overweight or obese (57% vs. 22%, p<0.001) and had an ASA score of 3 or 4 (33% vs. 13%, p<0.001) when compared to those who underwent surgery in Japan. A significantly higher proportion of patients who underwent surgery in the UK had undergone preoperative nCRT (15% vs. 0.01%, p<0.001). Although there was no significant difference in TNM stage or tumour site, a higher proportion of those patients who underwent surgery in the UK had poorly differentiated tumours (8% vs. 3%, p<0.001), but lower rates of venous invasion (57% vs. 66%, p<0.001) and tumour perforation (1% vs. 4%, p=0.001), at histopathological examination when compared to those who underwent surgery in Japan. A significantly higher proportion of patients who underwent surgery in the UK had a preoperative mGPS greater than 0 (22% vs. 15%, p=0.009), and a NLR greater than 3 (43% vs. 35%, p=0.004) when compared to those who underwent surgery in Japan.

11.3.2 Operative and postoperative characteristics in the unmatched cohort

A significantly lower proportion of patients who underwent surgery in the UK (Table 11-1) had a laparoscopic resection when compared to those who underwent surgery in Japan (35% vs. 44%, p=0.002). There was a significant difference in the mix of surgical procedures performed when the two groups were compared (p=0.019). A significantly higher proportion of patients who underwent surgery in the UK had 12 or more lymph nodes sampled and reported at histopathological examination when compared to those who underwent surgery in Japan (27% vs. 19%, p<0.001). A significantly higher proportion of patients who underwent surgery in the UK exceeded the established serum CRP threshold of 150mg/L on postoperative day 3 when compared to those who underwent surgery in Japan (46% vs. 7%, p<0.001). A significantly higher proportion of patients who underwent surgery in the UK had serum albumin concentration of less than 25g/L on postoperative day 3 when compared to those who underwent surgery in Japan (40% vs. 29%, p<0.001). Patients who underwent surgery in the UK had a significantly shorter

median length of postoperative stay when compared to those who underwent surgery in Japan (9 days vs. 13 days, p<0.001). There were no significant differences in operation duration, rate of margin involvement, 30 day postoperative mortality, or the proportion of patients referred for adjuvant treatment when the two centres were compared.

11.3.3 Operative and postoperative characteristics in the propensity score matched cohort

Propensity scores could not be assigned to 401 patients due to missing covariate data, leaving 793 patients with propensity scores, of which 306 underwent surgery in the UK and 487 underwent surgery in Japan. 612 patients (306 from each group) were matched based on their propensity score, with a subsequent improvement in the balance of distribution of propensity scores in each group (Figure 11-2).

In the propensity score matched cohort (Table 11-2), a significantly higher proportion of patients who underwent surgery in the UK exceeded the postoperative day 3 CRP threshold of 150mg/L when compared to those who underwent surgery in Japan (43% vs. 8%, p<0.001). A significantly higher proportion of patients who underwent surgery in the UK had a postoperative day 3 serum albumin concentration of <25g/L when compared to those who underwent surgery in Japan (38% vs. 27%, p=0.005). There was a significant difference in median length of stay when those patients who underwent surgery in the UK were compared to those who underwent surgery in Japan (8 vs. 13 days, p<0.001). There was no significant difference in 30 day mortality or the proportion of patients going on to adjuvant therapy.

11.3.4 Sensitivity analyses using other propensity score methods

Analysis of the impact of the country of surgery on exceeding the postoperative day 3 CRP threshold of 150mg/L (Table 11-3) found a similarly statistically significant probability of reduction in the unmatched cohort (OR 0.08, 95% CI 0.05-0.11) when using regression adjustment (OR 0.13, 95% CI 0.08-0.19), propensity score stratification (OR 0.12, 95% 0.08-0.19, and propensity score matching (OR 0.12, 95% CI 0.08-0.20).

11.3.5 Comparison of the reported literature of the magnitude of the postoperative systemic inflammatory response in Asia and Europe

The search strategy returned 197 abstracts of which 9 were reviews and 5 were pre-clinical animal studies. 169 studies were excluded due to either being outside colorectal surgery or not reporting an average serum CRP value for patients undergoing laparoscopic or open surgery on postoperative day 3. 14 studies, with 2,456 patients, were included, of which 9 were from Europe and 5 were from Asia (all from China and Japan), with no studies from North America or Australasia (Table 11-4).

When compared to the studies of open colorectal surgery in Europe (Table 11-5), the studies from Asia reported a statistically significantly lower CRP on postoperative day 3 (mean difference -30 mg/L, 95% CI -60 to -1 mg/L, p=0.049). When compared to the studies of laparoscopic colorectal surgery in Europe, the studies from Asia reported a statistically significantly lower CRP on postoperative day 3 (mean difference -45 mg/L, 95% CI -70 to -20 mg/L, $p<0.001$).

11.4 Discussion

The results of the present study indicate that even after adjustment for confounding factors, the magnitude of the postoperative systemic inflammatory response was lower in Japan when compared to the UK.

A large body of evidence now links the postoperative systemic inflammatory response and postoperative complications, (Adamina et al. 2015) which are associated with poorer oncologic outcome following surgery for colorectal cancer (Artinyan et al. 2014). In addition, there is some evidence that the postoperative systemic inflammatory response is itself associated with poorer long-term outcome independent of complications (McSorley, Chapter 4). Therefore, factors which modulate or attenuate the magnitude of the postoperative systemic inflammatory response are of interest. Indeed, it is already recognised that laparoscopic surgery is associated with a lower postoperative systemic inflammatory response and lower complication rate following surgery for colorectal cancer (McSorley Chapter 3). Furthermore, the use of corticosteroids in the perioperative period has been reported to be associated with both attenuation of the postoperative systemic inflammatory response and fewer complications following major abdominal surgery (Srinivasa et al. 2011). However, it remains to be determined whether specific CRP thresholds determined in European studies have similar associations with postoperative complications and long-term outcomes in patients undergoing surgery in Asia.

Indeed, the results of the present study are in keeping with previous reports suggesting a differential systemic inflammatory response to cancer dependent on nationality. The presence of systemic inflammation at diagnosis, as defined by the modified Glasgow Prognostic Score (mGPS), has been shown to have a negative prognostic impact across a variety of solid tumours, in both resectable and unresectable disease, across Europe, the USA, Australasia, South Korea, Japan, and China (McMillan 2013). Some prior reports suggest that a lower proportion of patients are systemically inflamed in Japanese cohorts when compared to Western cohorts (Ishizuka et al. 2009, Kobayashi et al. 2010, Jiang et al. 2012). This finding has recently been confirmed in a large observational study comparing cohorts undergoing surgery for stage I-III colorectal cancer in the UK and Japan (Park et al. 2017). A lower proportion of patients in the Japanese cohort were found to be systemically inflamed prior to surgery, however, the negative prognostic impact of a raised mGPS remained. Furthermore, the review of the existing literature reported in the present study suggests that patients who have undergone both open and laparoscopic surgery for

colorectal cancer in Asia have a lesser postoperative systemic inflammatory response when compared to those who have undergone the same surgery in Europe. Taken together this evidence suggests that differential innate inflammatory responses exist in these two groups of patients, which may be underpinned by differential expression or genetic polymorphisms in pro-inflammatory cytokines and acute phase reactants.

A further alternative explanation for the variation in the magnitude of the postoperative systemic inflammatory response found between the two centres in the present study is in variation amongst surgical and anaesthetic teams. Indeed, the results of the present study report significant differences in operative factors between the patients who underwent surgery in the UK and Japan, including the proportion of patients undergoing laparoscopic surgery, the type of procedure performed, and the number of lymph nodes excised and sampled. Although variation in outcomes dependent on surgeon and/or centre have been reported in the past (Burns et al. 2011, Oliphant et al. 2013), there have been no such reports focussing on the postoperative systemic inflammatory response. Indeed, the significant differences in case mix and length of stay reported by the present study imply variation in surgical technique and perioperative care between the two centres. However, although the magnitude of the postoperative systemic inflammatory response was significantly different between the two centres, other outcomes that would be expected to be affected by variation in care: the rates of postoperative mortality, and the proportion of patients going on to adjuvant therapy, were not.

The most significant limitation of the present study was the variation in surgical practice and perioperative care between the sites in the UK and Japan, as evidenced by the significant difference in postoperative length of stay. Around half of patients in the UK cohort received intraoperative dexamethasone to prevent postoperative nausea and vomiting whilst no patients in the Japanese cohort received perioperative steroids, a factor thought to influence the postoperative systemic inflammatory response. Very few Japanese patients received nCRT prior to surgery, again suggesting very different management not just around surgery, but of patients with colorectal cancer in general between the two centres. In addition, different histopathological techniques, reporting requirements, and TNM staging editions between centres may have introduced systematic differences in pathological variables. Furthermore, differences in the recording of postoperative complications between the two centres prevented meaningful comparison.

Finally, the differences in the patients themselves might be seen as a limitation. UK patients had greater obesity (BMI), comorbidity (ASA score), and existing evidence would suggest that these factors enhance the postoperative systemic inflammatory response. However, following adjustment for surgical approach, obesity and comorbidity through propensity score matching, there remained a difference in the postoperative systemic inflammatory response. Although propensity score matching can be used in attempt to improve balance between groups in observational studies, it only allows us to control for known confounders and a possible risk of the method is the introduction of unknown and unrecognised systematic bias. In the present study even after the matching process, the balance between groups was less than perfect.

The basis of the differential postoperative systemic inflammatory response between the cohorts is not clear. It may be that ethnicity and underlying differential gene expression might have a role in the magnitude of the postoperative systemic inflammatory response. However, it may be that differences in operative and anaesthetic techniques, along with variation in perioperative care, have an important role to play. These findings have implications for the comparison of postoperative outcomes across the globe. For example, in the application of established postoperative CRP thresholds and in the design of any prospective studies designed to investigate attenuation of the postoperative systemic inflammatory response outwith Europe.

11.5 Tables and Footnotes

Table 11-1: Characteristics of patients undergoing elective resection of stage I-III colorectal cancer in UK and Japan (n=1194)

Characteristic	All	Country		P
		UK	Japan	
N	1194	636	558	-
Age (<65/65-74/>74)	418/431/345	217/250/169	201/181/176	0.034
Sex (male/female)	713/481	362/274	351/207	0.038
BMI (<20/20-25/26-30/>30)	165/494/289/196	26/214/184/180	139/280/105/16	<0.001
ASA score (1/2/3/4)	239/632/256/23	147/280/186/22	92/352/70/1	<0.001
Site (colon/rectum)	759/429	413/222	346/207	0.397
TNM stage (0/I/II/III)	40/268/449/404	15/138/267/211	25/130/182/193	0.381
Neoadjuvant treatment (yes/no)	99/1078	96/523	3/555	<0.001
Preop mGPS (0/1/2)	939/84/144	484/56/86	455/28/58	0.009
Preop NLR >3 (yes/no)	470/704	273/348	197/356	0.004
Approach (open/laparoscopic)	709/465	403/221	306/244	0.002
Procedure (RH/LH/AR/APR/TC)	434/305/318/85/29	232/172/156/55/21	202/133/162/30/8	0.019
Surgery >4h (yes/no)	367/772	197/391	170/381	0.342
≥12 lymph nodes sampled (yes/no)	891/270	511/120	380/150	<0.001
Margin positive (yes/no)	55/1125	30/600	25/525	0.891
POD 3 CRP (median,IQR,mg/L)	96 (52-163)	147 (94-213)	60 (35-96)	<0.001
POD 3 CRP >150mg/L (yes/no)	329/806	292/307	37/499	<0.001
POD 3 albumin (median,IQR,g/L)	26 (23-29)	26 (23-29)	27 (24-30)	<0.001
POD 3 albumin <25g/L (yes/no)	386/707	237/349	149/358	<0.001
Complication (yes/no)	498/688	261/375	237/313	0.480
Anastomotic leak (yes/no)	71/1115	31/605	40/510	0.087
Length of stay (median,IQR,days)	11 (8-16)	9 (6-13)	13 (10-21)	<0.001
Thirty day mortality (yes/no)	14/1180	11/625	3/555	0.063
Adjuvant treatment (yes/no)	333/753	158/390	175/363	0.189

UK *United Kingdom*, BMI *Body Mass Index*, ASA *American Society of Anesthesiology*, mGPS *modified Glasgow Prognostic Score*, NPS *neutrophil platelet score*, NLR *neutrophil lymphocyte ratio*, LMR *lymphocyte monocyte ratio*, POD *postoperative day*, CRP *C-reactive protein*, IQR *interquartile range*, RH *right and extended right hemicolectomy*, LH *left and sigmoid colectomy*, AR *anterior resection*, APR *abdominoperineal resection*, TC *total colectomy*

Table 11-2: Characteristics of propensity score matched patients undergoing elective resection of stage I-III colorectal cancer in the UK and Japan (n=612)

Characteristic	All	Country		P
		UK	Japan	
N	612	306	306	-
Age (<65/65-74/>74)	208/209/195	101/113/92	107/96/103	-
Sex (male/female)	362/250	175/131	187/119	-
BMI (<20/20-25/36-30/>30)	48/340/195/29	24/170/97/15	24/170/98/14	-
ASA score (1/2/3/4)	131/353/119/9	84/139/75/8	47/214/44/1	-
Site (colon/rectum)	396/216	203/103	193/113	-
TNM stage (0/I/II/III)	21/142/247/202	6/68/140/92	15/74/107/110	-
Neoadjuvant treatment (yes/no)	49/555	47/251	2/304	-
Preop mGPS (0/1/2)	503/42/67	251/21/34	252/21/33	-
Preop NLR (<3/>3)	366/240	165/135	201/105	-
Approach (open/laparoscopic)	370/242	188/118	182/124	-
Procedure (RH/LH/AR/APR/TC)	232/161/163/40/11	110/92/74/23/7	122/69/89/17/4	-
Surgery >4h (yes/no)	191/404	89/200	102/204	-
≥12 lymph nodes sampled (yes/no)	464/147	245/61	219/86	-
Margin positive (yes/no)	22/590	13/293	9/297	-
POD 3 CRP (median,IQR,mg/L)	92 (52-153)	129 (82-200)	64 (40-99)	<0.001
POD 3 CRP >150mg/L (yes/no)	146/433	121/161	25/272	<0.001
POD 3 albumin (median,IQR,g/L)	26 (24-29)	26 (23-20)	27 (24-30)	0.001
POD 3 albumin <25g/L (yes/no)	181/373	105/172	76/201	0.005
Length of stay (median,IQR,days)	11 (7-16)	8 (6-12)	13 (10-21)	<0.001
Thirty day mortality (yes/no)	5/607	3/303	2/304	1.000
Adjuvant treatment (yes/no)	168/396	68/196	100/200	0.067

UK *United Kingdom*, BMI *Body Mass Index*, ASA *American Society of Anesthesiology*, mGPS *modified Glasgow Prognostic Score*, NPS *neutrophil platelet score*, NLR *neutrophil lymphocyte ratio*, LMR *lymphocyte monocyte ratio*, POD *postoperative day*, CRP *C-reactive protein*, IQR *interquartile range*, RH *right and extended right hemicolectomy*, LH *left and sigmoid colectomy*, AR *anterior resection*, APR *abdominoperineal resection*, TC *total colectomy*

Table 11-3: Odds ratios for exceeding the postoperative day 3 C-reactive protein threshold of 150mg/L with respect to country of surgery across the propensity score methods

Propensity Score Model	n	POD 3 CRP >150mg/L OR (95%CI)
Unadjusted	1194	0.08 (0.05-0.11)
Regression adjustment	793	0.13 (0.08-0.19)
Stratification by quintiles (ATE)	793	0.12 (0.08-0.19)
Matched 1:1	612	0.12 (0.08-0.20)

POD postoperative day, *CRP* C-reactive protein, *OR* odds ratio, *CI* confidence interval, *ATE* average treatment effect

Table 11-4: Studies reporting postoperative day 3 C-reactive protein concentrations following open and laparoscopic surgery for colorectal cancer in Asia and Europe

Country	Type	Author	Year	Journal	Patients (n)	mean POD 3 CRP (mg/L)
Europe						
Denmark	Prospective	Stage et al.	1997	Br J Surg	open = 14 laparoscopic = 15	open = 95 laparoscopic = 126
Spain	Retrospective	Delgado et al.	2001	Dis Colon Rectum	open = 58 laparoscopic = 39	open = 91 laparoscopic = 69
Germany	Prospective	Wichmann et al.	2005	Arch Surg	open = 35 laparoscopic = 35	open = 145 laparoscopic = 90
UK	Retrospective	Crozier et al.	2007	Br J Surg	open = 180	open = 145
Italy	Prospective	Vignali et al.	2009	Dis Colon Rectum	open = 13 laparoscopic = 13 (only control group included)	open = 82 laparoscopic = 74
Switzerland	Retrospective	Warschkow et al.	2011	Int J Colorectal Dis	open =1,238	open = 141
Denmark	Retrospective	Helvind et al.	2013	Surg Endoscp	lap = 162	laparoscopic = 68
UK	Retrospective	Selby et al.	2014	Int J Colorectal Dis	open = 127	open = 168
UK	Retrospective	Ramanathan et al.	2015	Ann Surg Oncol	open = 191 laparoscopic = 153	open = 169 laparoscopic = 122
Asia						
Hong Kong	Prospective	Leung et al.	2000	Ann Surg	open = 17 laparoscopic = 17	open = 78 laparoscopic = 58
Japan	Prospective	Hatada et al.	2000	Cytokine	open =100	open = 130
Japan	Prospective	Nishiguchi et al.	2001	Dis Colon Rectum	open = 12 laparoscopic = 15	open = 85 laparoscopic = 75
China	Prospective	Wang et al.	2012	J Gastrointest Surg	open = 41 laparoscopic = 40 (only fast track groups included)	open = 99 laparoscopic = 84
Japan	Prospective	Shibata et al.	2015	Tech Coloproctol	open = 8 laparoscopic = 23	open = 102 laparoscopic = 54

POD postoperative day, *CRP* C-reactive protein, *UK* United Kingdom

Table 11-5: Weighted average postoperative day 3 C-reactive protein concentrations in Asia and Europe following elective surgery for colorectal cancer

Postoperative day	Approach	Europe	Asia	P
		mean (SD)	mean (SD)	
POD 3 CRP (mg/L)	Open	144 (35)	114 (20)	0.049
	Laparoscopic	106 (26)	61 (14)	<0.001

POD postoperative day, *CRP* C-reactive protein, *SD* standard deviation

11.6 Figures and Legends

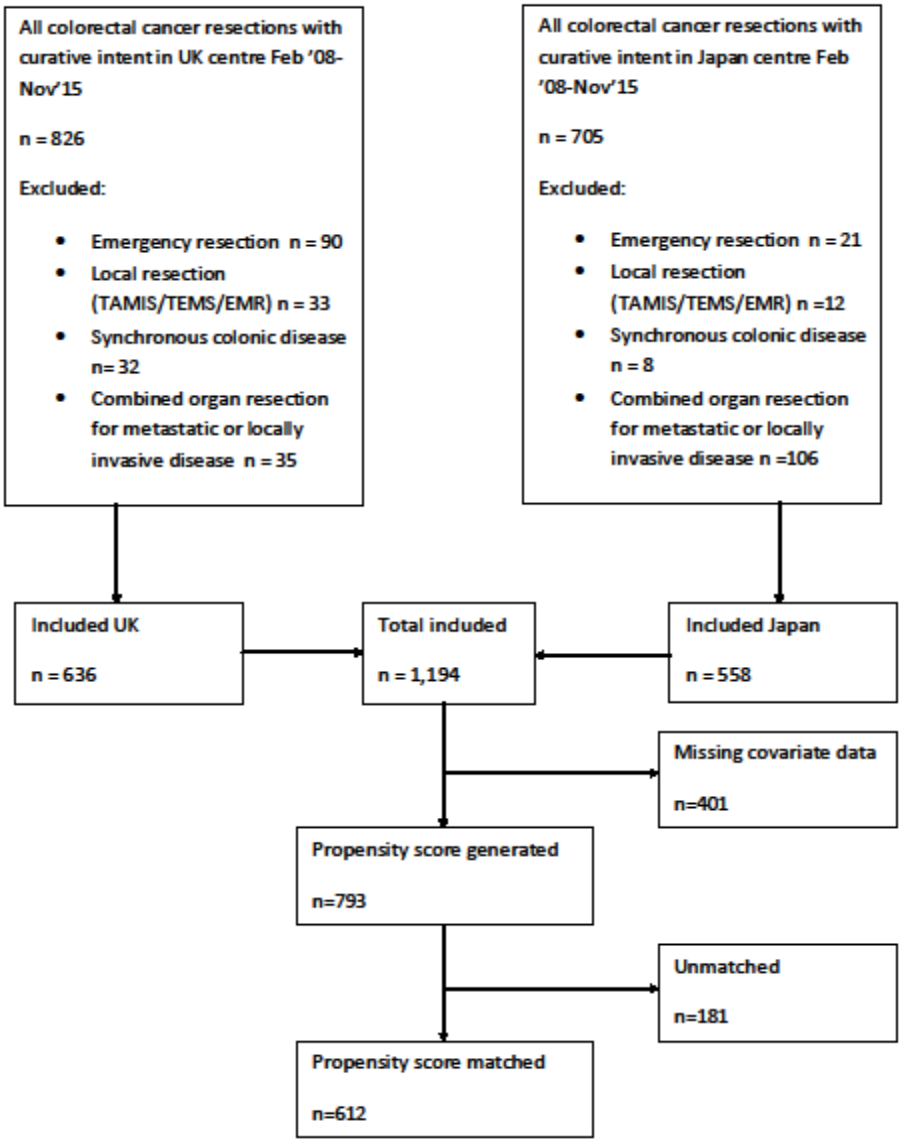

Figure 11-1: Flow chart of patients undergoing surgery for colorectal cancer in the UK and Japan

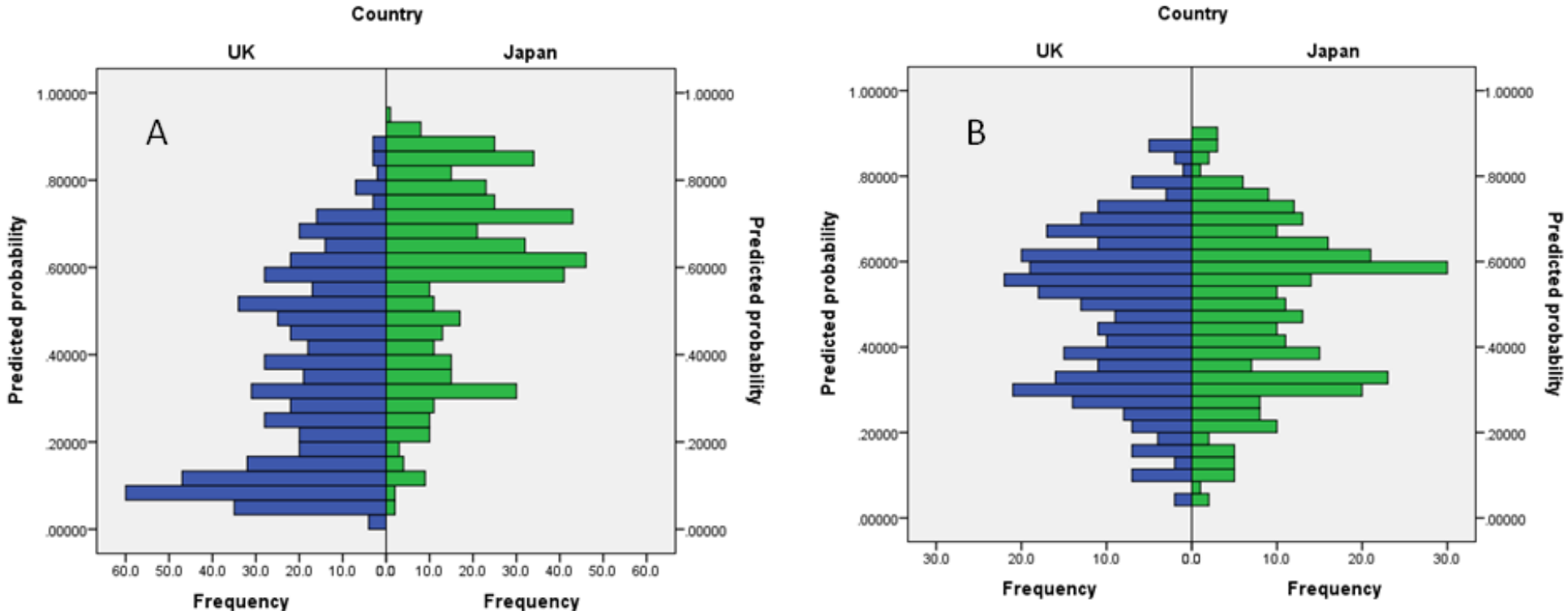

Figure 11-2: Distribution of propensity scores (A) before, and (B) after propensity score matching

12 Examination of a CRP first approach for the detection of postoperative complications in patients undergoing surgery for colorectal cancer: a pragmatic study

12.1 Introduction

Anastomotic leak and other significant postoperative complications can present in a subtle manner and often only become clinically evident relatively late in the postoperative course, which is likely to contribute to their impact on outcomes (Platt et al. 2012).

It is now well understood that the magnitude of postoperative systemic inflammatory response, measured by C-reactive protein (CRP), is associated with postoperative complications (Singh et al. 2014a, Adamina et al. 2015). Recent consensus suggests that CRP concentrations exceeding 150mg/L on postoperative days 3 to 5 should alert clinicians to possible postoperative complications, including anastomotic leak (McDermott et al. 2015). Furthermore, it has been suggested that measuring the magnitude of the postoperative systemic inflammatory response may be useful in determining safe discharge, or indeed delaying it for further investigation (Mullen 2017).

Computed Tomography (CT) is an important imaging technique commonly used, with or without the addition of rectal and/or oral contrast, to diagnose postoperative complications including anastomotic leak (Hyman et al. 2007, Kauv et al. 2015). Studies have shown CT to be both sensitive and specific in detection of these postoperative complications (Eckmann et al. 2004, Straatman et al. 2014). However, compared to most routine blood tests such as CRP, CT is resource intensive, requires patient exposure to ionising radiation, and is usually carried out upon the surgical team's suspicion. As a consequence, CT is often not requested until late in the postoperative course (Kornmann et al. 2014).

Due to this strong association with the development of postoperative complications, CRP may be a useful biomarker to identify those patients who would benefit from early CT. However, at present there is no data to inform as to whether a CRP first approach would result in the earlier detection of postoperative complications. The currently recruiting PRECious trial aims to test this hypothesis prospectively by allocating patients to standard care or to a postoperative care arm in which patients will undergo contrast CT if they exceed a CRP threshold of 140mg/L on postoperative day 3, 4, or 5 (Straatman et al. 2015). The investigators plan to use a stepped wedge design and will not blind clinicians in the control arm to postoperative CRP concentrations. Given that the current evidence for the association between CRP and postoperative complications is robust, this raises the possibility of selection bias and crossover of patients allocated to the control arm to early

CT dependent on their CRP concentrations. Another approach would be to audit surgical practice prior to the introduction of a CRP first postoperative protocol.

Therefore, the aim of the present study, in a prospective cohort, was to examine the relationship between the magnitude of the postoperative systemic inflammatory response, postoperative CT, and complications in patients who underwent surgery for colorectal cancer.

12.2 Patients and Methods

12.2.1 Patients

Patients with histologically confirmed colorectal cancer who underwent elective surgery with curative intent, between February 2008 and April 2015 at a single centre were included in the study. Patients who underwent emergency surgery, palliative procedures, with metastatic disease, or who had existing inflammatory conditions were excluded.

All patients received prophylactic antibiotics and venous thromboprophylaxis prior to the induction of anaesthesia as per hospital policy. Patients had routine preoperative blood sampling including a full blood count (FBC), serum CRP, and albumin concentration.

On each postoperative day patients were clinically assessed and had blood samples, including serum CRP, obtained routinely until discharged. Further postoperative investigation and intervention was at the discretion of the patient's surgical team, who were not blinded to blood results. All CT scans performed in the postoperative period were reported by a consultant radiologist at the request of the referring surgical team. The use of rectal, oral, and intravenous contrast was at the discretion of the supervising radiologist. There was no CRP first postoperative protocol in place during the study period. This study was approved as part of surgical audit by the West of Scotland Research Ethics Committee.

12.2.2 Methods

Data was collected prospectively in a database, anonymised, and subsequently analysed. Recorded information included patient demographics, clinicopathological, operative, and radiological (CT) data. As CRP on postoperative day 4 was the measurement analysed, only CT scans performed between postoperative days 4 and 14 were included. Earlier CT scans were not included as a resultant early intervention may have confounded the subsequent postoperative day 4 CRP value. Where multiple CT scans were performed during this period, only the result of the first scan in the postoperative period was included.

Serum concentrations of CRP (mg/L) were measured using an autoanalyzer (Architect; Abbot Diagnostics, Maidenhead, UK) with a lower detectable limit of 0.2 mg/L, as was serum albumin (normal range 35-50g/L). The preoperative modified Glasgow Prognostic Score (mGPS) was calculated in patients for whom serum CRP and albumin concentrations

were available (McMillan 2013). Breaching the established CRP threshold of 150mg/L on postoperative day 4 was recorded (McDermott et al. 2015).

Infective complications were categorised as described previously and are briefly summarised here (Platt et al. 2012). Wound (superficial surgical site) infection was defined as the presence of pus either spontaneously discharging from the wound or requiring drainage. Deep surgical site infection was defined as surgical or image-guided drainage of intra-abdominal pus. Anastomotic leak was defined as radiologically verified fistula to bowel anastomosis or diagnosed at laparotomy. Pneumonia was defined by fever above 38.5^{o}C and consolidatory chest X-ray findings requiring antibiotic treatment. Septicaemia was defined by the presence of sepsis combined with positive blood culture. Urinary tract infection (UTI) was only included if complicated by septicaemia and confirmed with positive urine culture. Complications were also classified by severity using the Clavien Dindo grade (Dindo et al. 2004).

12.2.3 Statistical Analysis

Categorical data were compared using the Chi square test and Chi square for linear association where appropriate. Continuous data were displayed as medians and ranges. These continuous data were compared using the Mann-Whitney U test. Missing data were excluded from analysis. Statistical analyses were performed using IBM SPSS version 22 for Windows (Chicago, IL, USA). Two sided p values <0.05 were considered statistically significant.

12.3 Results

12.3.1 Patients

In total, 495 patients were included in the study (Figure 12-1). The majority were male (286, 58%), over 65 years old (335, 68%), with node negative disease (328, 66%) and underwent open surgery (349, 70%) (Table 12-1). 170 (34%) patients exceeded the postoperative day 4 CRP threshold of 150mg/L. 93 (19%) patients underwent CT scan between postoperative days 4 and 14 following surgery, of which the majority received intravenous contrast (90, 97%) while 3 (3%) patients received additional rectal contrast. The median duration between surgery and CT scan was 7 days (range 4-14). 218 patients (44%) developed a postoperative complication, of which 146 (29%) were infective and 51 (10%) were Clavien Dindo grade 3-5. There were 22 anastomotic leaks (4%).

When those patients who underwent surgery for colonic and rectal cancers were compared, there was no significant difference in the proportion of patients exceeding the established postoperative day 4 CRP threshold of 150mg/L (p=0.923), undergoing a postoperative CT scan (p=0.239), having a postoperative complication (p=0.052), anastomotic leak (p=1.000), or the need for reoperation (p=0.402). Therefore, the two groups were subsequently analysed together.

12.3.2 Association between postoperative CT, CRP, and complications

Patients who underwent a CT scan (n=93), compared with those who did not (n=402, Figure 12-1, Table 12-2), were more likely to have a postoperative complication of any kind (84% vs. 35%, p<0.001), infective complication (67% vs. 21%, p<0.001), anastomotic leak (17% vs. 2 %, p<0.001), and have a higher Clavien Dindo grade (p<0.001). They were also significantly more likely to require postoperative percutaneous intervention or reoperation (25% vs. 4%, p<0.001), although there was no significant association with time between initial surgery and intervention.

In those patients who did not undergo a CT scan (n=402), exceeding CRP concentration of 150mg/L (n=117) on postoperative day 4 (Figure 12-1 and Table 12-3) was associated with a higher rate of any kind of postoperative complication (50% vs. 29%, p<0.001), infective complications (36% vs. 15%, p<0.001), anastomotic leak (4% vs. 0.5%, p=0.009), and higher Clavien Dindo grade (p<0.001). There was a trend toward greater need for postoperative intervention (7% vs. 3%, p=0.089). Those patients who required reoperation

but did not undergo CT did so for reasons including haemorrhage, wound dehiscence, stoma complications, and discharge of enteric content from abdominal wound.

In those patients who did undergo a CT scan (n=93), exceeding a CRP concentration of 150mg/L (n=53) on postoperative day 4 (Figure 12-1 and Table 12-4) was not associated with any clinicopathological variables, or postoperative complication rates. There was a significant association with earlier CT in those patients who exceeded the established CRP threshold of 150mg/L on postoperative day 4 (median postoperative day 6 vs. 8, p=0.001) and a trend toward earlier intervention (p=0.140).

12.3.3 CRP before CT, and the association with complications and reoperation

Patients who exceeded the postoperative day 4 CRP threshold of 150mg/L (n=170), compared with those who did not (n=325), were more likely to undergo a CT scan (30% vs. 12%, p<0.001) and at an earlier time (median postoperative day 6 vs. 8, p=0.001). They were more likely to have any kind of postoperative complication (61% vs. 36%, p<0.001), infective complications (47% vs. 21%, p<0.001), anastomotic leak (10% vs. 2%, p<0.001), and have a higher Clavien Dindo grade (p<0.001). They were also more likely to require postoperative percutaneous intervention or reoperation (14% vs. 5%, p=0.003). In those patients who exceeded the postoperative day 4 CRP threshold of 150mg/L (n=170), a subsequent CT scan (n=53) compared to those without a CT scan was associated with a higher rate of any kind of complication (87% vs. 50%, p<0.001), infective complications (72% vs. 36%, p<0.001), anastomotic leak (23% vs. 4%, p=0.001), and a greater requirement for postoperative percutaneous intervention or reoperation (28% vs. 7%, p<0.001).

12.4 Discussion

The results of the present study report that the combination of high CRP on postoperative day 4 followed by CT is associated with higher rates of postoperative complication and re-intervention in patients undergoing surgery for colorectal cancer.

In keeping with prior studies, the magnitude of the postoperative systemic inflammatory response was associated with complications and their severity (Adamina et al. 2015, McSorley Chapter 3). Furthermore, it was of interest that there was a significant rate of clinically important (i.e. Clavien Dindo grade ≥3) morbidity and mortality in those patients who exceeded the CRP thresholds on postoperative day 4 but did not undergo CT scanning. This may represent a group of patients who were "failed to rescue".

In contrast to the widely used measurement of CRP on postoperative day 4, postoperative CT scanning was only carried out in approximately 1 in 5 patients. In those patients who exceeded the CRP threshold on postoperative day 4, the use of CT scan was associated with a higher rate of all complications, infective complications, and anastomotic leak. In addition, the combination of postoperative day 4 CRP and subsequent CT scan was associated with a significantly higher rate of postoperative intervention.

A prior observational study by Straatman and colleagues reported a similar relationship between CRP and Clavien Dindo grade 3-5 complications, and a sensitivity and specificity of 92% and 100% respectively for contrast enhanced CT in the detection of these major complications in abdominal surgery (Straatman et al. 2014). Furthermore, a recent observational study reported earlier diagnosis of postoperative complications, including by CT, and earlier intervention following surgery for colorectal cancer after the adoption of routine postoperative CRP measurement (Mik et al. 2016). However, the accuracy of CT was not further stratified by CRP in either study.

In those patients who did not exceed the CRP threshold on postoperative day 4, the use of CT scan also increased the detection rate of complications and of anastomotic leak. Taken together with the above results it is clear that patients who underwent CT between postoperative days 4 and 14 and did not exceed the CRP thresholds on postoperative day 4, did so for reasons other than a raised CRP. Also, a small number of patients required reoperation without having undergone postoperative CT, primarily for complications

which would not necessarily require a CT in their diagnosis, e.g. wound and stoma complications, haemorrhage, and fistulation.

Even serious complications, such as anastomotic leak and those with a Clavien Dindo grade of 3 or more, are often not diagnosed until late in the postoperative course, in some cases as long as 12 days after surgery (Khan et al. 2008, Platt et al. 2012). In keeping with this, half of all CT scans were performed 7 days or more after surgery in the present study. However, there was no significant difference in time to CT or intervention between the CT and no-CT groups in the present study. Despite this, current evidence suggests that CT imaging can accurately diagnose significant intra-abdominal complications much earlier in the postoperative period (Kornmann et al. 2014). The currently recruiting PRECious trial aims to determine whether this is the case based on a CRP first approach.

The present study has several limitations. Due to the observational nature of the study, there were missing clinicopathological data. The analysis was retrospective, however the process of postoperative care, investigation, and re-intervention is a dynamic one and so difficult to model in this way. Only a small number of patients received rectal contrast, and a small number received no contrast via any route due to renal failure, which may have reduced the diagnostic accuracy of CT. In many cases in which patients did not go on to reoperation the diagnosis of any complication relied directly on the CT scan report, although the use of Clavien Dindo grading has hopefully increased the objectivity of complication recording. Furthermore, although the present study investigated CRP thresholds on day 4, the median time to CT imaging was 7 days. Therefore, the results may not reflect the accuracy of CT performed earlier in the postoperative course.

The present study suggests that current clinical postoperative management with CT imaging based on a combination of clinical suspicion, physiological parameters and blood tests is relatively successful in terms of detection and intervention in postoperative complications. However, a CRP of >150mg/L on postoperative day 4 should alert the clinical team that a postoperative complication may be present, or developing. Future prospective work should attempt to determine whether a CRP first approach to the diagnosis of major complications may result in earlier and improved diagnosis of major postoperative complications by CT imaging. This approach may result in improved postoperative morbidity and mortality following surgery for colorectal cancer.

12.5 Tables and Footnotes

Table 12-1: Clinicopathological and perioperative variables of patients undergoing elective surgery for colorectal cancer (n=495)

Characteristic	All
N	495
Demographic characteristics	
Age (<65/65-74/>74)	160/195/137
Sex (male/female)	286/206
BMI (<20/20-25/26-30/>30) kg/m^2	23/155/147/140
Smoking (never/ex/current)	209/197/75
ASA score (1/2/3/4)	96/222/153/20
Pathological characteristics	
Site (colon/rectum)	298/194
TNM stage (0/1/2/3)	13/105/207/167
Preoperative mGPS (0/1/2)	369/44/70
Neoadjuvant chemoradiotherapy (yes/no)	88/395
Operative characteristics	
Operative approach (open/laparoscopic)	349/136
Stoma (yes/no)	172/319
Surgery >4h (yes/no)	153/295
Intraop transfusion (yes/no)	26/368
Postoperative outcomes	
POD4 >150mg/L (yes/no)	170/322
CT scan during POD 4-14 (yes/no)	93/402
Time to CT scan (median,range,days)	7 (4-14)
Any postoperative complication (yes/no)	218/277
Anastomotic leak (yes/no)	22/473
Infective complication (yes/no)	146/349
Clavien Dindo grade (0/1-2/3-4/5)	277/167/47/4
Intervention (yes/no)	39/456
Time to intervention (median,range,days)	7 (0-29)

ASA American Society of Anaesthesiology, *BMI* Body Mass Index, *CRP* C-reactive protein, *mGPS* modified Glasgow Prognostic Score, *POD* postoperative day

Table 12-2: Relationship between postoperative outcomes and CT between postoperative days 4 and 14 in patients undergoing elective surgery for stage I-III colorectal cancer (n=495)

Characteristic	CT POD 4-14		P
	No	Yes	
N	402	93	-
Demographic characteristics			
Age (<65/65-74/>74)	130/153/116	30/42/21	0.490
Sex (male/female)	236/163	50/43	0.353
BMI (<20/20-25/26-30/>30) kg/m^2	18/129/122/105	5/26/25/35	0.157
Smoking (never/ex/current)	171/158/62	38/39/13	0.867
ASA score (1/2/3/4)	77/179/124/18	19/43/29/2	0.527
Pathological characteristics			
Site (colon/rectum)	247/152	51/42	0.239
TNM stage (0/1/2/3)	10/87/168/134	3/18/39/33	0.755
Preoperative mGPS (0/1/2)	302/33/55	67/11/15	0.376
Neoadjuvant chemoradiotherapy (yes/no)	71/321	17/74	0.881
Operative characteristics			
Operative approach (open/laparoscopic)	286/108	63/28	0.520
Stoma (yes/no)	131/267	41/52	0.053
Surgery >4h (yes/no)	111/247	42/48	0.006
Intraop transfusion (yes/no)	20/302)	6/64	0.472
Postoperative outcomes			
POD4 CRP >150mg/L (yes/no)	117/282	53/40	<0.001
Any postoperative complication (yes/no)	140/262	78/15	<0.001
Infective complication (yes/no)	84/318	62/31	<0.001
Anastomotic leak (yes/no)	6/396	16/77	<0.001
Clavien Dindo grade (0/1-2/3-4/5)	262/118/21/1	15/49/26/3	<0.001
Intervention (yes/no)	16/386	23/70	<0.001
Time to intervention (median,range,days)	6 (0-28)	9 (4-29)	0.117

ASA American Society of Anaesthesiology, *BMI* Body Mass Index, *CRP* C-reactive protein, *mGPS* modified Glasgow Prognostic Score, *POD* postoperative day

Table 12-3: Relationship between postoperative outcomes and CRP on postoperative day 4 in patients undergoing elective surgery for colorectal cancer who did not undergo CT between postoperative day 4 and 14 (n=402)

Characteristic	POD 4 CRP >150mg/L		P
	No	Yes	
N	285	117	-
Demographic characteristics			
Age (<65/65-74/>74)	89/112/81	41/41/35	0.791
Sex (male/female)	159/123	77/40	0.093
BMI (<20/20-25/26-30/>30) kg/m^2	14/88/97/66	4/41/25/39	0.339
Smoking (never/ex/current)	128/110/36	43/48/26	0.046
ASA score (1/2/3/4)	64/122/84/11	13/57/40/7	0.055
Pathological characteristics			
Site (colon/rectum)	175/107	72/45	1.000
TNM stage (0/1/2/3)	10/67/110/95	0/20/58/39	0.131
Preoperative mGPS (0/1/2)	226/21/27	76/12/28	<0.001
Neoadjuvant chemoradiotherapy (yes/no)	54/222	17/99	0.314
Operative characteristics			
Operative approach (open/laparoscopic)	197/82	89/26	0.214
Stoma (yes/no)	90/191	41/76	0.561
Surgery >4h (yes/no)	85/175	26/72	0.306
Intraop transfusion (yes/no)	13/227	7/75	0.312
Postoperative outcomes			
Any postoperative complication (yes/no)	82/203	58/59	<0.001
Infective complication (yes/no)	42/243	42/75	<0.001
Anastomotic leak (yes/no)	1/284	5/112	0.009
Clavien Dindo grade (0/1-2/3-4/5)	203/69/13/0	59/49/8/1	<0.001
Intervention (yes/no)	8/277	8/109	0.089
Time to intervention (median,range,days)	4 (0-28)	8 (4-21)	0.145

ASA American Society of Anaesthesiology, *BMI* Body Mass Index, *CRP* C-reactive protein, *mGPS* modified Glasgow Prognostic Score, *POD* postoperative day

Table 12-4: Relationship between postoperative outcomes and CRP on postoperative day 4 in patients undergoing elective surgery for colorectal cancer who did undergo CT between postoperative day 4 and 14 (n=93)

Characteristic	POD 4 CRP >150mg/L		P
	No	Yes	
N	40	53	-
Demographic characteristics			
Age (<65/65-74/>74)	11/19/10	19/23/11	0.415
Sex (male/female)	21/19	29/24	0.837
BMI (<20/20-25/26-30/>30) kg/m^2	2/15/10/12	3/11/15/23	0.142
Smoking (never/ex/current)	15/15/9	23/24/4	0.125
ASA score (1/2/3/4)	9/18/12/1	10/25/17/1	0.780
Pathological characteristics			
Site (colon/rectum)	19/21	32/21	0.293
TNM stage (0/1/2/3)	2/6/19/13	1/12/20/20	0.824
Preoperative mGPS (0/1/2)	29/3/8	38/8/7	0.706
Neoadjuvant chemoradiotherapy (yes/no)	9/30	8/44	0.420
Operative characteristics			
Operative approach (open/laparoscopic)	28/11	35/17	0.819
Stoma (yes/no)	19/21	22/31	0.674
Surgery >4h (yes/no)	16/24	26/24	0.293
Intraop transfusion (yes/no)	4/29	2/35	0.316
Postoperative outcomes			
Time to CT scan (median,range,days)	8 (4-12)	6 (4-14)	0.001
Any postoperative complication (yes/no)	32/8	46/53	0.406
Infective complication (yes/no)	24/16	38/15	0.271
Anastomotic leak (yes/no)	4/36	12/41	0.165
Clavien Dindo grade (0/1-2/3-4/5)	8/23/8/1	7/26/18/2	0.131
Intervention (yes/no)	8/40	15/53	0.468
Time to intervention (median,range,days)	13 (6-14)	8 (4-29)	0.140

ASA American Society of Anaesthesiology, *BMI* Body Mass Index, *CRP* C-reactive protein, *mGPS* modified Glasgow Prognostic Score, *POD* postoperative day

12.6 Figures and Legends

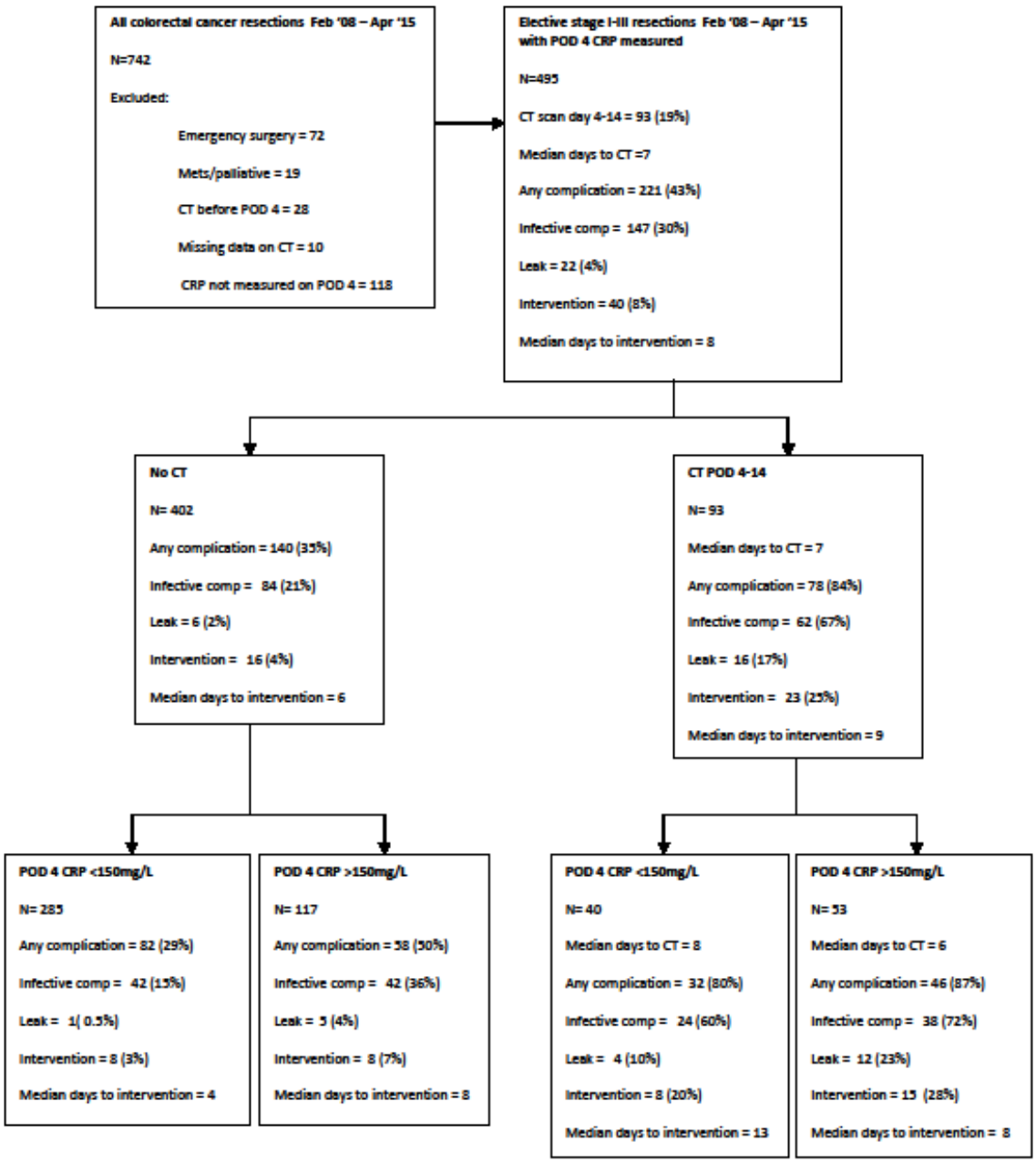

Figure 12-1: Flowchart of postoperative outcomes stratified by postoperative day (POD) 4 C-reactive protein (CRP), and CT imaging following surgery for colorectal cancer

13 The impact of preoperative corticosteroids on the systemic inflammatory response and postoperative complications following surgery for gastrointestinal cancer: a systematic review and meta-analysis

13.1 Introduction

As discussed in earlier chapters, postoperative IL 6, and CRP concentrations in particular, have been found to be useful markers of the magnitude of the surgical injury (Watt et al. 2015). The magnitude of this postoperative systemic inflammatory response, and in particular the routinely available CRP, is associated with the development of complications following colorectal surgery, oesophagectomy, and liver resection (Dutta et al. 2011, Platt et al. 2012, and Adamina et al. 2015). Furthermore, in colorectal cancer surgery, an association has been described between postoperative systemic inflammation measured by CRP, and cancer specific survival (McSorley Chapter 4).

One hypothesis which might link these observations is that the systemic inflammatory response is in some way a causal factor in the development of postoperative complications rather than just an epiphenomenon of it. If this were the case it would be assumed that attenuation of this postoperative stress response would results in fewer complications. Preoperative corticosteroids are a logical choice of intervention given their potential potency and duration of effect (Sapolsky et al. 2000, Holte et al. 2002). Indeed, preoperative corticosteroids have been used as they have been found to reduce postoperative nausea and vomiting and analgesic requirements following abdominal surgery (Karanicolas et al. 2008, Waldron et al. 2013). A recent meta-analysis reported that preoperative corticosteroids significantly reduced postoperative day one IL 6, postoperative complications, infective complications, and length of stay following abdominal surgery (Srinivasa et al. 2011). Preoperative corticosteroids have also been reported to reduce postoperative IL 6 and complication rates following liver resection and oesophagectomy in meta-analyses of small numbers of studies (Richardson et al. 2014, Raimondi et al. 2006, Gao et al. 2014).

To our knowledge, no prior meta-analysis has investigated comprehensively the impact of preoperative corticosteroids on the postoperative surgical stress response following surgery for gastrointestinal cancer. The present meta-analysis is the first to examine their impact on CRP. Both IL 6 and CRP are objective measures of the magnitude of the systemic inflammatory response to surgery, however CRP is more readily available in the clinical setting (Watt et al. 2015c). Furthermore, no meta-analysis has attempted to assess the dose response between preoperative corticosteroids and the magnitude of the postoperative systemic inflammatory response and postoperative complication rate.

Therefore, the objective of the present systematic review and meta-analysis was to examine the impact of preoperative corticosteroids compared to placebo, in the context of randomized controlled trials, on the surgical stress response, in particular postoperative IL 6 and CRP, and their relationship with the development of infective complications following surgery for gastrointestinal cancers.

13.2 Methods

The present systematic review and meta-analysis was performed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al. 2010).

13.2.1 Outcomes of interest

The primary outcome of interest was the impact of single dose preoperative corticosteroids on markers of the postoperative stress response following surgery for gastrointestinal cancer, in particular IL 6 and CRP. Those studies reporting chronic preoperative corticosteroid use, or dosing at other perioperative time points, were excluded. Secondary outcomes included the impact of preoperative corticosteroids on postoperative complications, infective complications, and anastomotic leak following surgery for gastrointestinal cancer, including pre-specified subgroup analysis based on surgical speciality/site. Postoperative complications were coded as categorised by the authors of the included studies where possible. Where there was doubt, the authors of the present study categorised complications using a schemata described previously (McSorley Introduction). Post hoc meta-regression of the impact of corticosteroid dose on postoperative day 1 IL 6 was performed following completion of the pre-specified analyses. Study selection and data extraction was performed by one author (SM) and any uncertainties resolved by consensus discussion with the senior authors (PH, DM).

13.2.2 Literature search and study selection

A systematic literature review was performed of the US National Library of Medicine (MEDLINE), PubMed, and the Cochrane Database of Systematic Reviews (CDSR) from inception to March 2015 inclusive. Subsequent to several pilot search strategies the following search term was used: “(cancer OR malignan* OR tumour OR tumor OR neoplasm*) AND (steroid OR corticosteroid OR glucocorticoid OR methylpredniso* OR predniso* OR dexamethasone) AND (surgery OR operati* OR perioperati* OR preoperati*)”, along with the Cochrane Highly Sensitive Search Strategy for RCTs (Higgins and Green 2011). Abstracts were screened for relevance and those studies which were animal and pre-clinical, those studies not published in English, and review articles were excluded. Relevant full text articles were then appraised. Randomized controlled trials of single dose preoperative corticosteroids in surgery for gastrointestinal cancer which reported on a marker of the postoperative systemic inflammatory response and

postoperative complications were included in the review. Reference lists of included studies were hand searched for further relevant studies.

13.2.3 Data extraction and meta-analysis

Data from included studies was extracted to tables and analysis was performed using Review Manager version 5.3 (RevMan 5.3, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Meta-analysis of the impact of corticosteroids on postoperative IL 6 and CRP was performed by calculating the mean difference and 95% confidence intervals (CI), using the inverse variance method and combining study outcomes using a random effects model. Where data other than means and standard deviations were reported, an attempt was made to calculate these values using published confidence intervals or p values as described by Hozo and colleagues or by the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green 2011, Hozo et al. 2005). Results of the meta-analysis of the impact of corticosteroids on infective complications was assessed by odds ratios and 95% CIs, using the Mantel-Haenzsel method and combining study outcomes using a random effects model. Peto odds ratios and their 95% CIs were combined using a fixed effects model to determine the impact of preoperative corticosteroids on anastomotic leak as there were a small number of events. Meta-regression, using a random effects model, was performed with respect to the impact of corticosteroid dose on postoperative day 1 IL 6, following conversion to hydrocortisone equivalents using a freely available Macro (Wilson, D. B.)(Version 2005.05.23). Meta-analysis macros for SAS, SPSS, and Stata. Retrieved, 7th May 2015 from http://mason.gmu.edu/~dwilsonb/ma.html) with IBM SPSS version 22 for Windows (Chicago, IL, USA) (Hozo et al. 2005). Two sided p values < 0.05 were considered statistically significant.

13.2.4 Assessment of bias

Assessment of the risk of bias was carried out using the Cochrane Collaboration tool provided by Review Manager version 5.3 (RevMan 5.3, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Data was assessed for heterogeneity using the I^2 statistic and Chi square test interpreted using the guidance from the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green 2011). Assessment of potential publication bias was carried out by visual inspection of funnel plots. Two sided p values <0.05 were considered statistically significant.

13.3 Results

13.3.1 Study selection process

The study selection process is summarised in Figure 13-1. Using the search protocol described, 2,428 abstracts were identified. At screening, 2,354 abstracts were excluded, of which 16 were animal or pre-clinical studies, 227 were not in the English language, 328 were review articles, 3 were duplicate publications, and 1,780 were not relevant to the review. Full text articles were reviewed of the remaining 74 studies.

After assessment of full text articles, 63 studies were excluded, of which 36 were not in gastrointestinal surgery patients, 6 did not include patients with malignancy, 14 did not include the intervention of interest or included corticosteroids at timings other than preoperatively, 3 did not measure either postoperative IL 6 or CRP, 2 used historical controls, 1 was a duplicate study, and 1 a co-intervention of epidural analgesia alongside preoperative corticosteroids. The remaining 11 randomised controlled trials including 474 patients were included in the review (Table 13-1) (Matsutani et al., 1998, Yamashita et al., 2001, Sato et al., 2002, Muratore et al., 2003, Takeda et al. 2003, Yano et al. 2005,Aldrighetti et al. 2006, Schmidt et al. 2007, Kirdak et al. 2008, Vignali et al. 2009, Zargar-Shoshtari et al. 2009).

Of the included studies, 3 including 139 patients, were in colorectal surgery (Kirdak et al. 2008, Vignali et al. 2009, Zargar-Shoshtari et al. 2009), 4 including 156 patients were in oesophageal surgery (Matsutani et al. 1998, Sato et al. 2002, Takeda et al. 2003, Yano et al. 2005), and 4 including 179 patients were in hepatic surgery (Yamashita et al. 2001, Muratore et al. 2003, Aldrighetti et al. 2006, Schmidt et al. 2007). Of the 474 included patients, 436 (92%) had surgery for gastrointestinal cancer while 38 (8%) from 6 studies had surgery for benign gastrointestinal disease but were included in the meta-analysis (Yamashita et al. 2001, Aldrighetti et al. 2006, Schmidt et al. 2007, Kirdak et al. 2008, Zargar-Shoshtari et al. 2009). All included patients underwent open surgery: no studies of minimally invasive surgery suitable for inclusion were returned by the search strategy.

13.3.2 Validity assessment

The risk of study bias is summarised using the RevMan 5.3 Risk of bias summary tool (Figure 13-8). Most studies were at low risk of bias, however 3 did not report outcomes for

patients who dropped out following randomisation (Muratore et al. 2003, Aldrighetti et al. 2006, Kirdak et al. 2008) and 6 did not adequately report allocation concealment and blinding (Matsutani et al. 1998,Yamashita et al. 2001, Muratore et al. 2003, Takeda et al. 2003, Yano et al. 2005, Aldrighetti et al. 2006).

13.3.3 Impact of preoperative corticosteroids on IL 6

Of the included studies, 10 including 422 patients, reported the impact of preoperative corticosteroids on postoperative IL 6 following surgery for gastrointestinal cancer and were included in meta-analysis (Figure 13-2) (Matsutani et al. 1998, Yamashita et al. 2001, Sato et al. 2002, Muratore et al. 2003, Takeda et al. 2003, Yano et al. 2005, Aldrighetti et al. 2006, Schmidt et al. 2007, Kirdak et al. 2008, Zargar-Shoshtari et al. 2009). Preoperative corticosteroids were significantly associated with lower serum concentrations of IL 6 following surgery for gastrointestinal cancer on postoperative day 1 ($p<0.001$), day 2 ($p=0.01$), and day 3 ($p=0.002$), but not postoperative day 5 ($p=0.11$) or day 7 ($p = 0.69$). There was a wide variation in heterogeneity between studies, with the greatest on postoperative day 1 ($I^2=86\%$, $p<0.001$) and the least on postoperative day 7 ($I^2=6\%$, $p=0.36$).

13.3.4 Impact of preoperative corticosteroids on C-reactive protein

Of the included studies, 6 including 206 patients reported the impact of preoperative corticosteroids on postoperative CRP following surgery for gastrointestinal cancer and were included in meta-analysis (Figure 13-3) (Yamashita et al. 2001, Yano et al. 2005, Schmidt et al. 2007, Kirdak et al. 2008, Vignali et al. 2009, Zargar-Shoshtari et al. 2009). Preoperative corticosteroids were significantly associated with lower serum concentrations of CRP following surgery for gastrointestinal cancer on postoperative day 3 ($p<0.001$) and day 7 ($p=0.04$), but not postoperative day 1 ($p=0.09$) or day 2 ($p=0.11$). There was a wide variation in heterogeneity between studies, with the greatest on postoperative day 2 ($I^2=87\%$, $p<0.001$) and the least on postoperative day 7 ($I^2=0\%$, $p=0.44$).

13.3.5 Impact of preoperative corticosteroid dose on postoperative IL 6 and CRP

Within the 10 studies reporting postoperative day 1 IL 6, there was a wide variation in preoperative corticosteroid dose in the intervention arm (Matsutani et al. 1998,Yamashita

et al. 2001, Sato et al. 2002, Muratore et al. 2003, Takeda et al. 2003, Yano et al. 2005, Aldrighetti et al. 2006, Schmidt et al. 2007, Kirdak et al. 2008, Zargar-Shoshtari et al. 2009). Following dose conversion to hydrocortisone equivalents (HEs) of both dexamethasone (1 mg = 30HEs) and methylprednisolone (1 mg = 5HEs) (Katzung 1995), it was found that 2 studies gave patients 240HEs (Schmidt et al., 2007 and Vignali et al., 2009), 3 studies gave 2,500HEs (Yamashita et al. 2001, Yano et al. 2005, Aldrighetti et al. 2006), 3 studies gave 3,500HEs (Matsutani et al. 1998, Sato et al. 2002, Takeda et al. 2003), and 2 studies gave 10,500HEs preoperatively (Muratore et al. 2003, Schmidt et al. 2007). Meta-regression revealed no significant relationship between the corticosteroid dose as measured by HEs and effect size on postoperative day 1 IL 6 (B= −0.0065, 95% CI −0.029 to 0.016, p=0.569). No further meta-regression of the impact of preoperative corticosteroid dose on postoperative IL 6 or CRP effect size was performed as the number of studies precluded meaningful analysis.

13.3.6 Impact of preoperative corticosteroids on all postoperative complications

Of the included studies 10, including 434 patients with 163 complications, reported the impact of preoperative corticosteroids on postoperative complications following surgery for gastrointestinal cancer and were included in meta-analysis (Figure 13-4) (Matsutani et al. 1998, Yamashita et al. 2001, Sato et al. 2002, Muratore et al. 2003, Takeda et al. 2003, Aldrighetti et al. 2006, Schmidt et al. 2007, Kirdak et al. 2008, Vignali et al. 2009, Zargar-Shoshtari et al. 2009). Preoperative corticosteroids were significantly associated with fewer postoperative complications following surgery for gastrointestinal cancer (OR 0.44, 95% CI 0.28–0.70, p<0.001) There was minimal heterogeneity between studies (I^2=2%, p=0.42). At subgroup analysis, preoperative corticosteroids were significantly associated with fewer postoperative complications following surgery for oesophageal (p=0.01) and liver malignancy (p=0.02) but not colorectal cancer (p=0.25).

13.3.7 Impact of preoperative corticosteroids on postoperative infective complications

Of the included studies 9, including 388 patients with 68 infective complications, reported the impact of preoperative corticosteroids on postoperative infective complications following surgery for gastrointestinal cancer and were included in meta-analysis (Figure 13-5) (Yamashita et al. 2001, Sato et al. 2002, Takeda et al. 2003, Yano et al. 2005, Aldrighetti et al. 2006, Schmidt et al. 2007, Kirdak et al. 2008, Vignali et al. 2009, Zargar-

Shoshtari et al. 2009). Preoperative corticosteroids were significantly associated with fewer postoperative infective complications following surgery for gastrointestinal cancer (OR 0.47, 95% CI 0.26–0.83, p=0.01). There was minimal heterogeneity between studies (I^2=0%, p=0.54). At subgroup analysis, preoperative corticosteroids were significantly associated with fewer postoperative infective complications following surgery for liver malignancy (p=0.02) but not colorectal (p=0.15) or oesophageal malignancy (p=0.58).

13.3.8 Impact of preoperative corticosteroids on anastomotic leak

Of the included studies, 7 including 295 patients and 19 events, reported the impact of preoperative corticosteroids on anastomotic leak following colorectal or oesophageal cancer surgery and were included in meta-analysis (Figure 13-6) (Matsutani et al. 1998, Sato et al. 2002, Takeda et al. 2003, Yano et al. 2005, Kirdak et al. 2008, Vignali et al. 2009, Zargar-Shoshtari et al. 2009). The remaining 5 studies were in hepatic surgery thus did not report anastomotic leak. There was no significant association between preoperative corticosteroids and anastomotic leak (OR 1.13, 95% CI 0.44–2.90, p=0.79). There was minimal heterogeneity between studies (I^2=0%, p=0.61). At subgroup analysis, there was no association between preoperative corticosteroids and anastomotic leak following surgery for either colorectal (p=0.71) or oesophageal malignancy (p=1.00).

13.3.9 Assessment of publication bias

Visual assessment of a funnel plot of studies reporting the impact of preoperative corticosteroids on postoperative CRP and all complications following surgery for gastrointestinal cancer (Figure 13-7) suggests that there may be evidence of publication bias with a positive skew amongst smaller studies

13.4 Discussion

The present systematic review and meta-analysis reports that preoperative corticosteroids reduce the magnitude of the systemic inflammatory response, in particular IL 6 on postoperative days 1 to 3 and CRP on postoperative days 3 and 7, following surgery for gastrointestinal cancer. Furthermore, preoperative corticosteroids were significantly associated with fewer postoperative complications following oesophageal and hepatic surgery, and with fewer infective complications in hepatic surgery.

The results of the present study, with regard to postoperative IL 6 are consistent with recent meta-analyses of randomized controlled trials of preoperative corticosteroids in colorectal surgery, liver surgery, and oesophagectomy (Srinivasa et al. 2011, Richardson et al. 2014, Raimondi et al. 2006, Gao et al. 2014, Orci et al. 2013). In addition, the present meta-analysis reports a significant reduction in IL 6 on postoperative days 2, 3, and 5 in those patients given preoperative corticosteroids. The present study reports a significant reduction in CRP on postoperative days 3 and 7 in those given preoperative corticosteroids, however found no significant impact of preoperative corticosteroids on postoperative day 1 or 2. As CRP is usually seen to reach its peak concentration around 48 hours after the initial surgical insult, it may be that comparison on postoperative day 1 and 2 does not accurately reflect the influence of preoperative corticosteroids on the postoperative systemic inflammatory response (Gabay and Kushner 1999). It is of interest that even within the control groups of the studies included in the present meta-analysis, the mean data were below postoperative CRP thresholds associated with the development of postoperative complications. For example, it has recently been advocated that simple objective postoperative CRP thresholds >150 mg/L on post-operative days 3 to 5 be used to alert clinicians to the risk of postoperative complications before clinical signs and symptoms (McDermott et al. 2015). Moreover, when examined in detail by operative site, the mean CRP concentrations reported by the studies included in the present meta-analysis were significantly lower than values reported in a comprehensive systematic review of the timing and peak magnitude of postoperative IL 6 and CRP following elective colorectal, oesophageal, and liver surgery (Watt et al. 2015c). Therefore, it may be that patients recruited to previous randomised controlled trials of preoperative corticosteroids had a lower systemic inflammatory response compared with unselected patients. If this were to be the case then this may have implications for the randomised trials that reported efficacy of preoperative corticosteroids on complication rates. In particular, it may be that the efficacy was underestimated.

As with previous meta-analyses, there was a wide variation in corticosteroid dose equivalence and timing (Udelsman and Ciarleglio 2011). The degree of heterogeneity between studies within each speciality in the present meta-analysis suggests that this does have an impact on the degree of attenuation of the postoperative systemic inflammatory response. Within the present meta-analysis, no significant association was found between varying corticosteroid dose equivalencies and postoperative day 1 IL 6 effect size between studies. However, this analysis was performed on a post hoc basis in response to data heterogeneity. In addition, dose timing and the differing half-life of dexamethasone and methylprednisolone were not considered and may be implicated (Udelsman and Ciarleglio 2011). The results of the present study do not define the ideal dose of preoperative corticosteroid to moderate the systemic inflammatory response or postoperative nausea and vomiting. For example, a recent meta-analysis of preoperative corticosteroids in the prevention of postoperative nausea and vomiting reported similar efficacy with lower doses of IV dexamethasone (4–5 mg) when compared to higher doses (8–10 mg) (De Oliveira et al. 2013). However, the efficacy of preoperative corticosteroids will depend on a number of factors, including the magnitude of the systemic inflammatory response (e.g. preventing patients breaching established threshold values of CRP) and the route and frequency of dose (e.g. large single dose or smaller multiple doses). Further work, in the context of randomised trials examining varying corticosteroid doses with reference to the magnitude of the postoperative systemic inflammatory response, is therefore required.

Postoperative IL 6 and CRP concentrations have been reported to be markers of the magnitude of the postoperative stress response (Watt et al. 2015c). In relation to short-term postoperative morbidity, several recent meta-analyses have demonstrated the utility of elevated postoperative serum CRP in the early diagnosis of infective complications and anastomotic leak in gastrointestinal surgery (Adamina et al. 2015, Singh et al. 2014a, Warschkow et al. 2012a). In addition, the magnitude of the postoperative CRP has been reported to be associated with complication severity following colorectal surgery (Selby et al. 2014, McSorley Chapter 3). Although this inflammatory response may represent an epiphenomenon rather than a cause of infective complications, given that the presence of a systemic inflammatory response (as evidenced by IL 6 or CRP) (Watt et al. 2015c) is primarily an upregulated innate immune response (with consequent suppression of adaptive immunity), it is plausible that the magnitude of the postoperative systemic inflammatory response plays a role in the development of postoperative complications (Roxburgh et al. 2013). However, there was no significant association between preoperative corticosteroids and complications following colorectal cancer surgery within

the present review. The recently published DREAMS trial, which compared 8mg dexamethasone to placebo in patients undergoing predominantly colorectal surgery, reported no significant difference in postoperative infective complications, however patients in the treatment arm had significantly fewer anastomotic leaks (Magill et al. 2017). Unfortunately no measurements of the postoperative systemic inflammatory response were made. Therefore, further interventional studies of preoperative corticosteroids would be required to prove such a relationship.

It is known that corticosteroids alter gene transcription, and thus protein synthesis, following intracellular receptor binding, however the exact mechanism by which they act to reduce inflammation is poorly understood (Barnes 1998). Glucocorticoids act on the innate immune system, including myeloid tissue, inhibiting the activity of neutrophils and macrophages via reduced transcription of several proinflammatory cytokines, and by increasing the transcription of lipocortins which themselves inhibit cyclo-oxygenase dependent inflammation pathways (Leung and Bloom 2003). They are also recognised to have a downregulatory effect on adaptive immunity and lymphoid tissue, probably via inhibition of nuclear factor κB (NF- κB) (Rhen and Cidlowski 2005). The results of the present review, taken with that of previous meta-analyses, suggest that in the postoperative period the action of corticosteroids may at least be partly due to reduced transcription and production of IL 6 by innate immune cells, and consequently, reduced synthesis of CRP by hepatocytes (Srinivasa et al. 2011, Raimondi et al. 2006, Gao et al. 2014).

There has long been a concern regarding the inhibitory effect of corticosteroids on collagen formation leading to postoperative wound dehiscence and potentially anastomotic leak. However, the present meta-analysis, along with prior randomised trials and meta-analyses, have failed to demonstrate a significant increase in either of these types of complication in patients given corticosteroids (Srinivasa et al. 2011, Gao et al. 2014, Schulze et al. 1992, Schulze et al. 1997). Much of the prior evidence regarding wound healing and infection has arisen from literature surrounding surgery for inflammatory bowel disease, in those undergoing transplant surgery, or in those with diseases of the hypothalamo-pituitary-adrenal axis (Nicholson et al. 1998). Indeed, recent meta-analysis of both experimental and clinical trials suggests that receiving corticosteroids at standard therapeutic doses for 10 days or less is unlikely to impair wound healing (Wang et al. 2013). Lastly, as recent preliminary reports suggest that preoperative corticosteroids may have a detrimental impact on oncologic outcome, some consideration should be given to

their impact on longer term outcomes, especially in surgery for gastrointestinal cancer (Singh et al. 2014b, Yu et al. 2015).

The main limitation of the present systematic review and meta-analysis is the relatively small number of patients included. To maximise the number of patients within the analysis, several gastrointestinal surgical specialities were considered together using a random effects model. In addition, there were a small number of patients included within the present meta-analysis who had undergone surgery for benign gastrointestinal disease. Indeed, these factors, to an extent, limit the generalisability of the results of the present study. However, the exclusion of the 6 studies which included a small proportion of patients without malignant disease would have significantly reduced the power of the present meta-analysis (Matsutani et al. 1998, Yano et al. 2005, Aldrighetti et al. 2006, Schmidt et al. 2007, Vignali et al. 2009). A significant degree of heterogeneity was reported in the analysis of postoperative IL 6 and CRP. This may reflect the pooling of the various surgical specialities. However, no study individually reported a statistically significant increase in either postoperative IL 6 or CRP in the corticosteroid treatment group. Thus, although there are likely to be differences in the studied patient groups or methodology, the direction of the treatment effect, at least, is very likely to be similar across the included studies. There was a wide variability in concentrations of IL 6 and CRP amongst studies within the same postoperative day. Both the biological variability of IL 6 and CRP, alongside the variety of surgical specialties included in the present study, may account for this (Macy et al. 1997). Other potential confounders include the use of a variety of preoperative corticosteroids, their dose, and timing, although a random effects model was used as an attempt to minimise this, alongside meta-regression techniques. In addition, there may be a degree of publication bias toward positive results amongst the smaller studies included in the meta-analysis. In the present study, despite a broad and inclusive search strategy, there were no trials conducted in the USA included in the analysis. Therefore, it would appear that although preoperative corticosteroids are used in routine clinical practice in the USA, no formal RCTs have been undertaken there. Finally, all of those studies included in the present meta-analysis were published prior to 2009. A single study in liver surgery, published in 2010, was excluded due to the use of postoperative corticosteroids in the treatment group, however it interestingly reported reduced concentrations of IL 6 and CRP in the treatment group with a trend toward fewer complications (Hayashi et al. 2011). The lack of more recent studies may relate to the rapid uptake of enhanced recovery or “fast track” postoperative protocols in gastrointestinal surgery which often include preoperative corticosteroids for the prevention of

postoperative nausea and vomiting (Watt et al. 2015d). Nevertheless, the results of the present review with regard to the effect of preoperative corticosteroids on IL 6 and CRP provide important new information since they suggest that the efficacy of such interventions may be dependent on the magnitude of the postoperative systemic inflammatory response.

The results of the present systematic review and meta-analysis suggest that preoperative corticosteroids are associated with a reduction in the magnitude of the postoperative stress response and, within some subgroups, the likelihood of postoperative complications following surgery for gastrointestinal cancer. Although the magnitude of this postoperative systemic inflammatory response, especially CRP, has been associated with the development of complications following surgery, relatively few studies have examined whether the attenuation of the systemic inflammatory response with preoperative corticosteroids is also associated with complication rates. Clearly, given the significant heterogeneity in the small number of studies included in the present meta-analysis, further work is warranted.

13.5 Tables and Footnotes

Table 13-1: Clinical trials investigating the impact of preoperative corticosteroids on the postoperative stress response following surgery for gastrointestinal cancer

Author	Year	Journal	Country	n	Speciality	Steroid/dose/route/timing	Surgical stress response	Period	Significant outcomes
Kirdak et al.	2008	Am Surg	Turkey	27	Colorectal	Dexamethasone 8mg IV at induction	Pain, nausea, IL 6, CRP	POD 1-3	None
Zargar-Shoshtari et al.	2009	Br J Surg	New Zealand	60	Colorectal	Dexamethasone 8mg IV, at induction	Pain, nausea, WCC, Neutrophils, CRP, IL 1β, IL 6, IL 8, IL 10, IL 13, TNFα, (serum and peritoneal cytokines), fatigue	Pain and nausea POD 1-3, Fatigue POD 1-60, CRP and cytokines POD 1	Higher WCC, neutrophils and lower pain, nausea, serum IL 6, serum IL 8, peritoneal IL 6, peritoneal IL 13 in steroid group
Vignali et al.	2009	Dis Colon Rectum	Italy	52	Colorectal	Methylprednisolone 30mg/kg IV, 60 mins preop	Pain, FVC, FEV1, CRP, IL 6, IL 8, TNFα	POD 1-5	Higher FVC, FEV1 and lower pain, CRP, IL 6, IL 8 in steroid group
Matsutani et al.	1998	J Surg Res	Japan	33	Oesophageal	Methylprednisolone 10mg/kg at induction	TNFα, IL 6, PT, APTT, AT III	POD 1-7	Higher AT III and lower TNFα, IL 6 in steroid group
Sato et al.	2002	Ann Surg	Japan	66	Oesophageal	Methylprednisolone 10mg/kg at induction	IL 1, IL 6, IL 8, IL 10, cortisol, lymphocytes, neutrophils	POD 1-7	Higher IL 10 and lower IL 1, IL 6, and IL 8 in steroid group
Takeda et al.	2003	J Nippon Med Sch	Japan	17	Oesophageal	Methylprednisolone 10mg/kg IV at induction	Serum and bronchioalveolar IL 6 and IL 8	POD 1	Lower serum IL 6 and IL 8, and lower bronchioalveolar IL 8 in steroid group

Yano et al.	2005	Hepatogastroenterology	Japan	40	Oesophageal	Methylprednisolone 500mg IV 2hrs preop	IL 6, IL 8, IL 10, WCC, rectal pHi, body weight	POD 1-3	Lower IL 6, IL 8 and CRP
Yamashita et al.	2001	Arch Surg	Japan	33	Liver	Methylprednisolone 500mg IV 2hrs preop	IL 6, IL 10, CRP, Bil, AST, ALT	POD 1-7	Higher IL 10 and lower Bil, IL 6, CRP in steroid group
Muratore et al.	2003	Br J Surg	Italy	53	Liver	Methylprednisolone 30mg/kg IV at induction	IL 6, Bil, AST, ALT, PT	POD 1	Lower IL 6 in steroid group
Aldrighetti et al.	2006	Liver Transpl	Italy	73	Liver	Methylprednisolone 500mg IV at induction	IL 6, TNFα, Bil, AST, ALT, PT, platelets, AT III, D-dimer	POD 1-5	Higher AT III, platelets, and lower IL 6, TNFα in steroid group
Schmidt et al.	2007	J Hepatobiliary Pancreat Surgery	Germany	20	Liver	Methylprednisolone 30mg/kg IV 90 mins preop	IL 6, IL 8, IL 10, CRP, TNFα, HLA-DR, Bil		Lower IL 6, IL 8, CRP, TNFα, Bil in steroid group

POD postoperative day, *IV* intravenous, *IL* interleukin, *CRP* C-reactive protein, *TNF* tumour necrosis factor, *WCC* white cell count, *FVC* forced vital capacity, *FEV* forced expiratory volume, *ADH* anti-diuretic hormone, *AT* antithrombin, Bil bilirubin, *AST* aspartate transaminase, *ALT* alanine transaminase, *PT* prothrombin time, *HLA* human leukocyte antigen

13.6 Figures and Legends

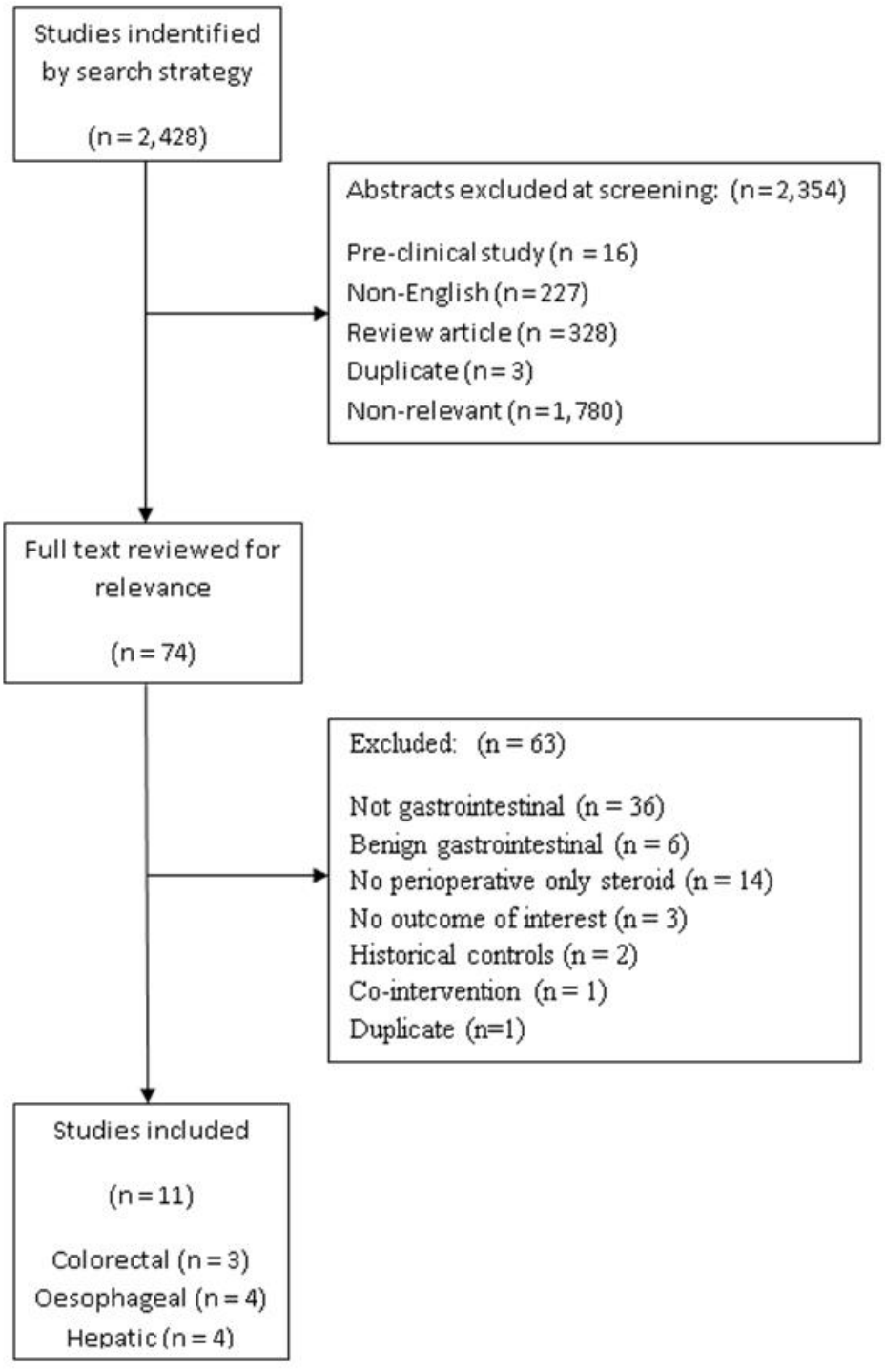

Figure 13-1: PRISMA flow chart of study selection

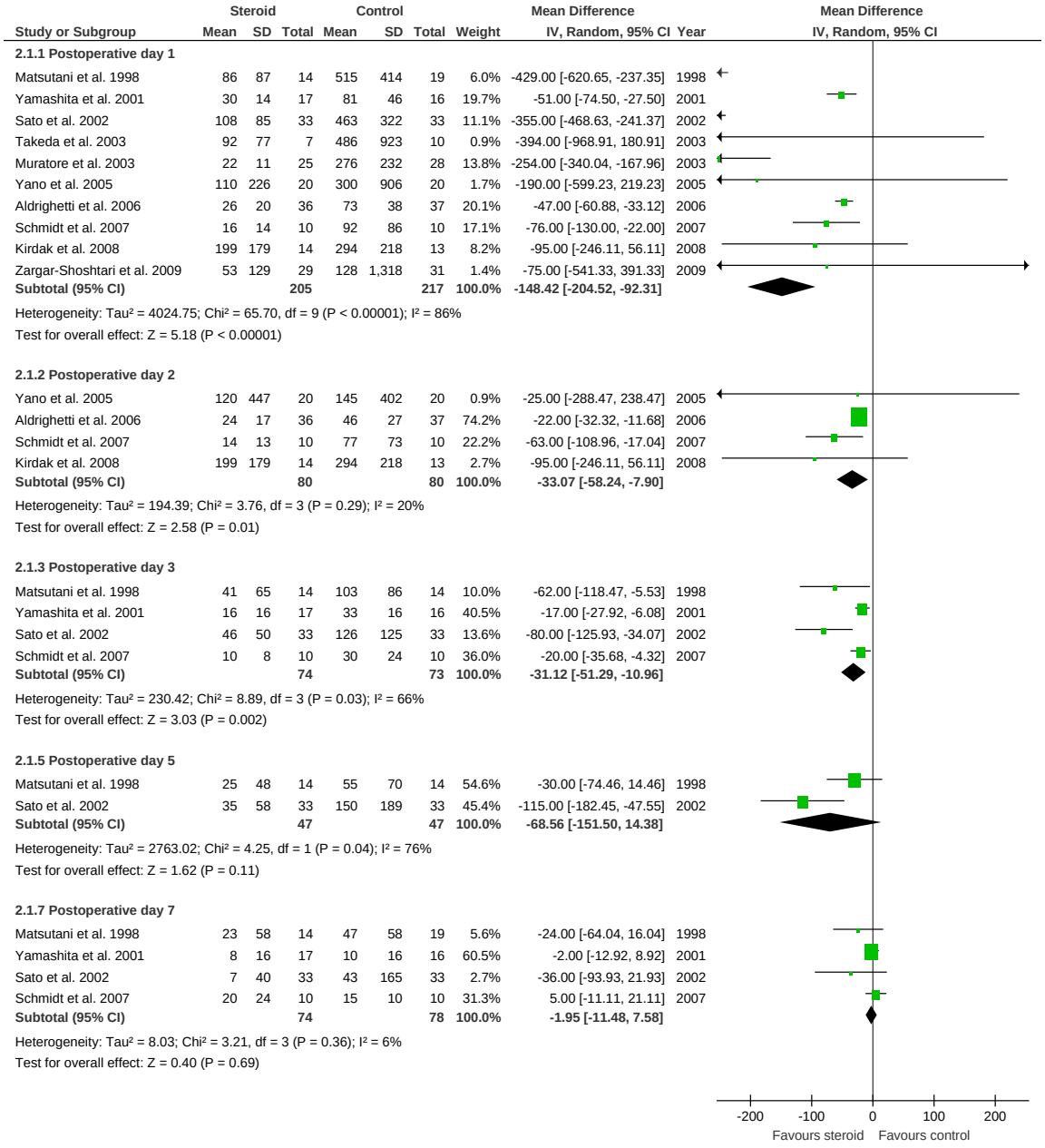

Figure 13-2: Impact of preoperative corticosteroids on serum interleukin 6 following surgery for gastrointestinal cancer

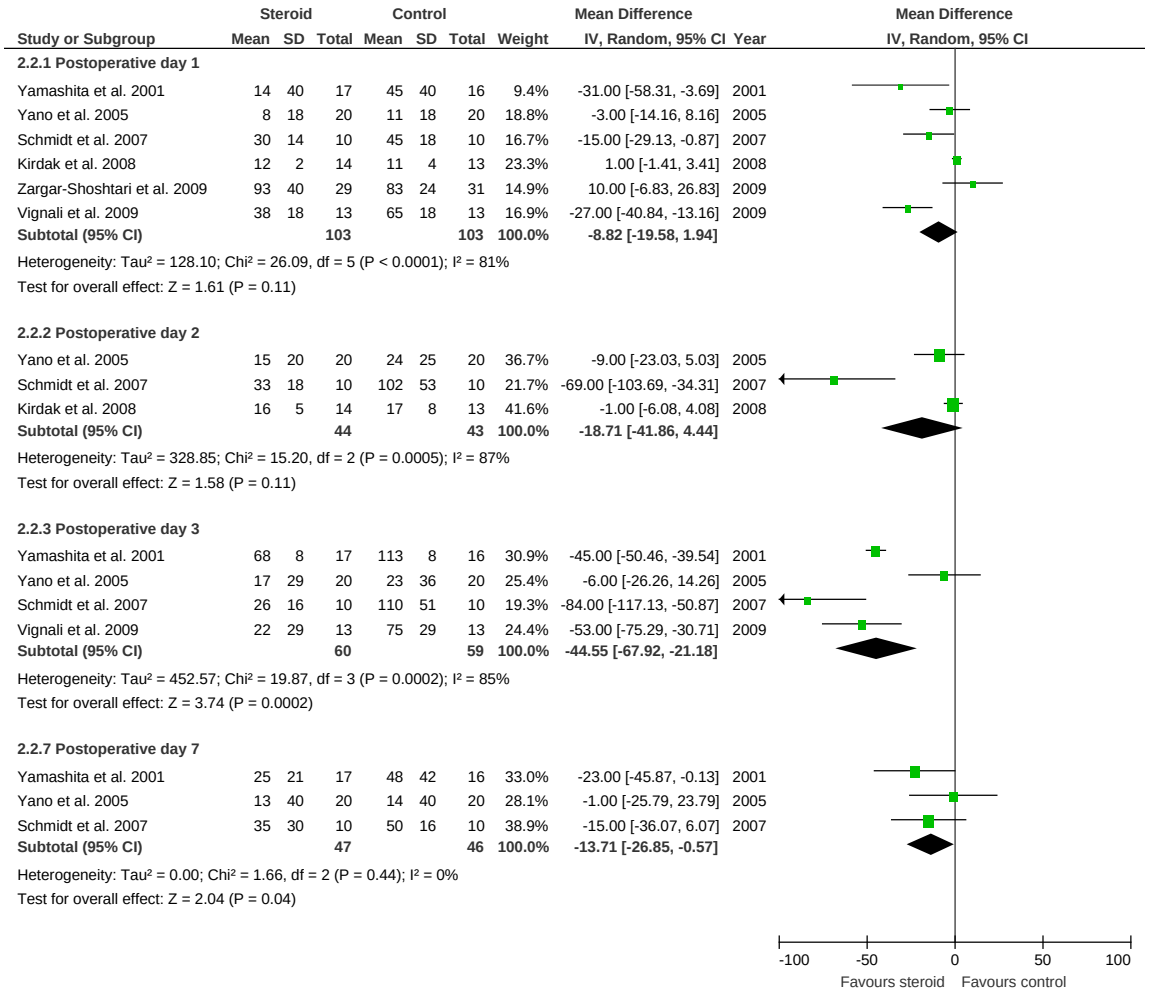

Figure 13-3: Impact of preoperative corticosteroids on serum C-reactive protein following surgery for gastrointestinal cancer

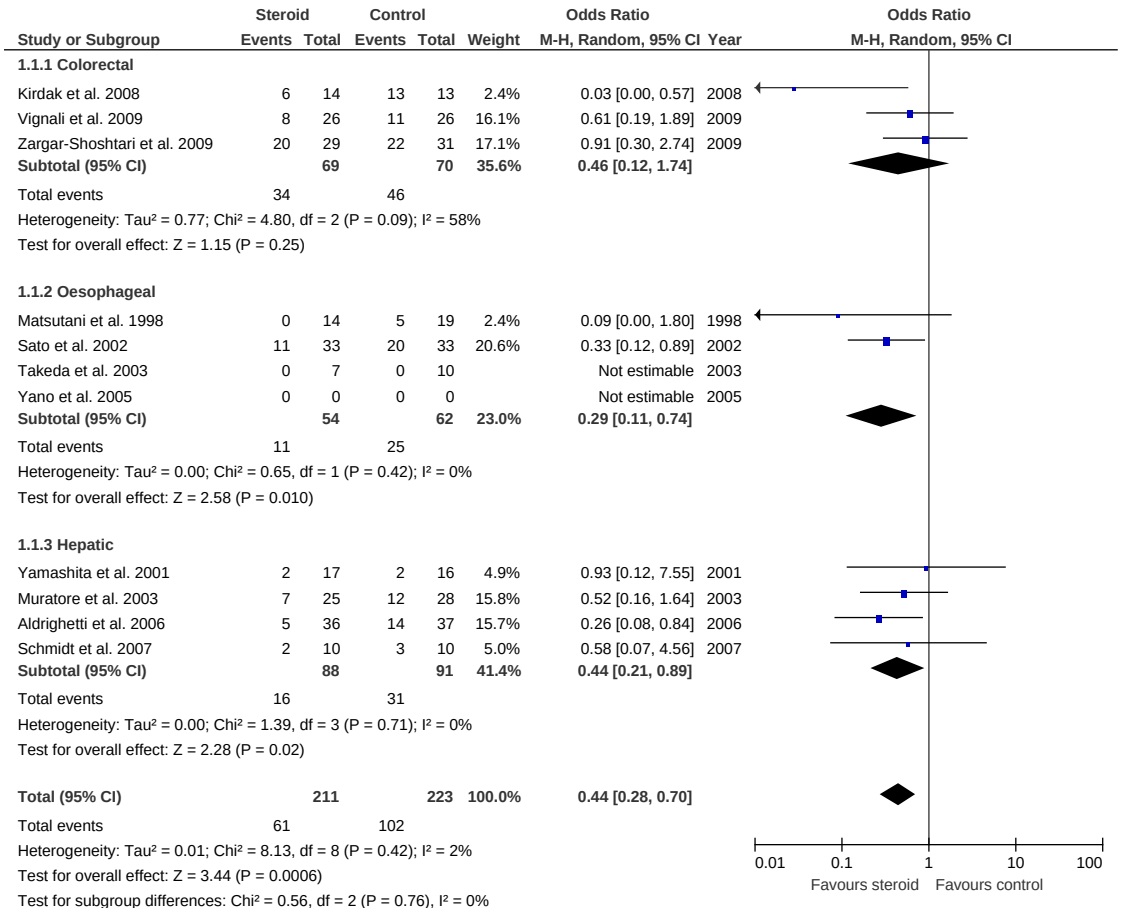

Figure 13-4: Impact of preoperative corticosteroids on all postoperative complications following surgery for gastrointestinal cancer

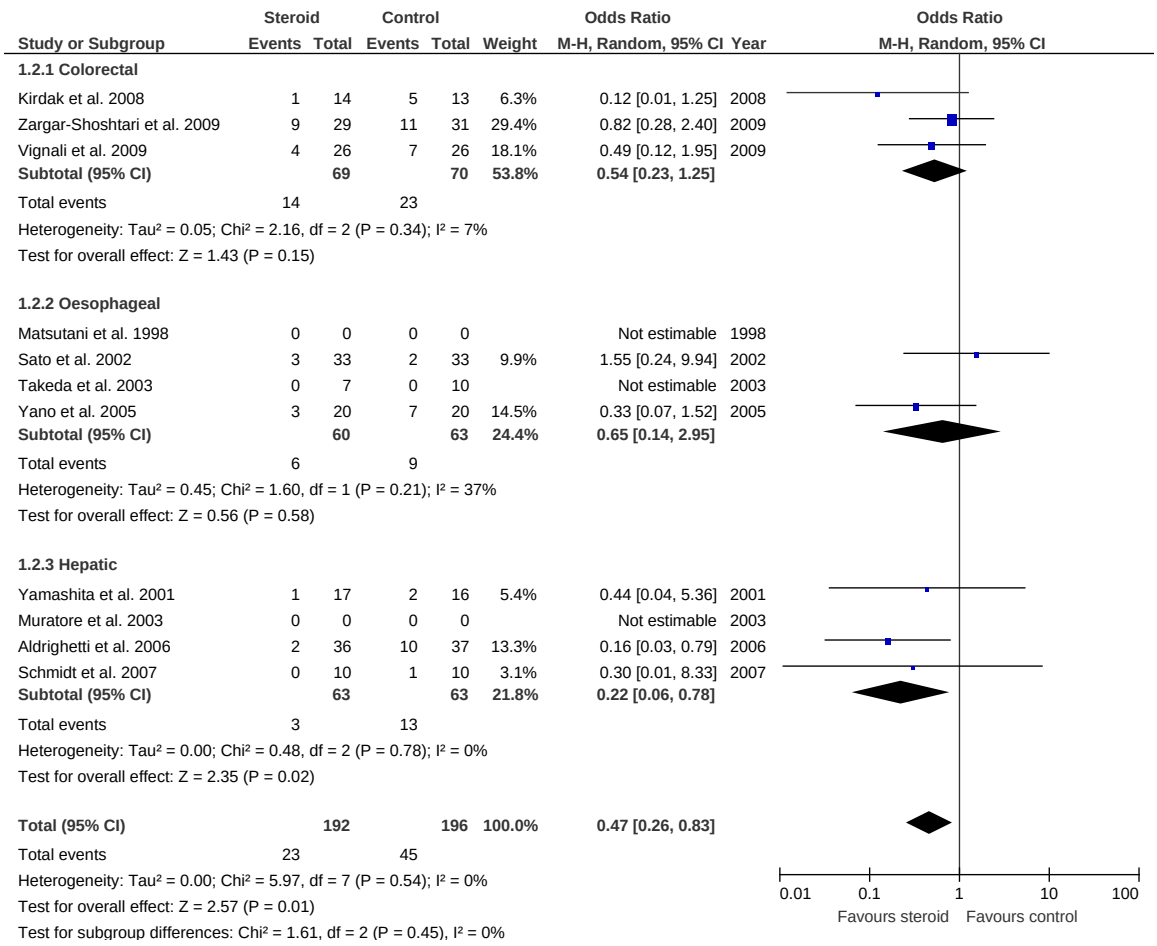

Figure 13-5: Impact of preoperative corticosteroids on infective postoperative complications following surgery for gastrointestinal cancer

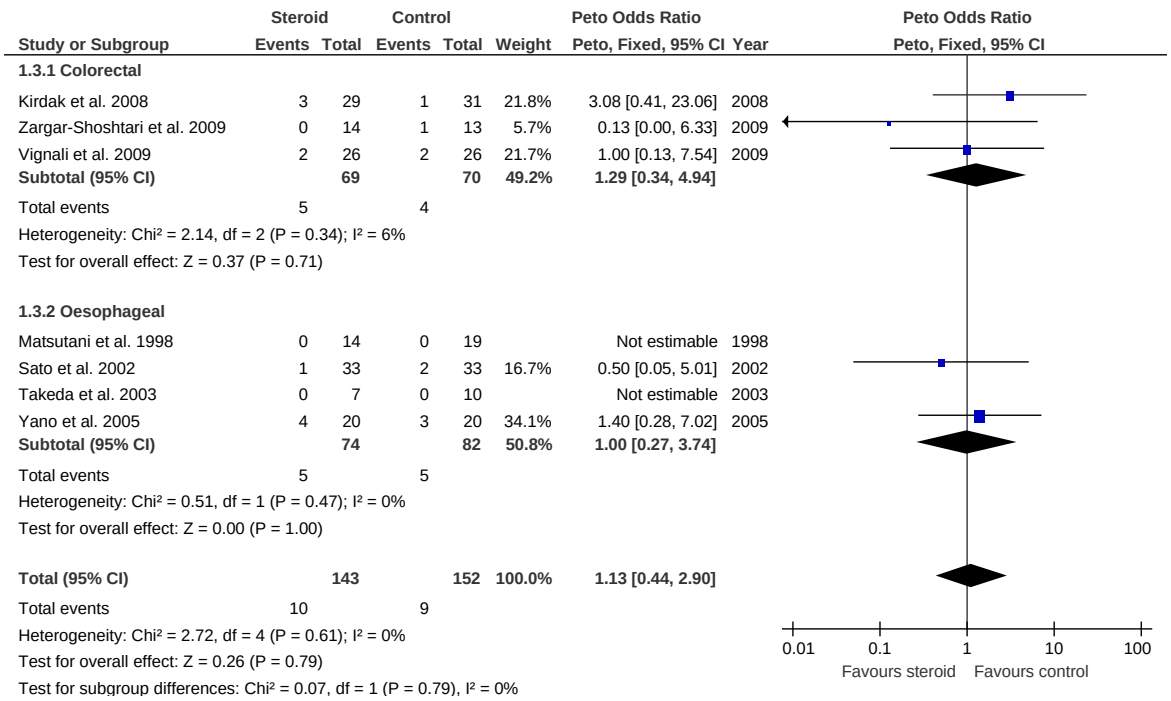

Figure 13-6: Impact of preoperative corticosteroids on anastomotic leak following surgery for gastrointestinal cancer

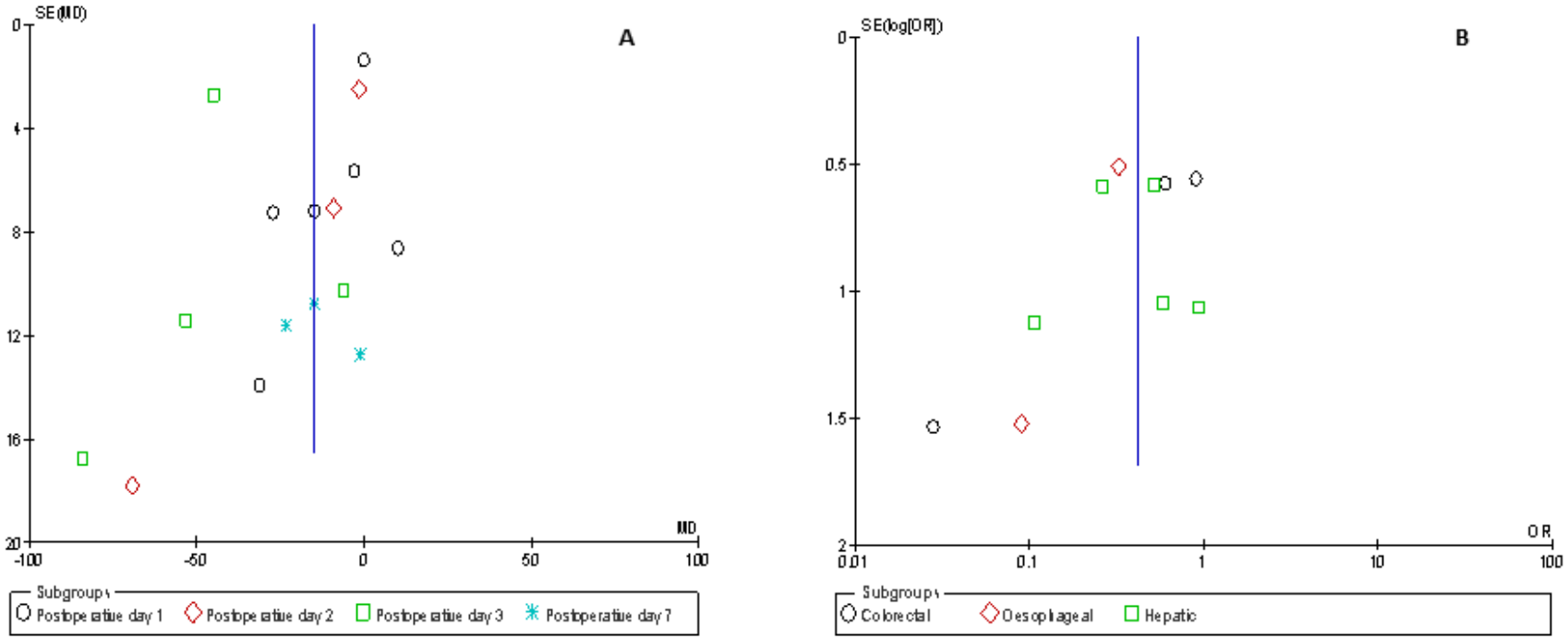

Figure 13-7: Funnel plots of studies reporting the impact of preoperative corticosteroids on (A) C-reactive protein, and (B) complications following surgery for gastrointestinal cancer

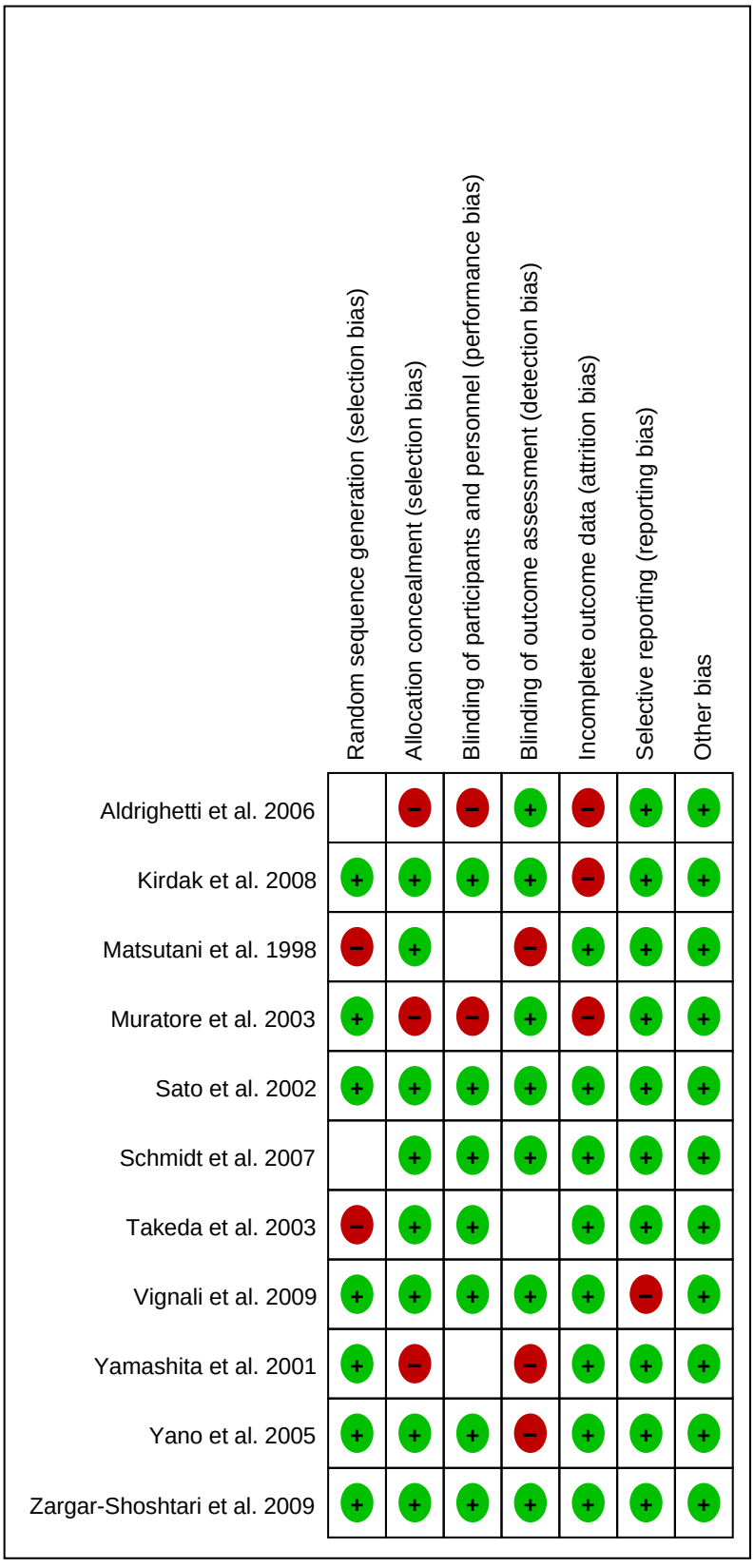

Figure 13-8: Risk of bias summary of included studies (green symbol=low risk, red symbol=high risk, empty=unclear risk)

14 The impact of preoperative dexamethasone on the magnitude of the postoperative systemic inflammatory response and complications following surgery for colorectal cancer

14.1 Introduction

There is good evidence that, compared with open surgery, laparoscopic surgery is associated with a reduction in the postoperative systemic inflammatory response (Watt et al. 2015c). However, no definite causal relationship has yet been defined between attenuation of the postoperative systemic inflammatory response and postoperative complications. Furthermore, it remains to be seen whether strategies which attenuate the postoperative systemic inflammatory response may also reduce postoperative complication rates.

Corticosteroids, administered at the induction of anaesthesia are associated with the prevention of postoperative nausea and vomiting (Karanicolas et al. 2008). Indeed, preoperative dexamethasone has now been integrated into many "enhanced recovery" and "fast track" perioperative care protocols, although the underlying mechanism remains unclear (Watt et al. 2015d). Also, there is evidence that preoperative administration of corticosteroids is associated with a reduction in the postoperative systemic inflammatory response following abdominal surgery (Srinivasa et al. 2011, McSorley Chapter 13).

The meta-analysis performed in the previous chapter reported a reduction in postoperative complications in patients given corticosteroids at the time of hepatic and oesophagogastric surgery. However, when the same analysis was performed in a subgroup of RCTs of patients undergoing surgery for colorectal cancer, the association did not reach statistical significance (McSorley Chapter 13). This may be due to the small number of such studies performed in colorectal cancer surgery.

Therefore, the aim of the present study was to examine the impact of preoperative dexamethasone on the magnitude of the postoperative systemic inflammatory response and complications following surgery for colorectal cancer. A propensity score analysis was performed due to significant imbalances in patient and operative variables potentially associated with both the postoperative systemic inflammatory response and complications.

14.2 Patients and Methods

14.2.1 Patients

This retrospective observational study of a prospectively collected database included patients who underwent resection with curative intent for histologically confirmed colorectal cancer in a single centre between 2008 and 2016. Patients without available anaesthetic records, receiving long term steroids, who had existing inflammatory conditions, who had emergency surgery, or metastatic disease were not included in the analysis.

Clinical, radiological, and pathological data of all patients were reviewed by a specialist colorectal oncology multi-disciplinary team before and after surgery. All patients received prophylactic antibiotics and venous thromboprophylaxis prior to the induction of anaesthesia as per hospital policy. The use of epidural anaesthesia was at the discretion of the anaesthetic and surgical teams. Patients were given dexamethasone intravenously prior to the induction of anaesthesia, and at the discretion of the anaesthetist, to reduce the likelihood of postoperative nausea and vomiting.

On each postoperative day patients were clinically assessed and had blood samples, including serum CRP, obtained as standard until discharged. Further postoperative investigation and intervention was at the discretion of the patient's surgical team who were not blind to serum CRP results.

14.2.2 Methods

Clinicopathological data was collected prospectively in a database, anonymised, and were subsequently analysed. Recorded information included patient demographics, tumour site, TNM stage (TNM, 5th ed, AJCC), surgical approach, complications, preoperative and postoperative serum CRP measurements.

Serum concentrations of CRP (mg/L) were measured using an autoanalyzer (Architect; Abbot Diagnostics, Maidenhead, UK) with a lower detectable limit of 0.2 mg/L, as was serum albumin (normal range 35-50g/L). Exceeding the established CRP threshold of 150 mg/L on postoperative days 3 or 4 was recorded (McDermott et al. 2015). The preoperative modified Glasgow Prognostic Score (mGPS) was calculated in patients for whom preoperative serum CRP and albumin were available (McMillan 2013).

Data regarding the use of dexamethasone for the prevention of postoperative nausea and vomiting at induction of anaesthesia, the use of epidural anaesthesia, and the need for intraoperative blood transfusion were collected by retrospective review of anaesthetic notes.

Complications were recorded and categorised by severity using the Clavien Dindo scale (Dindo et al. 2014). Infective complications were categorised as described elsewhere and summarised here briefly (Platt et al. 2012). Wound (superficial surgical site) infection was defined as the presence of pus either spontaneously discharging from the wound or requiring drainage. Deep surgical site infection was defined as surgical or image-guided drainage of intra-abdominal pus. Anastomotic leak was defined as radiologically verified fistula to bowel anastomosis or diagnosed at laparotomy. Pneumonia was defined by fever above 38.5^{o}C and consolidatory chest X-ray findings requiring antibiotic treatment. Septicaemia was defined by the presence of sepsis combined with positive blood culture. Urinary tract infection (UTI) was only included if complicated by septicaemia and confirmed with positive urine culture.

The study was approved by the West of Scotland Research Ethics Committee, Glasgow, as part of surgical audit.

14.2.3 Statistical Analysis

In the initial unmatched cohort, categorical data were compared using the Chi square test. Data regarding postoperative CRP were non-normal and are presented as medians and ranges. Medians of two groups were compared using the Mann-Whitney U test. The treatment effect of preoperative dexamethasone in terms of exceeding the postoperative CRP threshold and complications was displayed as odds ratios (OR) and 95% confidence intervals (CI). The magnitude of CRP by each postoperative day was displayed graphically as 95% confidence intervals of the median.

Multivariate logistic regression was used to generate a propensity score for each patient, predicting the probability of having received preoperative dexamethasone or not, based on the following variables thought to be associated with the postoperative systemic inflammatory response or complications: age, sex, BMI, smoking status, ASA score, mGPS, tumour site, TNM stage, nCRT, surgical approach (open or laparoscopic), operation duration, blood transfusion, stoma formation, and the use of epidural anaesthesia.

Patients who received preoperative dexamethasone were then matched 1:1 with a patient who did not, using the closest propensity score on the logit scale (calliper <0.05, order of match selection randomised). Categorical data were compared using McNemar's test. Continuous data were compared using the related samples Wilcoxon sign rank test. The appropriateness of the propensity score matching was assessed visually by frequency of propensity scores in each group before and after matching. In addition, the propensity scores were included as a linear covariate alongside preoperative dexamethasone in multivariate binary logistic regression models for exceeding the postoperative day 3 CRP threshold and postoperative complications. Finally, the propensity scores were used to stratify the patients by quintiles, from which an average treatment effect was calculated for both the postoperative day 3 CRP threshold and postoperative complications as an OR and 95% CI.

In all tests, a two sided p value <0.05 was considered statistically significant. Propensity scoring, matching, and all statistical analyses were performed using IBM SPSS version 22 for Windows (Chicago, IL, USA).

14.3 Results

14.3.1 Patient characteristics

In total, 556 patients were included in the study (Table 14-1) of which 310 were male (56%) and 360 (65%) were over 65 years old. Most had colonic (355, 64%) and node negative disease (375, 67%). Laparoscopic resection was performed in 212 patients (38%) with the remainder having open surgery. A postoperative complication occurred in 234 cases (42%), of which 151 (27%) were infective and 47 (8%) were classified Clavien Dindo grade 3-5 severity. Anastomotic leak occurred in 19 cases (3%). There were 5 (1%) postoperative deaths.

14.3.2 Impact of dexamethasone in all patients

In the unmatched cohort, exceeding the CRP threshold of 150mg/L on postoperative day 3 was significantly associated with higher rates of any complication (60% vs 29%, OR 3.60, $p<0.001$), infective complication (42% vs. 16%, OR 3.87, $p<0.001$), anastomotic leak (6% vs. 1%, OR 4.16, $p=0.011$), and Clavien Dindo grade ≥3 complications (13% vs. 5%, OR 3.10, $p=0.001$). In the unmatched cohort (Table 14-1), 311 patients (56%) received dexamethasone at induction of anaesthesia, of which 194 received 4mg and 117 received 8mg, while 245 (44%) did not. There were significant differences between those patients who did receive preoperative dexamethasone and those who did not, in ASA score ($p=0.003$), preoperative mGPS ($p=0.007$), laparoscopic surgery (52% vs. 20%, $p<0.001$), surgery lasting more than 4 hours (41% vs. 23%, $p<0.001$), blood transfusion (3% vs. 9%, $p=0.002$), and epidural anaesthesia (28% vs. 64%, $p<0.001$). A significantly lower proportion of those who received preoperative dexamethasone exceeded the established CRP threshold of 150mg/L on postoperative day 3 (33% vs. 55%, $p<0.001$) but not on day 4. Preoperative dexamethasone was significantly associated with fewer postoperative complications (36% vs. 50%, OR 0.40, $p=0.001$) and infective complications (23% vs. 32%, OR 0.57, $p=0.021$) but not anastomotic leak or complication severity.

14.3.3 Impact of dexamethasone in propensity score matched cohort

Propensity scores could not be assigned to 156 patients due to missing covariate data, leaving 400 patients with propensity scores, of which 262 had received dexamethasone at induction of anaesthesia and 138 did not (Figure 14-1). 276 patients (138 from each

group) were matched based on their propensity score, with a subsequent improvement in the balance of the distribution of propensity scores in each group (Figure 14-2).

In the propensity score matched cohort, exceeding the CRP threshold of 150mg/L on postoperative day 3 was significantly associated with higher rates of any complication (59% vs 28%, OR 3.58, p<0.001), infective complication (44% vs. 15%, OR 4.38, p<0.001), and Clavien Dindo grade ≥3 complications (13% vs. 6%, OR 2.56, p=0.032), but not anastomotic leak (7% vs. 2%, OR 3.29, p=0.068). Following propensity score matching the distribution of patient and operative variables was balanced between the two groups (Table 14-2). A significantly lower proportion of those who received preoperative dexamethasone exceeded the established CRP threshold of 150mg/L on postoperative day 3 (36% vs. 56%, OR 0.42, p=0.001) but not on day 4. Preoperative dexamethasone was significantly associated with fewer postoperative complications (34% vs. 49%, OR 0.53, p=0.001).

14.3.4 Sensitivtiy analyses using other propensity score methods

Analysis of the impact of preoperative dexamethasone on exceeding the postoperative day 3 CRP threshold (Table 14-3) found a similarly statistically significant probability reduction using regression adjustment (OR 0.53, 95% CI 0.34-0.83), propensity score stratification (OR 0.41, 95% 0.25-0.57), and propensity score matching (0.42, 95% CI 0.26-0.70). The same analysis of the impact of preoperative dexamethasone on postoperative complications (Table 14-3) found a similarly statistically significant probability reduction using regression adjustment (OR 0.62, 95% CI 0.40-0.96), propensity score stratification (OR 0.62, 95% 0.29-0.95), and propensity score matching (0.53, 95% CI 0.33-0.86).

14.3.5 Time dependent effect of preoperative dexamethasone

Dexamethasone at the induction of anaesthesia had a similar time dependent effect on postoperative CRP in both the unmatched and matched cohorts. There was a significant reduction in CRP on postoperative days 1 to 3 in those given dexamethasone, with similar CRP concentrations observed in both groups from postoperative day 4 onward.

14.4 Discussion

The present study reports that dexamethasone, given at the induction of anaesthesia prior to surgery for colorectal cancer, was associated with a reduction in the magnitude of the postoperative systemic inflammatory response and fewer postoperative complications.

Currently, corticosteroids are given in the perioperative period to reduce postoperative nausea and vomiting (Karanicolas et al. 2008, Watt et al. 2015d). However, when taken together with existing evidence (McSorley Chapter 13, Laaninen et al. 2016), the results of the present study also suggest an important role for reducing the complication rate following surgery for colorectal cancer by attenuating the postoperative stress response. Indeed, the use of preoperative corticosteroids represents a potentially simple and cost effective method of improving surgical outcomes for a large surgical population. It was of interest that postoperative CRP retained its association with postoperative complications in those patients who had received preoperative dexamethasone. In particular, the CRP threshold of 150mg/L on postoperative day 3 remained significantly associated with all complications, and infective complications, in this group of patients in whom the magnitude of the postoperative systemic inflammatory response was lower as a whole. Indeed, the results of the present study suggest that the measurement of postoperative CRP in this subgroup remains useful in the clinical setting. For these reasons, the present study in colorectal cancer is timely.

There remain long standing concerns that corticosteroids may inhibit collagen formation and, therefore, wound healing in the post-operative period. However, neither the present study, or previous meta-analyses, have identified a significant negative association with either wound complications or anastomotic leak (Srinivasa et al. 2011, McSorley Chapter 13). Furthermore, there have been some concerns that preoperative corticosteroids may have a negative impact on oncologic outcome following surgery for colorectal cancer, however the evidence for this is limited in both numbers and length of follow up (Singh et al. 2014b).

The mechanisms by which corticosteroids exert their anti-inflammatory action remain poorly understood. Inhibition of nuclear factor κB (NF- κB) leads to a downregulatory effect on lymphoid tissue and thus adaptive immune responses (Chu et al. 2014). In addition, attenuation of the innate immune response and myeloid tissues occurs as a consequence of reduction of the transcription of pro-inflammatory cytokines such as IL 6,

alongside the inhibition of cyclo-oxygenase dependent pathways by increasing transcription of lipocortins (Leung et al. 2003, Rhen et al. 2005).

An important implication of the present and previous results is that postoperative complications are themselves recognised to have a negative impact on oncologic outcomes (McSorley Chapter 4). Indeed, the generation of a pro-metastatic environment through systemic inflammation, as part of the surgical injury and the severity of postoperative complications, has been proposed to promote metastatic disease progression (McAllister et al. 2014). Furthermore, it has been proposed that this host response to both the tumour and surgery should become a target for intervention (Roxburgh et al. 2013). Indeed, it may be hypothesised that a reduction in the magnitude of the postoperative systemic inflammatory response with a consequent reduction in postoperative complication rates may improve long-term outcomes following surgery for colorectal cancer. Strategies such as the prospective evaluation of perioperative corticosteroids represent a logical starting point.

The main limitation of the present study was its retrospective nature. This lead to some missing data both clinicopathological and in terms of postoperative CRP measurements. Significant imbalance between the two groups meant that propensity score matching was used to obtain balanced groups for determination of the treatment effect. However, this resulted in the exclusion of a significant proportion of patients and does not necessarily help those confounders that are either unmeasured or unknown (Austin 2011). However, it was reassuring that the overall treatment effect and its magnitude were similar amongst the unmatched cohort, the matched cohort, and when propensity regression was applied (Shida et al. 2016). Dexamethasone was used throughout the study period although was never "routine" or part of a formal protocol and was used at the discretion of the anaesthetist. The proportion of patients receiving dexamethasone changed from around 30% during the first half of the study period to around 50% in the second half of the study period. This change was in line with the increasing use of minimally invasive surgery. This may represent a potential source of bias which matching cannot adjust for. In addition, the nature of the analysis prevented the assessment of any dose response relationship.

In summary, the results of the present study suggest that the use of preoperative corticosteroids is associated with both attenuation of the magnitude of the systemic inflammatory response and fewer complications, following surgery for colorectal cancer. This adds evidence to the hypothesis that the magnitude of the postoperative systemic inflammatory response and postoperative complications are causally related. Optimal

doses and treatment regimens are yet to be determined. Indeed, further prospective randomized trials are necessary before recommendations regarding the use of preoperative dexamethasone in the context of the postoperative systemic inflammatory response can be made.

14.5 Tables and Footnotes

Table 14-1: Association between clinicopathological characteristics, perioperative factors, and preoperative dexamethasone in patients undergoing surgery for colorectal cancer (n=556)

Characteristic	All	Preoperative dexamethasone		P
		No	Yes	
N	556	245	311	-
Age (<65/65-74/>74)	196/219/141	85/88/72	111/131/69	0.214
Sex (male/female)	310/246	139/106	171/140	0.731
BMI (<20/20-25/26-30/>30)	38/170/172/156	14/74/65/76	24/96/107/80	0.242
Smoking (never/ex/current)	251/223/73	114/94/34	137/129/39	0.706
ASA score (1/2/3/4)	136/248/155/16	50/108/74/13	86/140/81/3	0.003
Preop mGPS (0/1/2)	429/40/48	179/21/29	250/19/19	0.007
Site (colon/rectum)	355/201	159/86	196/115	0.658
TNM stage (0/I/II/III)	13/127/229/181	5/47/112/80	8/80/117/101	0.261
Neoadjuvant treatment (yes/no)	82/466	34/209	48/257	0.630
Approach (open/lap)	337/212	195/49	142/163	<0.001
Surgery >4h (yes/no)	183/370	57/187	126/183	<0.001
Intraop transfusion (yes/no)	29/517	21/221	8/296	0.002
Stoma (yes/no)	164/390	72/173	92/217	0.926
Epidural (yes/no)	244/308	158/87	86/221	<0.001
POD 3 CRP (median,range,mg/L)	138 (9601)	166 (22-601)	118 (9-430)	<0.001
POD 3 CRP >150 mg/L (yes/no)	239/292	136/101	103/191	<0.001
POD 4 CRP (median,range,mg/L)	112 (13-528)	118 (13-528)	105 (15-415)	0.018
POD 4 CRP >150 mg/L (yes/no)	153/308	79/142	74/166	0.277
POD 3 albumin (median,range,g/L)	26 (7-40)	25 (14-35)	27 (7-40)	<0.001
POD 3 albumin <25g/L (yes/no)	189/332	104/130	85/202	0.001
POD 4 albumin (median,range,g/L)	26 (13-35)	25 (14-35)	27 (13-35)	<0.001
POD 4 albumin <25g/L (yes/no)	170/285	97/121	73/164	0.003
Any complication (yes/no)	234/321	122/123	112/198	0.001
Infective complication (yes/no)	151/404	79/166	72/238	0.021
Anastomotic leak (yes/no)	19/536	12/233	7/303	0.103
Clavien Dindo (0-2/3-5)	47/508	23/222	24/286	0.540
Thirty day mortality (yes/no)	5/550	3/242	2/308	0.659
Adjuvant treatment (yes/no)	152/325	61/165	91/160	0.031

BMI body mass index. *ASA* American Society of Anaesthesiologists. *POD* postoperative day. *CRP* C-reactive protein, *mGPS* preoperative modified Glasgow Prognostic score, *CR-POSSUM* Colorectal Physiologic and Operative Severity Score for the Enumeration of Mortality and Morbidity

Table 14-2: Association between preoperative dexamethasone and outcomes in propensity score matched patients undergoing surgery for colorectal cancer (n=276)

Characteristic	All	Preoperative dexamethasone		P
		No	Yes	
N	276	138	138	-
Age (<65/65-74/>74)	102/106/68	54/49/35	48/57/33	-
Sex (male/female)	161/115	79/59	82/56	-
BMI (<20/20-25/26-30/>30)	16/97/82/81	8/54/34/42	8/43/48/39	-
Smoking (never/ex/current)	130/113/33	64/52/11	66/61/11	-
ASA score (1/2/3/4)	72/116/80/8	36/59/37/6	36/57/43/2	-
Preop mGPS (0/1/2)	224/26/26	107/15/16	117/11/10	-
Site (colon/rectum)	170/106	86/52	84/54	-
TNM stage (0/I/II/III)	7/69/109/91	4/30/60/44	3/39/49/47	-
Neoadjuvant treatment (yes/no)	49/227	25/113	24/114	-
Approach (open/lap)	184/92	93/45	91/47	-
Surgery >4h (yes/no)	94/182	44/94	50/88	-
Intraop transfusion (yes/no)	13/263	6/132	7/131	-
Stoma (yes/no)	90/186	43/95	47/91	-
Epidural (yes/no)	132/144	66/72	66/72	-
POD 3 CRP (median,range,mg/L)	143 (17-430)	166 (22-382)	126 (17-430)	<0.001
POD 3 CRP >150 mg/L (yes/no)	123/145	75/58	48/87	0.001
POD 4 CRP (median,range,mg/L)	121 (13-415)	121 (13-369)	121 (19-415	0.241
POD 4 CRP >150 mg/L (yes/no)	80/158	46/75	34/83	0.349
POD 3 albumin (median,range,g/L)	26 (7-35)	25 (15-35)	26 (7-35)	0.058
POD 3 albumin <25g/L (yes/no)	96/166	52/78	44/88	0.392
POD 4 albumin (median,range,g/L)	26 (14-35)	25 (14-35)	26 (16-35)	0.768
POD 4 albumin <25g/L (yes/no)	88/150	48/72	40/78	0.749
Any complication (yes/no)	115/161	68/70	47/91	0.009
Infective complication (yes/no)	78/198	45/93	33/105	0.134
Anastomotic leak (yes/no)	13/263	9/129	4/134	0.227
Clavien Dindo (0-2/3-5)	26/250	17/121	9/129	0.152
Thirty day mortality (yes/no)	2/274	2/136	0/138	-
Adjuvant treatment (yes/no)	65/168	31/92	34/76	0.728

BMI body mass index. *ASA* American Society of Anaesthesiologists. *POD* postoperative day. *CRP* C-reactive protein, *mGPS* preoperative modified Glasgow Prognostic score,

Table 14-3: Odds ratios for exceeding the C-reactive protein threshold of 150mg/L on postoperative day 3, and postoperative complications, with respect to preoperative dexamethasone across the propensity score methods

Propensity Score Model	n	POD 3 CRP >150mg/L OR (95%CI)	Complication OR (95% CI)
Unadjusted	556	0.40 (0.28-0.57)	0.57 (0.41-0.80)
Regression adjustment	400	0.53 (0.34-0.83)	0.62 (0.40-0.96)
Stratification by quintiles (ATE)	400	0.41 (0.25-0.57)	0.62 (0.29-0.95)
Matched 1:1	276	0.42 (0.26-0.70)	0.53 (0.33-0.86)

POD postoperative day, *CRP* C-reactive protein, *OR* odds ratio, *CI* confidence interval, *ATE* average treatment effect

14.6 Figures and Legends

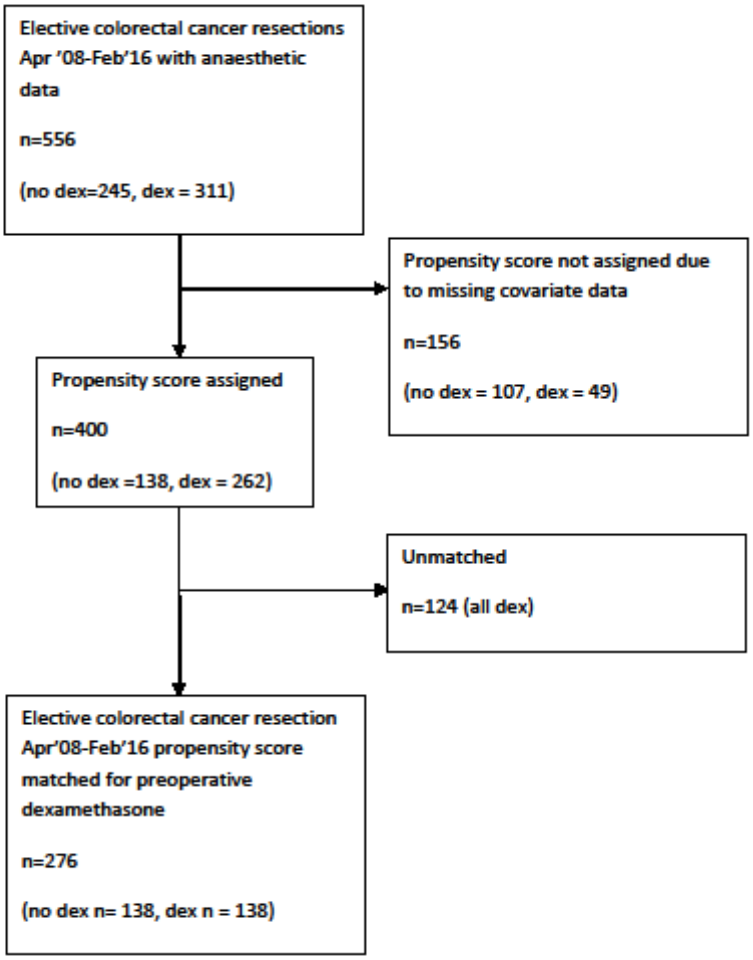

Figure 14-1: Patient flow chart for preoperative dexamethasone before elective surgery for colorectal cancer

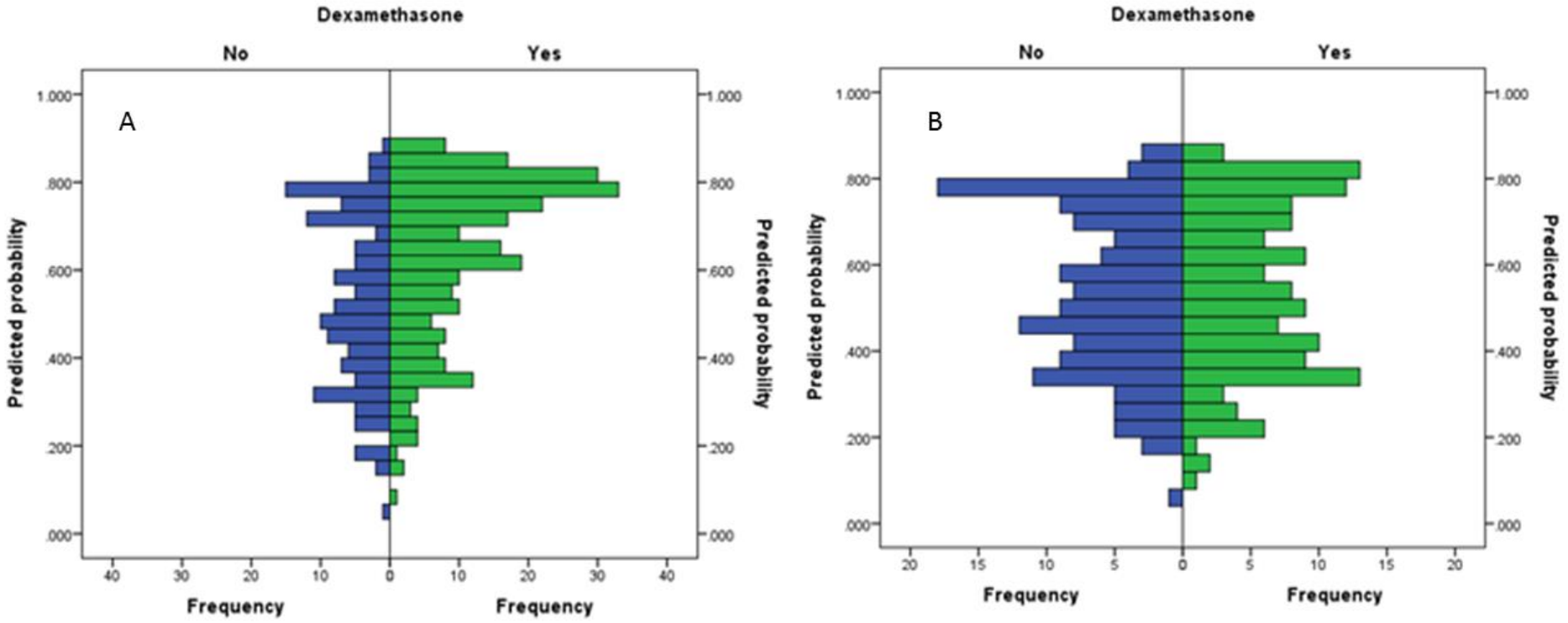

Figure 14-2: Distribution of propensity scores (A) before (n=400) and (B) after matching (n=276)

15 The CORTISONE Trial: CORticosteroids To reduce Inflammation and improve Short-term Outcomes after surgery for colorectal NEoplasia

15.1 Study synopsis

Title of Study:	The CORTISONE Trial: CORticosteroids To reduce Inflammation and improve Short-term Outcomes after surgery for colorectal NEoplasia
Study Centre:	Glasgow Royal Infirmary (GRI), Queen Elizabeth University Hospital (QEUH), Royal Alexandra Hospital (RAH)
Duration of Study:	24 Months
Primary Objective:	To determine whether there is a dose response relationship between perioperative dexamethasone and complications following surgery for colorectal cancer
Secondary Objective:	To determine whether there is a dose response relationship between perioperative dexamethasone and the magnitude of the postoperative systemic inflammatory response following surgery for colorectal cancer
Primary Endpoint:	Proportion of any postoperative complication in each group at first clinic follow up.
Rationale:	The magnitude of the postoperative systemic inflammatory response, measured by CRP, is widely reported to be associated with the development of complications after surgery for colorectal cancer. However, the potentially causal nature of this relationship remains unclear. Observational data suggests that dexamethasone given in the perioperative period to prevent postoperative nausea and vomiting (PONV) is associated with lower CRP on POD 3 and fewer postoperative complications. However, the presence of a dose dependent effect is less clear. This requires

	prospective study as a simple intervention, such as dexamethasone, may significantly improve postoperative morbidity through attenuation of the postoperative systemic inflammatory response.
Methodology:	Multi-centre, double blind, randomised controlled trial
Sample Size:	183
Screening:	Patients will be screened for eligibility at the time of diagnosis with colorectal cancer by the Multi-Disciplinary team meeting.
Registration/Randomisation:	Initial contact at preoperative assessment clinic two weeks prior to surgery. Informed consent will be sought at the Same Day Admissions Units at GRI, QEUH and RAH on the morning of surgery. Patients will be randomised immediately prior to surgery by telephone using a computer generated randomisation key held by the CTU data manager. Randomisation will be stratified by surgical approach; open or laparoscopic resection, and centre.
Main Inclusion Criteria:	Elective surgery for stage I-III colorectal cancer at GRI, QEUH or RAH Male or female aged >18 years Understand verbal and written information in English
Main Exclusion Criteria:	Emergency surgery Metastatic disease

	Existing systemic inflammatory disease; e.g. rheumatoid arthritis (RA), vasculitis, inflammatory bowel disease (IBD) Already prescribed systemic steroids Intolerance or documented prior adverse reaction to dexamethasone/corticosteroids
Product, Dose, Modes of Administration:	Treatment Dexamethasone IV in 100ml normal saline Group 1: 2 x placebo at induction of anaesthesia and POD 1 Group 2: 4mg x 1 at induction of anaesthesia, x1 placebo (normal saline) on POD 1 Group 3: 8mg x 1 at induction of anaesthesia, and 8mg x 1 on POD 1
Duration of Treatment:	Day of surgery and POD 1
Statistical Analysis:	Proportions of patients experiencing postoperative complications, in each treatment group will be compared using the Chi square test, and the treatment effect size will be estimated using odds ratios (OR) and their 95% confidence intervals (CI). Statistical analysis will be performed using SPSS v22 (IBM, Chicago, IL, USA).

15.2 Study flow chart

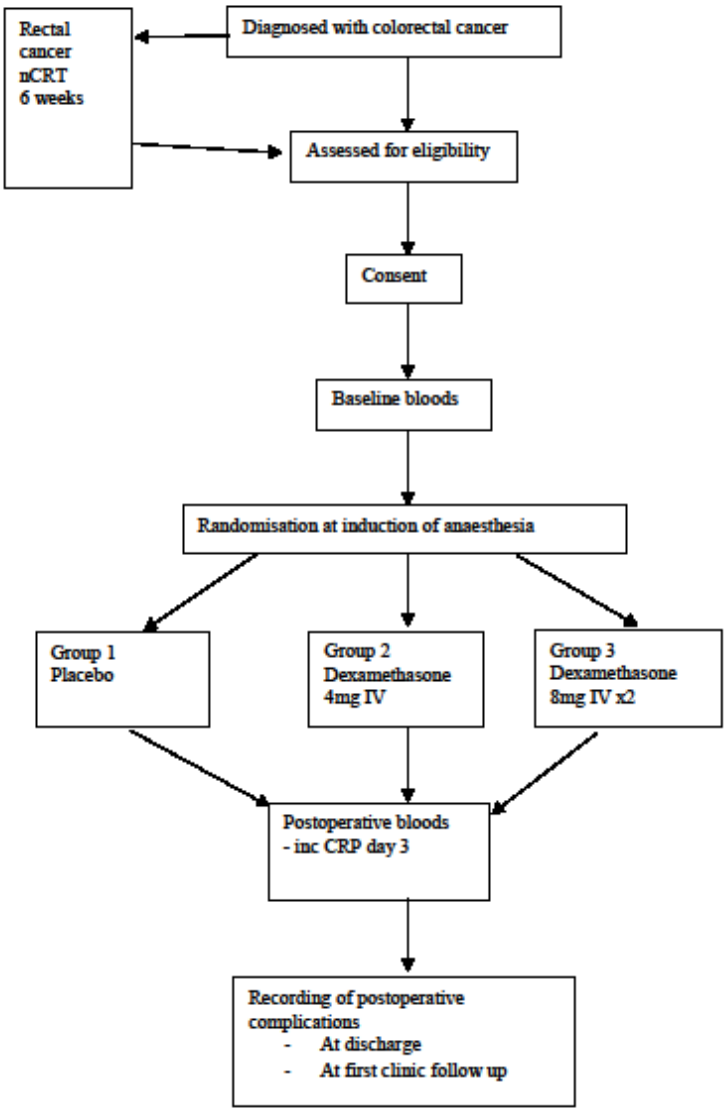

Figure 15-1: Trial flow chart

15.3 Introduction

15.3.1 Background

Colorectal cancer remains a leading cause of mortality in the UK (CRUK 2014). Surgical resection is the cornerstone of curative management but is itself associated with morbidity and mortality (Ghaferi et al. 2011). Long-term survival is primarily related to disease stage, however it is now well recognised that postoperative complications have a negative impact on oncologic outcome (Mirnezami et al. 2011, Artinyan et al. 2015). In addition, they are associated with a significant health care and societal cost due to prolonged hospital stay and delay in return to function.

The routinely measured acute phase marker C-reactive protein (CRP), measured in the postoperative period, has been reported to be a reliable measure of the magnitude of the postoperative systemic inflammatory response (Watt et al. 2015a). Furthermore, an association between the magnitude of this postoperative systemic inflammatory response and the development of postoperative infective complications has been reported following surgery for colorectal cancer (Platt et al. 2012, Singh et al. 2014, Adamina et al. 2015), independent of presentation (Straatman et al. 2016) and surgical approach (Ramanathan et al. 2015). Indeed, threshold concentrations of CRP in the postoperative period have been established to predict the development of severe complications (Selby et al. 2014, McSorley Chapter 3). A recent comprehensive review suggested that CRP concentrations greater than 150mg/L on postoperative days 3 to 5 should prompt investigation of potential postoperative complications such as anastomotic leak (McDermott et al. 2015). However, the nature of the relationship between the postoperative systemic inflammatory response and complications remains unclear. Is high CRP in the postoperative period merely an epiphenomenon of the developing complication or is it causally implicated through immunologic dissonance?

15.3.2 Rationale

Corticosteroids administered at the induction of anaesthesia are associated with the prevention of postoperative nausea and vomiting (PONV) across a variety of surgical specialities (Karanicolas et al. 2008). Indeed, preoperative dexamethasone has now been integrated into many “enhanced recovery” and “fast track” perioperative care protocols (Watt et al. 2015b). At present, dexamethasone forms part of the NHS GG&C Enhanced Recovery After Surgery (ERAS) protocol and, in a recent audit at GRI (unpublished data),

was given to around 80% of patients undergoing colorectal surgery. Despite this, the underlying mechanism by which corticosteroids reduce the risk of PONV remains unclear. In addition, recent meta-analyses of randomized controlled trials have reported that preoperative administration of corticosteroids is associated with a reduction in the postoperative systemic inflammatory response and complications following abdominal surgery, and surgery for gastrointestinal cancers (Srinivasa et al. 2011, McSorley Chapter 13, McSorley Chapter 14). However, there is as yet no evidence of a dose response relationship between steroids, the postoperative systemic inflammatory response, and postoperative complications. Furthermore, it may be that by reducing postoperative complication rate, perioperative corticosteroids can lead to improved long term outcomes. As dexamethasone is now routinely used for the prophylaxis of PONV, an alternative parenteral anti-emetic, ondansetron, will be used perioperatively in both groups.

15.4 Study hypothesis

There is a dose dependent relationship between dexamethasone given in the perioperative period and both complications and the magnitude of the systemic inflammatory response, measured by CRP, following surgery for colorectal cancer.

15.4.1 Primary Endpoint

- Proportion of patients experiencing any postoperative complication, classified by type and Clavien Dindo grade, at first clinic follow up

15.4.2 Secondary endpoints

- Length of hospital stay
- Unplanned readmission within 30 days of surgery
- Proportion of patients exceeding established CRP threshold of 150mg/L on postoperative day 3
- 30 day Mortality
- Health economic analysis
- Postoperative quality of life measures at first clinic follow up
- Multiplex analysis of postoperative cytokines inc IL1, IL 2, IL 6, IL 10, TNF alpha, TNF beta, GM-CSF
- Flow cytometry of postoperative circulating immune cells populations

15.5 Study design

The study design is that of a multi-centre, prospective, double-blind, randomised controlled trial. The three centres, GRI, QEUH and RAH, have been chosen by the investigators due to the similar nature of their multi-disciplinary colorectal cancer care, and perioperative care. The sites each perform around 140 cancer resections per year.

15.5.1 Study Population

The study would aim to include patients undergoing elective colorectal surgery for stage I-III colorectal cancer at GRI, QEUH, and RAH. Inclusion and exclusion criteria are listed below. Patients would be identified for potential inclusion through the weekly Glasgow Colorectal Cancer Multi-Disciplinary Team meetings.

15.5.2 Inclusion criteria

- Patients undergoing elective colorectal surgery for stage I-III colorectal cancer at GRI, QEUH or RAH
- Male and female patients aged ≥18 years
- Able to understand verbal and written information in English

15.5.3 Exclusion criteria

- Emergency surgery
- Metastatic disease (unless planned staged metastastectomy)
- Palliative/defunctioning surgery
- Underlying inflammatory disease (e.g. IBD, RA, vasculitis)
- Already prescribed systemic corticosteroids

15.5.4 Identification of participants and consent

Participants will be identified from the weekly Glasgow Colorectal Cancer Multi-Disciplinary team meetings prior to their preoperative anaesthetic assessment. The trial will first be discussed, and patient information leaflets supplied at the preoperative assessment clinic by the preoperative assessment nurse, usually around two weeks prior to surgery (Appendix A). This will provide patients with adequate time to read the information and contact the investigators with any questions prior to consent being sought. Informed consent will be sought at the Same Day Admissions Units at GRI, QEUH, and RAH on the morning of surgery by a member of the surgical or anaesthetic team (Appendix B).

15.5.5 Withdrawal of subjects

Withdrawal will be permitted at any time prior to, or during, enrolment in the study, at the patient's request, or at the request of the surgical or anaesthetic team providing care. There will be no change to the patient's planned operative care, perioperative care, or follow up. Those patients who do not wish to take part, or withdraw prior to randomisation, may receive intravenous dexamethasone during their surgery as this forms part of the existing NHS GG&C Enhanced Recovery After Surgery (ERAS) protocol. Those patients who do not wish to take part, or withdraw prior to randomisation, will not form part of the study and data-analysis. Any patients withdrawing after randomisation will be included in the intention-to-treat analysis.

15.6 Study Outcome Measures

15.6.1 Primary Outcome Measure

1. Postoperative complications recorded at first clinic return (usually postoperative week 4-6), both by type (e.g. infective and non-infective complications) and severity (by Clavien Dindo grade). The presence of complications will be assessed by the clinical trial nurse, using a standardised pro-forma (Appendix C), blind to the treatment allocation of the patients.

15.6.2 Secondary Outcome Measure

1. The proportion of patients exceeding the threshold serum CRP value of 150mg/L on postoperative day 3. This data will be recorded from the laboratory reporting systems by the local research team.

2. Length of hospital stay. Duration measured from day of surgery to date of discharge. This will be recorded by the local research team.

3. Unplanned readmission within 30 days of surgery. This will be recorded by the local research team.

4. Mortality within 30 days of surgery. This will be recorded by the local research team.

5. Health economic analysis will be performed to examine the cost/benefit implications of routine administration of perioperative dexamethasone at the different doses in comparison to savings relating to postoperative complications and length of stay

6. Quality of life questionnaires (MSAS, FACT-G) will be administered at the first postoperative clinic visit

7. Multiplex analysis of blood samples taken and stored from the immediate postoperative period will be used to compare circulating cytokine profiles between treatment groups

8. Flow cytometry of blood samples taken and stored from the immediate postoperative period will be used to compare circulating immune cell subsets and populations between treatment groups.

15.7 Trial procedures

Table 15-1: Schedule of enrolment, interventions, and assessments

Time period	Pre-surgery		Surgery	Post-surgery		
Visit	Diagnosis/ MDT - 2 weeks to surgery	Preassessment clinic - 1 week to surgery	Operative day	Postop - days 3+4	Postop discharge - days 5-7	Outpatient clinic - 6 weeks
Identification	x					
Eligibility	x					
Consent		x				
Demographics		x				
Medical history		x				
Baseline bloods		x				
Randomisation			x			
Intervention (placebo/4mg/8 mg x 2 dexamethasone IV)			x			
Postoperative bloods (CRP and albumin)				x		
Postoperative complication recording					x	x

15.7.1 Preoperative period

Following identification of patients suitable for study inclusion at the MDT around 2 weeks prior to surgery, patients will be invited to participate by post which includes the participant information sheet and consent form. At the pre-assessment clinic, around 1 week prior to surgery, data including demographics, comorbidities, and medication will be recorded, as is the usual standard of care. The completed pre-assessment documentation will then be used to exclude those patients meeting the above criteria. The Clinical Research Fellow will meet the patient at their pre-assessment clinic visit. The trial will be discussed and the patient will be invited to give informed written consent to participate. In addition, baseline routine blood tests will be taken at the pre-assessment clinic including haemoglobin, CRP, and albumin, which is the usual standard of care.

15.7.2 Day of surgery

Patients will attend the Same Day Admission Unit on the morning of surgery, usually around 2 weeks prior to surgery, as per unit standard protocol. Written informed consent will be sought on the morning of the procedure if it has not already been sought at pre-

assessment. Written informed consent is required prior to any trial specific interventions being performed. Those procedures which form part of the usual standard care can be carried out in advance of such consent. The use of conventional open or laparoscopic surgery will be at the discretion of the consultant surgeon. Patients who are eligible and consent to take part in the trial will be computer randomised in the anaesthetic room immediately prior to the induction of anaesthesia. Prior to the skin incision, all patients will be given prophylactic intravenous antibiotics as per unit protocol. The surgical technique, including formation of ostomies will be at the discretion of the consultant surgeon.

15.7.3 Postoperative period

Patients will be cared for in line with a unit standardised ERAS program including the use of early mobilisation, early oral nutrition, multimodal analgesia and antiemesis, and the avoidance of routine nasogastric and peritoneal drainage. The use of regional anaesthetic techniques including spinal, epidural, and rectus sheath analgesia will be at the discretion of the consultant anaesthetist. Blood tests will be taken daily as routine until discharge, including CRP. The surgical team will not be blind to these blood results. Investigation of, and treatment for, any postoperative complications will be at the discretion of the patient's clinical team.

15.7.4 Randomisation

Patients will be randomised and given a participant number immediately prior to surgery by telephone. The allocation will be computer generated so will not be known to the research team. The computer generated randomisation key will be held by the CTU data manager. Randomisation will be stratified by surgical approach; open or laparoscopic resection, and centre. At the end of the trial the randomisation key will be given to the research team to allow patient allocation to be revealed.

15.7.5 Blinding

For the purposes of double blinding, all doses of dexamethasone will be prepared in 100ml bags of normal saline which will appear identical, be labelled with trial labelling only, and be administered via an intravenous cannula over 30 mins. The first dose will be given at the induction of anaesthesia, with patients in group 1 administered 100ml normal saline placebo, group 2 administered 4mg of dexamethasone in 100ml normal saline

intravenously over 30 mins, and those patients in group 3 administered 8mg of dexamethasone in 100ml normal saline over 30 mins. On the first postoperative day those patients in group 3 will receive 8mg dexamethasone intravenously prepared in 100ml normal saline over 30 mins and those patients in groups 1 and 2 will receive placebo of 100ml normal saline only intravenously over 30 mins. Both the patients and the clinical teams caring for the patients will be blind to treatment allocation until the data is de-anonymised following the closure of the trial. Clinicians will not be blind to postoperative CRP blood results. Investigation and treatment of postoperative complications will be at the discretion of the patient's surgical team.

15.8 Assessment of safety

15.8.1 Risk assessment

A formal risk assessment, which acknowledges the risks associated with the conduct of the trial and proposals of how to mitigate them through appropriate quality control (QC) and quality assurance (QA) processed, will be undertaken by the CTU. Risks will be assessed in terms of their impact on: the rights and safety of participants; trial design, reliability of results and institutional risk; and project management.

QA is defined as all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the principles of GCP. QC is defined as the operational techniques and activities performed within the QA system to verify that the requirements for quality of the trial related activities are fulfilled.

15.8.2 Adverse events

The principles of Good Clinical Practice (GCP) require that investigators and sponsors follow specific procedures when notifying and reporting adverse events or adverse reactions in clinical trials. These procedures are described below. All AEs, ARs, and SAEs should be recorded in the patient's medical notes and the case report form (CRF). The investigators should assess the severity of the AE using the standardised definitions and the nature of its cause.

Investigators should record any SAEs related to the trial intervention occurring from the time of randomisation until the first postoperative follow up clinic visit or 30 days after surgery, whichever is first. If the event is classified as 'serious' and related to the trial intervention then an SAE form must be completed and the CTU notified within 24 hours. If the event is classified as 'serious' and assessed as not being related to exercise or reported as a post-operative morbidity (POM) these should still be reported to the CTU. The minimum data required for reporting an SAE are the participant number and date of birth, name of reporting investigator and sufficient information on the event to confirm seriousness. Any further information regarding the event that is unavailable at the time of the first report should be sent as soon as it becomes available. The Chief Investigator, or a co-investigator, will review all SAE forms. If an SAE is considered to be related to the

trial intervention then continuation of the trial for that patient should be discussed with the Chief Investigator.

Adverse events in the trial include:

- Postoperative mortality (within 30 days of surgery)
- Postoperative morbidity, within 30 days of surgery or up to the first follow up clinic visit – this should be graded according to the type and Clavien Dindo classification and reported on the appropriate CRF
- Readmissions relating to post-operative morbidities within 30 days of surgery
- A new condition that is detected after the trial intervention, prior to the first clinic follow up visit.

Adverse events in this trial do not include:

- Recurrence of primary cancer- this should be reported on the appropriate CRF
- Death due to primary cancer- this should be reported on the appropriate CRF
- Medical or surgical procedures; the condition that led to the procedure is the adverse event
- Pre-existing disease or a condition present that was diagnosed before trial entry and does not worsen
- Hospitalisation where no untoward or unintended response has occurred e.g. elective surgery, social admissions

15.9 Statistics and data analysis

15.9.1 Sample size

This would be a 1:1:1 study. The maximum study size would be 183 patients, based on a difference in proportions of success of 20% (50% vs 70%) with 90% power and a 10% 1-sided level of statistical significance. There would be 2 equally spaced interim analyses (after 1/3 and 2/3 of patients) where consideration would be given to dropping the 0mg arm.

The interims would compare (4 and 16mg) vs. 0mg, i.e. any treatment vs. no treatment (2:1). There would be a 13% probability of dropping 0mg at the first interim ($p<0.004$; after 60 patients {~20 per arm}) and 53% probability of dropping 0mg at the second interim ($p<0.043$; after 121 patients {~40 per arm}) If the 0mg arm was dropped at an interim the study would continue to recruit 1:1 to 4mg and 16mg to a maximum of 61 patients per arm.

The null hypothesis (H0) of the study is that the complication rate is the same for all 3 groups (0mg, 4mg, 16mg).

The first alternative hypothesis (H1A) is to test whether any treatment is better than no treatment {(4mg and 16mg) vs 0mg}. There are 2 possible outcomes here:

1. If having any treatment is statistically significantly superior to 0mg (a lower complications rate is seen) the second alternative hypothesis (H1B) of comparing the 16mg and 4mg would be tested at a 10% significance level. With 122 patients (61 per arm) and success rates of 60% and 80% for 4mg and 16mg respectively, the power of the test would be 88%.

2. If having any treatment is not statistically significantly superior to 0mg the third alternative hypothesis (H1C) of comparing the 16mg (n = 61) and 0mg would be tested. With 122 patients (61 per arm) and success rates of 50% and 70%* for 0mg and 16mg respectively, the power of the test would be 85%.

* A more modest success level than the original hypothesised 80% as, if that level been observed, the test of treatment versus no treatment would have been significant and the final analysis would have been to compare the 16mg and 4mg.

Note that, as a sequential gateway testing procedure is being employed, H1A and H1B operate at 10% level of statistical significance. As H1C is a fall-back analysis the overall significance level for this is 20%.

15.9.2 Management and delivery

Data will be entered by the local research team onto the case report form (CRF) of the trial database which will be held securely on University of Glasgow servers. The database will be password protected and only available to members of the trial team. The servers are protected by firewalls and patched and maintained according to University of Glasgow IT service practice. The physical location of the servers, as with the terminals used to access them, is protected by CCTV and security door access.

The results of the trial will be disseminated regardless of the direction of effect. Ownership of the data arising from the study resides with the trial team. The publication policy will be in line with rules of the International Committee of Medical Journal Editors.

The trial protocol will be published and made available for public access throughout the trial period.

15.9.3 Statistical analysis plan

All statistical analyses will be performed using IBM SPSS v22 for Windows (IBM, Chicago, IL, USA). Two sided p values <0.05 will be considered statistically significant.

Initially patients will be randomized 1:1:1 to each group. Interim analyses following recruitment of 1/3 and then 2/3 of patients will compare complication rates in Group 1 (placebo) to combined Group 2 and 3 (dexamethasone, any dose), to determine whether a significant treatment effect exists. If a significant difference is found then no further patients will be randomized to placebo, with all further recruited patients randomized 1:1 to Group 2 or 3. Final analysis will then determine whether a significant difference in complication rate is found between Groups 2 (4mg dexamethasone) and Group 3 (8mg x 2 dexamethasone). If no significant difference is found between placebo and any dexamethasone dose at interim analysis then the remaining patients with be randomized to Group 1 (placebo) and Group 3 (8mg x 2). The final analysis will then determine whether a significant difference in complication rate is found between placebo and any dose of dexamethasone.

15.9.4 Study closure / Definition of end of trial

The end of the trial is defined as the first clinic visit, or 30 days after the last patient's randomisation to the trial, whichever occurs first. This is anticipated to be around 24 months after trial commencement.

15.9.5 Data Handling

15.9.5.1 Case Report Forms / Electronic Data Record

Individual CRFs will be held in the trial database, held securely on University of Glasgow Servers as above. These data will be anonymised and the only identifier used will be the participant number. The randomisation/anonymisation key will link participant number to a patient identifier, the CHI number, for the purposes of linkage, and will be held separately by the CTU data manager. Access to these files and information will be restricted to trial staff.

15.9.5.2 Record Retention

The anonymised data, including individual enrolment and CRFs, will be held on the University of Glasgow server for a minimum of 10 years following trial closure. In addition, a password protected copy of the randomisation key will be kept securely on the University server to allow linkage if required in the future.

The patient consent form will explain that if a participant wishes to withdraw from the study, the data acquired prior to that point will be retained unless the patients requests otherwise. Reason for withdrawal will be recorded if given, as will loss to follow up.

15.10 Study monitoring/auditing

The Sponsor (NHS GG&C) randomly selects 10% of research studies for audit per annum.

15.11 Protocol amendments

Any change in the study protocol will require an amendment. Any proposed protocol amendments will be initiated by the CI and submitted to the ethics committee and sponsor. The CI will liaise with the study sponsor to determine whether an amendment is non-substantial or substantial. All amended versions of the protocol will be signed by the CI and Sponsor representative. Before the amended protocol can be implemented favourable opinion/approval must be sought from the original reviewing REC and Research and Development (R&D) office(s).

15.12 Ethical considerations

The study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and its revisions (Tokyo [1975], Venice [1983], Hong Kong [1989], South Africa [1996], Edinburgh [2000], Seoul [2008] and Fortaleza [2013]).

Favourable ethical opinion will be sought from an appropriate REC before patients are entered into this clinical trial. The CI will be responsible for updating the Ethics committee of any new information related to the study.

The rights of the participant to refuse to participate in the trial without giving a reason must be respected. After the participant has entered the trial, the clinician remains free to give alternative treatment to that specified in the protocol, at any stage, if s/he feels it to be in the best interest of the participant. The reasons for doing so must be recorded. After randomisation, the participant must remain within the trial for the purpose of follow up and data analysis according to the treatment option to which they have been allocated. However, the participant remains free to change their mind at any time about the protocol treatment and follow up without giving a reason and without prejudicing their further treatment.

As this is a Clinical Trial of Investigational Medicinal Product (CTIMP), as defined by EU directive 2001/20/EC, the trial will be registered in the European Clinical Trials Database

and submitted to the Medicines Healthcare Products Regulatory Agency (MHRA) for a Clinical Trial Authorisation (CTA).

15.13 Insurance and indemnity

Trial and clinical staff with NHS and Honorary NHS contracts will be covered by their NHS insurance and indemnity, and as such a research passport will not be required for these individuals. University of Glasgow employees will be covered by the University of Glasgow Clinical Trials Insurance Policy.

The NHS has a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and the NHS remains liable for clinical negligence and other negligent harm to patients under its duty of care.

16 Conclusions

16.1 Overview of work

It is already well documented that an exaggerated postoperative systemic inflammatory response is associated with infective complications following surgery for colorectal cancer. In addition, these postoperative complications have been shown to have negative implications for long-term prognosis. Serum C-reactive protein (CRP) has been recognised as a marker of the magnitude of the postoperative systemic inflammatory response, and clinically relevant threshold values have already been derived. However, the nature of the relationship between the postoperative systemic inflammatory response and oncologic outcomes, along with factors which influence the postoperative systemic inflammatory response, were less well understood. Therefore, the aims of this thesis were to further examine the relationship between the postoperative systemic inflammatory response, postoperative complications, and long term oncologic outcomes and ask whether attenuation of the postoperative systemic inflammatory response might result in improved outcomes following surgery for colorectal cancer.

The results of Chapter 3 report that an exaggerated postoperative systemic inflammatory response is associated with postoperative complications regardless of our method of classification. In addition, it reported the association between exceeding established postoperative CRP thresholds and the need for reintervention following surgery for colorectal cancer. However, perhaps of more interest are the results of Chapter 4, which suggest that the postoperative systemic inflammatory response has a direct effect on cancer specific survival, independent of complications. We hypothesise that this relates to downregulation of the useful anti-tumour adaptive immune response by the overwhelming postoperative innate response. This would have profound implications. Firstly, it perhaps suggests a mechanism by which postoperative complications, regardless of type, lead to disease recurrence and cancer death. Second, by having a direct impact on survival, the question of whether attenuation of the postoperative systemic inflammatory response to improve both short and long-term outcomes becomes pressing.

Existing evidence suggests that patient and operative factors influence the magnitude of the postoperative systemic inflammatory response. Patient factors such as comorbidity, BMI, and the presence of preoperative systemic inflammation act to increase the magnitude of the postoperative systemic inflammatory response. The use of minimally invasive

laparoscopic surgery, however, is well recognised to reduce the postoperative systemic inflammatory response. Chapters 5 to 11 examined some other important patient and perioperative factors which might have an influence on the postoperative systemic inflammatory response. Chapter 5 reported that female patients with higher BMI and visceral obesity, measured by preoperative CT, were more likely to exceed the established CRP thresholds on postoperative days 3 and 4, and that this was also associated with a higher rate of postoperative complication. Visceral fat is well understood to be an active endocrine and immunological tissue and it may be that an increased quantity promotes postoperative systemic inflammation. The same relationship was not found amongst male patients, however the reasons for this were not clear. It may be that it relates to sex specific differences in fat distribution.

Chapter 6 reported no significant association between patients with poorer exercise tolerance and a lower anaerobic threshold, as measured by cardiopulmonary exercise testing (CPEX), and the postoperative systemic inflammatory response. However, this was in a small number of patients, and it may well be that a small effect is present, but that the sample size did not have the requisite power to detect it. The idea that measures of physical fitness derived from CPEX might relate to the postoperative systemic inflammatory response remains plausible. A low anaerobic threshold at CPEX might simply reflect the burden of comorbidity. However, it could be hypothesised that a lower anaerobic threshold predisposes patients to relative hypoxia and oxygen debt in the perioperative period which drives systemic inflammation. Furthermore, relative hypoxia is known to be an adverse prognostic factor at the tumour level, although whether a short period of relative whole body hypoxia at the time of surgery could have an effect on the tumour itself is less clear. Further work in this area might involve the increasingly popular use of CPEX for "prehabilitation" in patients undergoing surgery for colorectal cancer. In particular, if it could be demonstrated that prehabilitation improved patients' anaerobic threshold, and in turn reduced the magnitude of the postoperative systemic inflammatory response, a more causal argument could be drawn.

Several other patient and operative factors investigated were not found to influence the postoperative systemic inflammatory response. Chapter 7 reported no association between the magnitude of the postoperative systemic inflammatory response and the formation of a temporary defunctioning stoma, which is often a useful technique to protect high risk anastomoses and lessen the consequences of subsequent leakage. Chapter 8 reported that operation duration is not directly associated with the postoperative systemic inflammatory

response, instead suggesting that the surgical approach is more important. Chapter 9 reported no significant association between perioperative blood transfusion and the magnitude of the postoperative systemic inflammatory response, although preoperative systemic inflammation and anaemia were found to be strongly related. Chapter 10 reported no association between preoperative neoadjuvant chemoradiotherapy (nCRT) and the magnitude of the postoperative systemic inflammatory response in patients undergoing surgery for rectal cancer. This finding is of interest given that patients who have undergone nCRT often have more difficult pelvic dissection due to localised post radiation inflammation. In combination with Chapter 8, the results of this chapter reassure that what might be perceived as longer and more difficult surgery does not necessarily equate to greater surgical trauma.

Chapter 11 reported that the postoperative systemic inflammatory response of patients undergoing surgery for colorectal cancer in the UK was much greater than that of patients in Japan. This was the case even after accounting for the very dramatic differences in patient characteristics between the cohorts. This is, of course, not a modifiable risk factor from the point of view of patient or surgeon, however it raises important issues with regard to the reporting of the postoperative systemic inflammatory response from cohorts around the world. It may also lead to further fruitful avenues of research with regard to why some populations appear to have a greater propensity for systemic inflammation than others following trauma.

At present, postoperative care following surgery for colorectal cancer in the UK is dominated by the use of Enhanced Recovery (ERAS) and "fast track" protocols. The investigation of potential complications following surgery is a reactive and clinician driven paradigm of care, based on markers of patient physiology such as heart rate, core body temperature, blood pressure etc. Chapter 12 examined the use of CRP on day 4 to prompt early investigation of such potential complications by computed tomography (CT) in the presence of an exaggerated postoperative systemic inflammatory response. The use of such an objective method of "flagging" patients at high risk of postoperative complication may result in the earlier and more accurate diagnosis of postoperative complications. Given their prognostic impact, this early and thorough detection is of utmost importance.

Although an exaggerated postoperative systemic inflammatory response is clearly associated with postoperative complications, it was not clear whether attenuation of it would result in better outcomes. Chapters 13 and 14 examined the use of single dose

preoperative corticosteroids for the attenuation of the postoperative systemic inflammatory response and whether it might improve short term outcomes following surgery for colorectal cancer. These results are important for several reasons. First, a relatively simple intervention was shown to reduce the magnitude of the postoperative systemic inflammatory response. Second, the same intervention was also associated with lower rates of postoperative complications not only within the existing literature but within our own cohort. Although these observations cannot definitely show that the postoperative systemic inflammatory response has a causal role in the development of postoperative complications, they add weight to this argument and should prompt prospective studies which aim to explore a possible dose response relationship between the postoperative systemic inflammatory response, methods of its attenuation, and complications following surgery. In addition, the evidence with regard to the use of corticosteroids at surgery and long-term oncologic outcomes is lacking, and future work should also focus on this issue.

Finally, evidence of the impact of individual components of ERAS protocols on the postoperative systemic inflammatory response is lacking, with the exception of minimally invasive surgery. The work presented in this thesis lays the foundation for future work, such as the simplification of postoperative care protocols by removing components found to have no objective or measurable impact on the postoperative systemic inflammatory response.

16.2 Future work

Since the completion of this work, several relevant additions to the literature surrounding the postoperative systemic inflammatory response have been made which will influence future work. The measurement of the magnitude of the postoperative systemic inflammatory response has been further refined with the postoperative Glasgow Prognostic score (poGPS), which combines serum CRP and albumin to further stratify the risk of infective complications following surgery for colorectal cancer (Watt et al. 2017b). Indeed, the introduction of the poGPS has validated the finding of the present thesis that the postoperative systemic inflammatory response is itself prognostic in this group of patients. Furthermore, the clinicopathological determinants of the magnitude of the postoperative systemic inflammatory response, other than those considered within the present thesis, have been further elucidated, with confirmation that comorbidity, the preoperative systemic inflammatory response, obesity, and surgical approach are key (Watt et al. 2017a). In addition, a recent randomised controlled trial has reported that a single dose of 8mg of intravenous dexamethasone, given at the induction of anaesthesia, reduces the incidence of postoperative nausea and vomiting (PONV) and the need for additional anti-emetics following gastrointestinal surgery (Magill et al. 2017). Although the overall rate of infective complications reported was no different between the steroid and placebo groups, there was a significantly lower rate of anastomotic leak in the steroid group. The authors suggest that one of the possible mechanisms by which dexamethasone reduces the incidence of PONV is by its anti-inflammatory effects, however no measure of the postoperative systemic inflammatory response was included in the presented paper. The lack of such a measure means that in that study no conclusions can be drawn between steroid, postoperative systemic inflammation, and the reported complications. This further suggests that future trials of corticosteroids with postoperative outcome endpoints, such as complications, should take the postoperative systemic inflammatory response into account as a potential mechanism of action.

With the objective definition of the postoperative systemic inflammatory response, and its established relationship with postoperative complications, it will be easier to define the likely benefits of perioperative interventions, such as robotic surgery, prehabilitation programmes, regional and general anaesthetic techniques, and anti-inflammatory medications. In particular, it will allow the dissection of factors contributing to the magnitude of the postoperative systemic inflammatory response. These include factors pertaining to the patient, the surgery itself, anaesthesia, and postoperative care.

Table 16-1: Relationship between perioperative factors and the postoperative systemic inflammatory response, a summary

Category	Factor	Impact on postoperative systemic inflammatory response	Comment
Preoperative and patient	Comorbidity	Increases	Also associated with complications
	Obesity	Increases	Also associated with complications
	Preoperative systemic inflammation	Increases	Also associated with complications
	Neoadjuvant therapy	No effect	Some conflicting evidence of association with complications
	Preop drugs – NSAIDS, statins etc.	More data required	
	Preoperative counselling	More data required	
	Prehabilitation programmes	More data required	Low anaerobic threshold at cardiopulmonary exercise testing associated with complications
	Preoperative carbohydrate loading	More data required	Single study reporting no relationship with postop IL 6 and CRP. Evidence relating to reduction in perioperative insulin resistance.
	Mechanical bowel preparation	More data required	No association with complication unless combined with oral antibiotics
Intraoperative	Laparoscopic surgery	Decreases	Impact on complications beyond wound related remains uncertain
	Perioperative steroid	Decreases	Associated with fewer complications
	Operation duration	No effect	
	Defunctioning stoma	No effect	Reversal associated with morbidity
	Blood transfusion	No effect	Evidence that preoperative transfusion in context of systemic inflammation associated with poorer outcomes
	Regional anaesthesia	More data required	
	General anaesthetic techniques and drugs	More data required	
	Goal directed fluid therapy	More data required	Single study reporting association between goal directed fluid therapy and lower postop IL6, not replicated in other studies
Postoperative	Pre-emptive antibiotics	No effect	Unpublished data
	Early mobilisation	More data required	
	Early enteral nutrition	More data required	

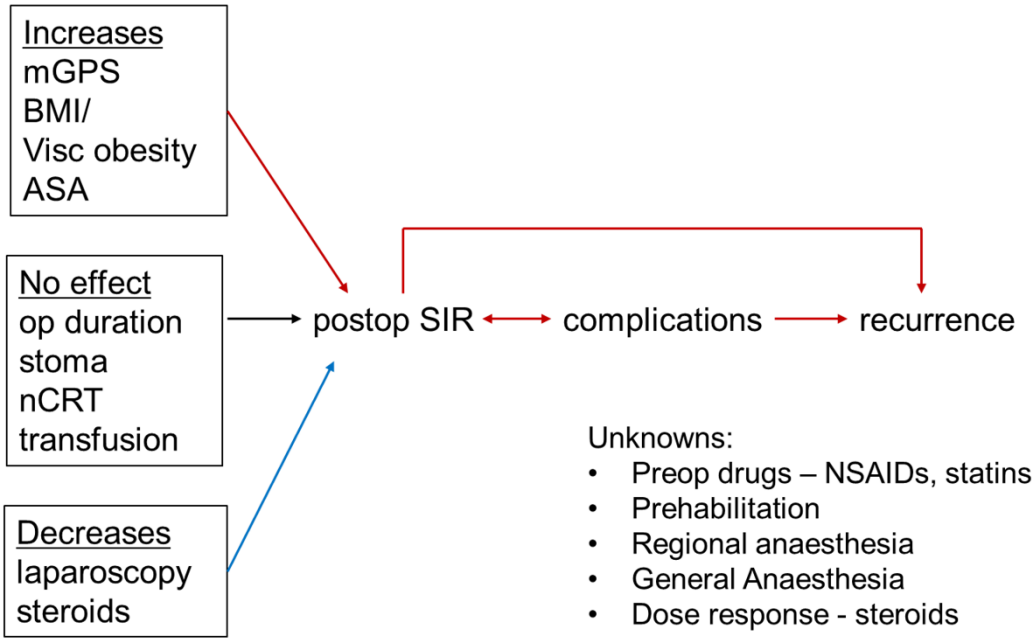

Figure 16-1: Schematic of factors associated with the postoperative systemic inflammatory response and their association with outcomes after surgery for colorectal cancer

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Appendices

Appendix A: Sample Patient Information Sheet

Investigators: Mr Campbell Roxburgh, Mr Stephen McSorley, Prof Paul Horgan
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Participant Information Sheet

Title of study
The CORTISONE Trial: CORticosteroids To reduce Inflammation and improve Short-term Outcomes after surgery for colorectal NEoplasia

Invitation to take part
Thank you for reading this information sheet. You are being invited to take part in a research study, which is part of a doctoral thesis to be submitted at the University of Glasgow.
Before you decide to take part in this study, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Please ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?
Surgery is at present the main method of cure for patients diagnosed with colorectal cancer. However, the major surgery required is associated with complications in as many as 1 in 3 patients. These postoperative complications are recognised to cause lengthier postoperative recovery, poorer quality of life for affected patients, and an increased risk of death, both in the early postoperative period, and years after surgery.
The postoperative stress response (also sometimes called the postoperative systemic inflammatory response) is increasingly thought to be associated with these complications. This stress response is the body's natural way of dealing with the trauma of surgery, however in some patients it becomes inappropriately exaggerated. This is thought to cause the immune system to be less effective at fighting infection, allowing complications to develop. The exact reason why some people develop such a large stress response after surgery is not yet known. However, there may be methods to dampen it and so reduce the risk of postoperative complications.
Dexamethasone is a steroid medication and it may be one of such methods. It is already very commonly given, to patients having surgery for colorectal cancer because it has been shown to reduce nausea and vomiting after surgery. In this situation, it is normally given during the anaesthetic, into a vein using a "drip", at a low dose. Some research also suggests

that it dampens the stress response after surgery, and might reduce complications, although how it does this, and what the best dose would be is not yet known.
Patients entering this study will receive either placebo (no dexamethasone), or one of two doses of dexamethasone at the time of their surgery, either a "low" dose or a "high" dose. Blood tests taken as part of routine care after surgery will then be analysed and markers of the postoperative stress response measured to determine if the different doses have a different effect on the stress response. Postoperative complications will be recorded up to the first clinic follow up visit after discharge, as is routine after this kind of surgery, and the effect of the different doses of dexamethasone will be analysed.
This study is what is known as a "double blind, randomised controlled trial". This means that neither you, nor the surgical and anaesthetic teams looking after you, will know which steroid treatment you have received during surgery. However, they will be able to see your postoperative blood tests, and will investigate and treat any postoperative complications as they normally would after this kind of surgery.
The study is being undertaken towards obtaining the degree of Medical Doctorate (M.D.)

Why have I been chosen?
You have been chosen because you have been diagnosed with colorectal cancer, are attending the anaesthetic pre-assessment clinic, and will be undergoing surgery at either Glasgow Royal Infirmary, Queen Elizabeth University Hospital, or the Royal Alexandra Hospital.

To take part in this study:

-You should be attending for elective surgery for colorectal cancer at Glasgow Royal Infirmary, Queen Elizabeth University Hospital, or the Royal Alexandra Hospital.

-You should be aged 18 years or over

-Male or female

-You should NOT have an existing illness involving the immune system, for example; rheumatoid arthritis, lupus, vasculitis, ulcerative colitis, Crohn's disease

-You should NOT already be taking steroid tablets or be receiving steroid injections, for example: prednisolone, dexamethasone, triamcinolone, hydrocortisone. However, steroid creams for skin conditions, or inhalers for respiratory illness, are allowed.

-You should NOT have previously had an adverse reaction to steroid medication such as those named above

Do I have to take part?
It is up to you whether or not to take part. If you do decide to take part you will be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?
You should read this information sheet. A member of the surgical team will ask you whether you wish to take part in the study on the morning of your surgery. If you agree you will be asked to sign a consent form. A trial participant number will be assigned to you at random and this will determine what dose of dexamethasone or placebo you receive during surgery. This will be given via the "drip" that will be inserted by the anaesthetist routinely, and

through which you would normally receive anaesthetic medication. Postoperative blood tests will be taken daily, as would happen normally after surgery. When you attend your first clinic visit after discharge a member of the trial team will record whether you experienced a postoperative complication, and its nature. Otherwise, your postoperative care and follow up will be entirely the same as if you were not taking part in the study.

What do I have to do?
Think about whether you would like to take part in the study. You can then tell the surgical team on the morning of surgery. If you have any questions please contact a member of the trial team on the above contact information. After the study has ended, your samples will be stored in an anonymised fashion and after 10 years they will be destroyed.

What are the possible disadvantages and risks of taking part?
Steroid medications like dexamethasone have been known to cause adverse reaction such as poor wound healing, infections, and high blood sugars, although these are much more likely when the drug is used over the long term for chronic conditions.

What are the possible benefits of taking part?
Studies to date suggest that dexamethasone and other steroid medications are associated with fewer complications after surgery for colorectal cancer. Complications are associated with longer hospital stay and recovery, poorer quality of life, and even death after surgery. However, very few of these have been randomised controlled trials. Furthermore, most have compared a steroid to a placebo (or no steroid), and very few have compared two different doses of steroid medication. Therefore, there may in fact be no benefit to receiving a higher dose of steroid. This study aims to clarify this.

Will my taking part in this study be kept confidential?
All information which is collected about you during the course of the research will be kept strictly confidential. Your GP will not routinely be informed of your participation. However, should any of your blood tests show anything unexpected, or should you have an adverse reaction to the trial medication, we will write to your GP and inform them. Your GP will then decide if this requires further investigation. The GP will contact you if this is the case. The research team members will need to access your medical records for the study purpose and all information will be kept confidential. Representatives of the study Sponsor, NHS Greater Glasgow and Clyde, may look at your information to make sure that the study is being conducted properly.

What will happen to the results of the research study?
Results will be presented at meetings of learned societies and published in scientific journals. Results will also be included in student project reports, when applicable. We will arrange a meeting to discuss the results with participant volunteers if they would like that. Again, your data will be anonymised and you will not be identifiable.

Who is organising and funding the research?
This project is being organised by the Academic Unit of Surgery at the University of Glasgow and NHS Greater Glasgow and Clyde.
Funding TBC

Who has reviewed the study?
TBC

Contact for further information

If you require further information please contact Mr Campbell Roxburgh or Mr Stephen McSorley by telephone at 0141 2018675 or via e-mail at campbell.roxburgh@glasgow.ac.uk or stephen.mcsorley@glasgow.ac.uk.

If you have any questions about colorectal cancer, or involvement in research and want to seek advice or support, you can contact Macmillan's free helpline on 0808 808 00 00.

Thank you for reading this information sheet.

Appendix B: Sample Consent Form

Investigators: Mr Campbell Roxburgh, Mr Stephen McSorley, Prof Paul Horgan

Tel: 01412018676 or 01412018675
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CONSENT FORM

Title of Project: The CORTISONE Trial: CORticosteroids To reduce Inflammation and improve Short-term Outcomes after surgery for colorectal NEoplasia

Please initial box

1. I confirm that I have read and understand the information sheet dated.... (version …) for the above study. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of my medical notes and my study information may be looked at by the research team and representatives of the study Sponsor (NHS GG&C) where it is relevant to my taking part in the research. I give my permission for this access to my information. ☐
4. I agree to my samples (blood and tissue samples) being stored and used for further analysis for further research as new techniques become available. All future work will be ethically approved. ☐
5. I agree for any surplus tissue from tissue to be examined in the laboratory for the purpose of the research study. ☐
6. I consent to my GP being informed of any information that arises from participation. ☐
7. I agree to take part in the above study. ☐

Name of subject/Participant Number	**Date**	**Signature**
Name of researcher	**Date**	**Signature**

Appendix C: Sample Case Report Form

Investigators: Mr Campbell Roxburgh, Mr Stephen McSorley
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CASE REPORT FORM

Title of Project: The CORTISONE Trial: CORticosteroids To reduce Inflammation and improve Short-term Outcomes after surgery for colorectal NEoplasia

Participant identification number_____ Date of birth___/___/_____

Date of surgery___/___/_____ Date of discharge___/___/_____ Length of stay (days)_____

Surgical approach: laparoscopic / converted / open

CRP concentration on postoperative day 3: _____mg/L

Did the patient die during the 30 days after surgery?: no / yes

- If yes, what was the recorded date ___/___/_____ and cause of death:
    - Ia_____
    - Ib_____
    - Ic_____
    - Id_____
    - II_____

Did the patient have an unplanned readmission during the 30 days after surgery?: no / yes

- If yes, what was the date ___/___/_____ and cause of readmission _____ _____ _____

Did the patient have a complication during the period between randomisation and the first clinic follow up visit?: no / yes

- If yes, then on what date was it diagnosed?: ___/___/_____
- If yes, did it require intervention?: no / yes
    - If it did, was the intervention: radiological / surgical / endoscopic

      and on what date was it ___/___/_____
- If yes did it require admission to ICU?: no / yes
    - If it did, on what date: ___/___/_____

If the patient had a complication during the period between randomisation and the first clinic follow up visit, please circle the appropriate Clavien Dindo grade based on the corresponding definition below. If the patient had more than one complication then circle the grade of the most severe complication:

Clavien Dindo grade		Description
0		No complication
1		Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Acceptable therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
2		Requiring pharmacological treatment with drugs other than such allowed for grade 1 complications
3		Requiring surgical, endoscopic or radiological intervention
	3A	Intervention not under general anaesthesia
	3B	Intervention under general anaesthesia
4		Life threatening complication requiring ICU management including CNS complications
	4A	Single organ dysfunction (including dialysis)
	4B	Multi organ dysfunction
5		Death

ICU: intensive care unit, CNS: central nervous system

If the patient had a postoperative complication, please circle the most appropriate type, location, and complication based on the corresponding definition below. If the patient had more than one complication please circle as many as appropriate:

Type	Location	Complication	Definition
Infective			
	SSI	wound infection	The presence of pus in the wound either discharging spontaneously or requiring drainage
		anastomotic leak	Anastomotic defect diagnosed radiologically, at endoscopy or laparotomy
		Intra-abdominal collection	Surgical or radiologically guided aspiration of pus from abdominal cavity
	RSI	pneumonia	Fever above 38.5C, or SIRS, associated with positive chest x-ray findings
		septicaemia	SIRS with positive blood culture
		UTI	Lower urinary tract symptoms, or fever, with positive urinalysis and/or urine culture
Non-infective			
	wound	seroma	Sterile superficial wound collection without fever or surrounding cellulitis
		dehiscence	Deep or superficial separation of the wound without fever, pus or surrounding cellulitis
	surgical site	haemorrhage	Bleeding requiring radiological or operative intervention
	cardiac	MI	Myocardial ischaemia causing ECG changes and raised cardiac enzymes/markers
		arrhythmia	New, resting ECG arrhythmia, requiring medical intervention
	vascular	VTE	Deep or pulmonary venous thrombosis with clinical symptoms, confirmed radiologically
		CVA	Persistent focal neurological deficit with radiological evidence of cerebral vascular territory infarction
	urinary	renal failure	Oliguria/anuria with decreasing GFR, with or without need for renal replacement therapy
		acute urinary retention	Painful/painless anuria with inability to void requiring urinary catheterisation
	GI	ileus	Paralytic/non-mechanical small bowel obstruction

SSI: surgical site infection, RSI: remote site infection, SIRS: systemic inflammatory response syndrome, UTI: urinary tract infection, MI: myocardial infarction, ECG: electrocardiogram, VTE: venous thromboembolism, CVA: cerebrovascular accident, GFR: glomerular filtration rate, GI: gastrointestinal

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