An Investigation into the Relationship Between Mode of Presentation, Clinicopathological Factors and Outcomes in Colon Cancer

By

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Abstract

Colorectal cancer is the 4th most common cancer in the United Kingdom and the second most common cause of cancer related death after lung cancer. Resectional surgery remains the cornerstone of treatment with curative intent however, despite this, a large proportion of patients eventually succumb due to recurrent or metastatic disease.

Despite the widespread introduction of bowel cancer screening programmes, a significant proportion of cases of colorectal cancer continues to require investigation and treatment on an emergency basis. Emergency presentations have been reported to have significantly worse short-term and long-term outcomes than elective presentations even after adjustment for disease stage. It seems likely that as opposed to emergency presentations per se being associated with adverse outcomes in colorectal cancer, clinicopathological factors – tumour, host and other factors – are likely to be associated with emergency presentation and that it is these factors that are associated with adverse oncological outcomes.

The work presented in this thesis examines the impact of emergency presentation on short-term and long-term outcomes of patients with colorectal cancer. It examines, in detail, the association between mode of presentation and tumour and host factors in patients undergoing treatment with curative intent for colon cancer and subsequently the association between these factors and long-term oncological outcomes.

Chapter 1 provides an overview of colorectal cancer including epidemiology, risk factors, routes to presentation, presenting symptoms and signs and the investigation and management of patients with colorectal cancer.

Chapter 2 examines 30 years of published literature in a systematic review and meta-analysis and summarises the existing literature regarding the association between mode of presentation and tumour and host factors in patients with colorectal cancer. The results conclude that there are multiple differences in tumour and host factors between elective and emergency presentations of colorectal cancer. However, the studies identified were heterogenous, and it was not possible to carry out a review of the effect of these factors on short-term and long-term outcomes.

Chapter 3 examines the association between mode of presentation and basic clinicopathological factors within a regional cohort of patients presenting with colon or rectal cancer in the West of Scotland regardless of disease stage or treatment received. The results show that patients with colon cancer are more likely to undergo investigation and definitive treatment on an emergency basis in comparison to rectal cancer. Patients presenting emergently with colorectal cancer were more likely to have advanced disease at diagnosis. Furthermore, in a subgroup analysis of patients undergoing curative resectional surgery for TNM Stage I-III colon cancer, emergency presentation was associated with adverse short-term and long-term outcomes even after adjustment for disease stage.

Chapter 4 examines the association between basic clinicopathological factors (tumour and host factors identified within Chapter 2), mode of presentation and short-term and long-term survival within a regional cohort of patients undergoing resectional surgery with curative intent for TNM I-III colon cancer.

Younger age, increased comorbidity (as measured by ASA classification), lower BMI, more advanced T stage and extramural venous invasion were associated with both emergency presentation and with adverse oncological outcomes. However, emergency presentation remained independently associated with both adverse short-term survival and long-term oncological outcomes despite adjustment for these factors. Increased co-morbidity as measured by the Charlson Co-morbidity index was not associated with emergency presentation. When the association between mode of presentation and individual components of the Charlson Index was examined, only Diabetes Mellitus was associated with mode of presentation and was protective against emergency presentation. Within a subgroup analysis of patients with Diabetes Mellitus, no clear association between diabetic factors (Type 1 vs Type 2 Diabetes, type of diabetic control, metformin/sulfonylurea/insulin use) and mode of presentation was identified.

Chapter 5 examines the association between the systemic inflammatory response, mode of presentation and short-term and long-term survival in a regional cohort of patients undergoing resectional surgery with curative intent for TNM I-III colon cancer. Both the neutrophil-lymphocyte ratio and the modified Glasgow Prognostic Score were independently prognostic and combined into a Systemic Inflammatory Grade. This Systemic Inflammatory Grade was independently associated with emergency presentation. When the association between clinicopathological factors, including mode of presentation and Systemic Inflammatory Grade, and short-term and long-term outcomes were analysed, Systemic Inflammatory Grade remained independently associated with short-term and long-term survival. Mode of presentation remained associated with short-term but not long-term survival.

Chapter 6 examines the association between mode of presentation and CT-derived body composition. High subcutaneous fat index and low skeletal muscle index were independently associated with emergency presentation and were associated with Systemic Inflammatory Grade even after adjustment for TNM Stage.

Chapter 7 examines the prior interaction with the bowel screening programme of a regional cohort of patients diagnosed with colorectal cancer. Only 19% of patients were diagnosed through screening. Screening diagnosis was associated with significantly improved long-term outcomes. The most common reasons for failure to diagnosis through screening were non-invitation to screening (either above or below routine screening age), non-return of screening test (associated with male sex, increased socio-economic deprivation, increased comorbid status and current smokers) and negative screening test (associated with female sex, preoperative anaemia, less comorbid status, right-sided tumours and screening with gFOBT testing).

Chapter 8 examines the association between tumour mutational status, mode of presentation and long-term outcomes in patients undergoing resectional surgery with curative intent for TNM I-III colon cancer. The results show that on unadjusted analysis, APC wild-type, KRAS mutant and BRAF wild-type colon cancer were associated with improved long-term outcomes. There may be an association between KRAS mutant status and an elevated systemic inflammatory response. On adjusted analysis, KRAS mutational status was independently associated with adverse long-term outcomes after adjustment for other clinicopathological factors. In this study, no statistically significant associations were seen between mutational status and mode of presentation however there

were trends between P53 wild-type, KRAS mutant and PIK3CA mutant status and emergency presentation.

Chapter 9 examines the association between the preoperative systemic inflammatory response, emergency presentation and short-term and long-term outcomes in patients undergoing resectional surgery with curative intent for TNM Stage II colon cancer when controlled for the established high-risk factors of TNM Stage II disease. The results show that after adjustment for these factors, emergency presentation was not independently associated with either short-term or long-term outcomes however a significant association was seen between the preoperative systemic inflammatory response and outcomes.

Chapter 10 presents the results from a national survey with regards to attitudes towards and the use of perioperative steroids in patients undergoing resectional surgery with colorectal cancer. The results show that perioperative steroids are widely used at the discretion of the anaesthetist with the primary aim of preventing postoperative nausea and vomiting. The results show that there is sufficient equipoise to carry out a randomised controlled trial examining the impact of single dose corticosteroid administration at induction of anaesthesia on the postoperative systemic inflammatory response and outcomes following colorectal resection.

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Author's Declaration

The work presented in this thesis was undertaken during a period of research between 2018 and 2021 in the University of Glasgow Academic Unit of Surgery at Glasgow Royal Infirmary. This was completed whilst working as a Specialty Registrar in General Surgery in the West of Scotland Deanery between 2021 and 2022.

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

- The initial acquisition of basic regional data was carried out prior to commencing my research by Mr David Mansouri

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Publications

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

1. Attitudes towards the use of perioperative steroids in resectional colorectal cancer surgery in the UK: A qualitative study.
   Golder AM, McSorley ST, Kearns RJ, McMillan DC, Horgan PG, Roxburgh CS.
   Ann Med Surg (Lond). 2019 Oct 11;48:23-28. doi: 10.1016/j.amsu.2019.10.007. PMID: 31687135; PMCID: PMC6820077.

2. Effect of preoperative oral antibiotics in combination with mechanical bowel preparation on inflammatory response and short-term outcomes following left-sided colonic and rectal resections.
   Golder AM, Steele CW, Conn D, MacKay GJ, McMillan DC, Horgan PG, Roxburgh CS, McSorley ST.
   BJS Open. 2019 Oct 16;3(6):830-839. doi: 10.1002/bjs5.50224. PMID: 31832590; PMCID: PMC6887908.

3. The prognostic value of combined measures of the systemic inflammatory response in patients with colon cancer: an analysis of 1700 patients.
   Golder AM, McMillan DC, Park JH, Mansouri D, Horgan PG, Roxburgh CS.
   Br J Cancer. 2021 May;124(11):1828-1835. doi: 10.1038/s41416-021-01308-x. Epub 2021 Mar 24. PMID: 33762720; PMCID: PMC8144393

4. Golder AM, McMillan DC, Horgan PG, Roxburgh CSD. Determinants of emergency presentation in patients with colorectal cancer: a systematic review and meta-analysis. Sci Rep. 2022 Mar 14;12(1):4366. doi: 10.1038/s41598-022-08447-y. PMID: 35288664; PMCID: PMC8921241.

5. Golder AM, Mshihadani A, McMillan DC, Horgan PG, Roxburgh CS, Mansouri D. Route to diagnosis of colorectal cancer and association with survival within the context of a bowel screening programme. Public Health. 2022 Aug 23;211:53-61. doi: 10.1016/j.puhe.2022.06.032. Epub ahead of print. PMID: 36027788.
6. Golder AM, Sin LKE, Alani F, Alasadi A, Dolan R, Mansouri D, Horgan PG, McMillan DC, Roxburgh CS. The relationship between the mode of

presentation, CT-derived body composition, systemic inflammatory grade and survival in colon cancer. J Cachexia Sarcopenia Muscle. 2022 Oct 11. doi: 10.1002/jcsm.13097. Epub ahead of print. PMID: 36218135.

Definitions/Abbreviations

ASA	American Society of Anaesthesiologists physical status classification
AP	Abdominoperineal
APC	Adenomatous polyposis coli
BCSP	Bowel cancer screening programme
BSG	British Society of Gastroenterology
BMI	Body mass index
CEA	Carcinoembryonic antigen
CIN	Chromosomal instability pathway
CCE	Colon capsule endoscopy
CCF	Congestive cardiac failure
CEA	Carcinoembryonic antigen
CKD	Chronic kidney disease
CI	Confidence Interval
CIN	Chromosomal instability pathway
CIMP	CpG Island Methylator Phenotype
CRP	C-reactive protein
CSS	Cancer specific survival
CT	Computed Tomography
ctDNA	Circulating tumour DNA
CVA	Cerebrovascular accident
El	Elective
Em	Emergency
EMVI	Extramural venous invasion
ERAS	Enhanced recovery after surgery
FAP	Familial adenomatous polyposis
FIT	Faecal immunochemical testing
gFOBT	Guaiac acid faecal occult blood testing
GI	Gastrointestinal
GMC	Glasgow Microenvironment Score
Hb	Haemoglobin
HDI	Human development index
HIV	Human immunodeficiency virus
HNPCC	Hereditary non-polyposis colorectal cancer
HR	Hazard Ratio
HU	Hounsfield Units
IL	Interleukin
KRAS	Kirsten rat sarcoma virus
LMR	Lymphocyte monocyte ratio
LVI	Lymphovascular invasion
M Stage	Metastatic Stage
MCN	Managed Clinical Network
MDT	Multidisciplinary team
mGPS	Modified Glasgow Prognostic Score
MI	Myocardial Infarction
MMR	Mismatch repair
MSS	Microsatellite stability
MSI	Microsatellite instability
MMR	Mismatch repair
MRI	Magnetic resonance imaging
MVA	Multivariate analysis

N Stage	Nodal Stage
NET	Neutrophil extracellular trap
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NLR	Neutrophil-Lymphocyte Ratio
NRS	National Records of Scotland
OR	Odds Ratio
OS	Overall survival
PBPP	Public Benefit and Privacy Panel
PLR	Platelet lymphocyte ratio
PLS	Platelet lymphocyte score
POD3	Postoperative day 3
POD4	Postoperative day 4
poGPS	Postoperative Glasgow Prognostic Score
PONV	Postoperative nausea and vomiting
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PVD	Peripheral Vascular disease
QFIT	Quantitative faecal immunochemical testing
RCS	Royal College of Surgeons
RevMan	Review Manager
SE	Standard Error
SFI	Subcutaneous fat index
SIG	Systemic Inflammatory Grade
SIGN	Scottish Intercollegiate Guideline Network
SIMD	Scottish Index of Multiple Deprivation
SIR	Systemic inflammatory response
SMD	Skeletal muscle density
SMI	Skeletal muscle index
SSI	Surgical Site Infections
TNM	Tumour, Nodes Metastases
T Stage	Tumour Stage
TAMIS	Transanal minimally invasive surgery
TNF A	Tumour Necrosis Factor Alpha
UK	United Kingdom
USA	United States of America
UVA	Univariate analysis
VFA	Visceral fat area
VO	Visceral obesity
WHO	World Health Organisation

1 Chapter 1 - Introduction

1.1 Epidemiology

Worldwide, cancer represents a major burden of disease with 19.3 million new cases and 20 million deaths in 2020 alone[1]. Colorectal cancer accounted for a significant proportion of these cases - approximately 1.8 million cases (colon - 1.1 million, rectal - 0.7 million) and 0.9 million deaths (colon - 0.6 million, rectal - 0.3 million).

As reported by Globocan 2020[1], across both sexes, colorectal cancer was the third most commonly diagnosed cancer (10%) after breast (11.7%) and lung (11.4%) cancer and the second most common cause of cancer related death (9.4%) after lung cancer (18%). In males, colorectal cancer was the third most commonly diagnosed cancer (10.6%) after lung (14.3%) and prostate (14.1%) cancer and the third most common cause of cancer related death (9.3%) after lung (21.5%) and liver (10.5%) cancer. In females, colorectal cancer was the second most commonly diagnosed cancer (9.4%) after breast cancer (24.5%) and the third most common cause of cancer related death (9.5%) after breast (15.5%) and lung (13.7%) cancer.

Within the United Kingdom, colorectal cancer was the fourth most common cancer in males and females between 2016 and 2018 with approximately 43,000 new cases (23,878/19,007 in males/females respectively) per year (Figure 1-1)[2] and between 2017 and 2019 was the second most common cause of cancer death across males and females with approximately 17,000 deaths (9,193/7,614 in males/females respectively) per year (Figure 1-2).

Colorectal cancer is recognised to predominantly be a disease of developed nations with an incidence four times higher than that of developing nations – this variation in incidence between nations has been reported to be as high as 25-fold[3-5]. This is likely due to differences in age, obesity, dietary and lifestyle factors between high and low human development index (HDI) countries. Furthermore, studies have shown that in transitioning regions including Eastern Europe, South America and Central Asia the incidence of colorectal cancer has increased, likely as a result of dietary and lifestyle changes. Meanwhile, within some developed nations colorectal cancer incidence has stabilised and in some cases has been reported to be decreasing, probably the result of the widespread introduction of bowel screening programmes and healthy lifestyle choices[6]. It has been shown within the Japanese migrant population that within one generation of migration, colon cancer rates are equivalent to that of white Americans, likely due to lifestyle related changes. A study of British Indians reported that although British Indians had an incidence of colorectal cancer significantly higher than that in Ahmedabad and Mumbai, it remained significantly lower than that of the White British population – it was hypothesised that this may be due to persistent dietary differences between ethnic groups[1,7]. The inverse association has been reported between development and mortality, likely due to more advanced healthcare systems and established bowel screening programmes.

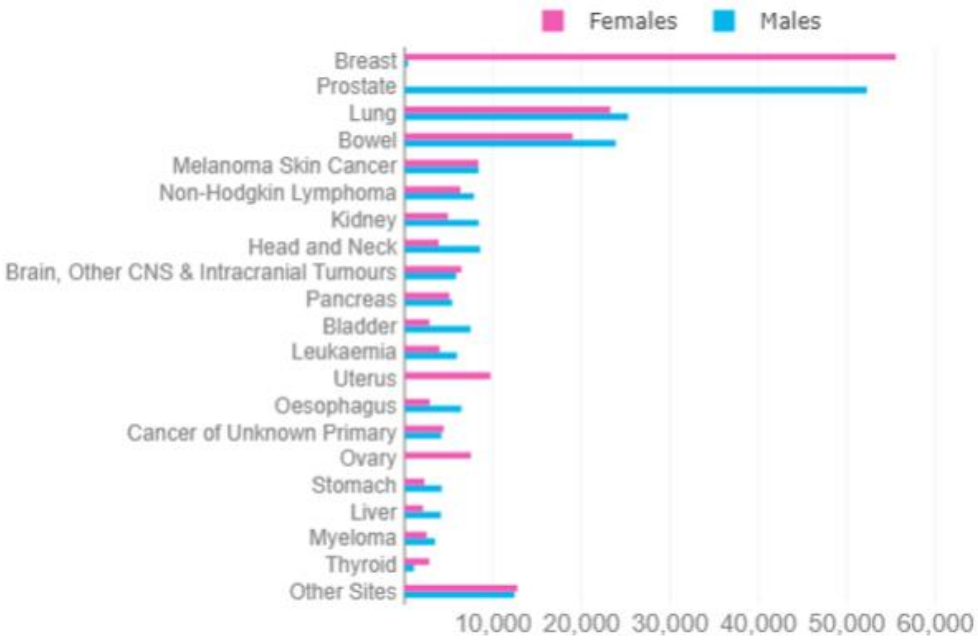

Figure 1-1 The twenty most common cancers in the UK: 2016-2018.

Credit: Cancer Research UK

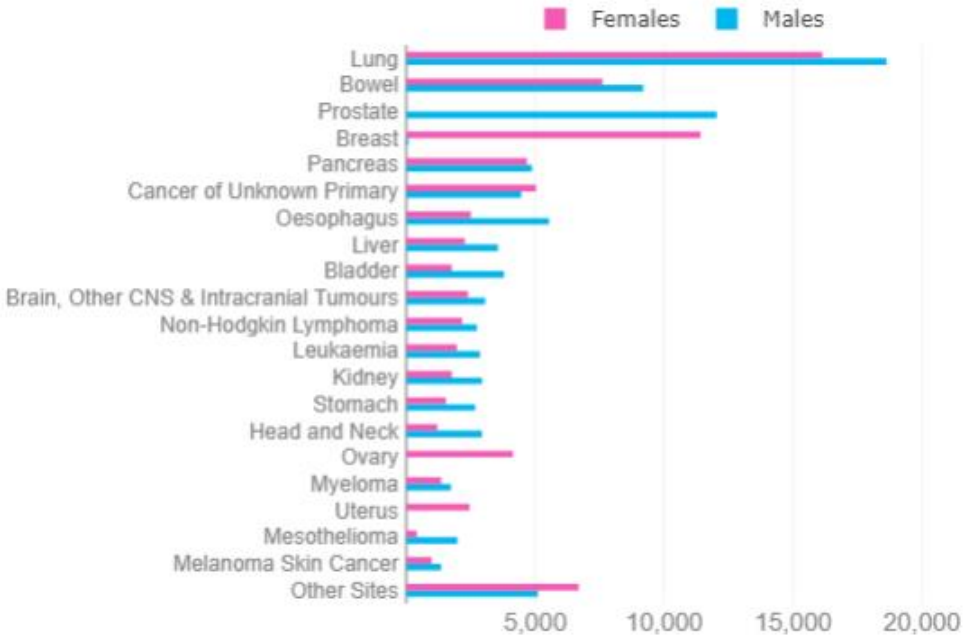

Figure 1-2 The twenty most common causes of cancer deaths in the UK: 2017-2019.

Credit: Cancer Research UK

1.2 Colorectal Carcinogenesis

Tumour development and progression is the result of a series of complex interactions between tumour and host and incorporates multiple genetic events and cell signalling pathways. Colorectal cancer is now recognised to be a heterogeneous condition that can occur through three pathways: the chromosomal instability pathway (CIN), the microsatellite instability pathway (MSI) and the CpG Island Methylator Phenotype (CIMP) pathway[8]. In reality, this is likely to be an oversimplification as these pathways may coexist in some patients.

1.2.1 Chromosomal Instability Pathway

The Chromosomal Instability (CIN) pathway represents the traditional adenoma-carcinoma sequence of tumour development first described by Vogelstein and Fearon[9]. This is the most common molecular pathway through which colorectal cancer develops accounting for 85% of new cases. The model initially described remains important however is now recognised to be over-simplistic as it is now clear that many other mutations may be involved[10].

The adenoma-carcinoma sequence is a series of stepwise mutations resulting in a change from normal colorectal epithelium to early adenomatous polyp, advanced adenomatous polyp and finally invasive carcinoma. The first step in this pathway is the deletion of the adenomatous polyposis coli (APC) gene through the mutation or loss of chromosome 5q and results in the development of an adenomatous polyp through deregulation of the WNT signalling pathway[11].

This mutation is recognised in approximately 80% of adenomatous polyps/adenocarcinomas and results in upregulation in the RAS-RAF-MAPK signalling cascade. This may be either sporadic or inherited (Familial Adenomatous Polyposis, subsequently described). Subsequent mutational changes within the KRAS proto-oncogene of codons 12 and 13 are seen in 30-60% of patients with colorectal cancers[12,13]. Mutation of this gene drives cell growth and differentiation and results in dysplastic change of the polyp. Finally, mutation of the p53 tumour suppressor gene (that normally regulates the cell cycle and induces apoptosis) is recognised to result in progression from advanced polyp to adenocarcinoma.

1.2.1 Microsatellite Instability Pathway

The microsatellite instability (MSI) pathway accounts for approximately 15% of cases of colorectal cancer[14]. This may be sporadic or inherited (Hereditary Non-Polyposis Colorectal Cancer, subsequently described). Microsatellite instability is caused by a loss of function of the DNA mismatch repair (MMR) mechanism that normally rectifies DNA replication errors. This loss of function results in microsatellites – repetitive nucleotide sequences typically associated with carcinogenesis. A number of genetic mutations within mismatch repair genes (MMR) are associated with tumour development through the MSI pathway, in particular MLH1, MLH3, MSH2, MSH3, MSH6, PMS1 and PMS2[14]. As recommended by the National Cancer Institute (NCI), there are five validated microsatellites (D2S123, D5S346, D17S250, BAT-25 and BAT-26). Tumours are considered as having high frequency microsatellite instability (MSI-H) if two or more of these

are unstable, low frequency microsatellite instability (MSI-L) if one is unstable and microsatellite stability (MSS) if none are unstable.

Tumours arising from the MSI pathway are typically: poorly differentiated, right-sided and have been shown to be associated with favourable outcomes in comparison to non-MSI related colorectal cancers[15,16].

1.2.2 CpG Island Methylation Phenotype

CpG Island Methylation Phenotype (CIMP) colorectal cancers, as described by Toyota and colleagues[17], represent tumours that develop through an epigenetic instability pathway (known as the serrated pathway) and account for 10-20% of colorectal cancer. This results from hypermethylation of CpG Islands that surround tumour suppressor genes with resultant silencing of the adjacent gene. Serrated polyps (polyps with a saw-toothed pattern of crypt epithelium) were previously considered to be benign polyps that had no malignant potential however are now recognised to have malignant potential and typically progress through this pathway. Indeed, serrated polyposis syndrome has now been defined by the World Health Organisation as either: (1) ≥5 serrated lesions/polyps proximal to the rectum, all being ≥5mm in size, within ≥2 being ≥10mm in size or (2) >20 serrated lesions/polyps of any size distributed throughout the large bowel, with ≥5 being proximal to the rectum[18]. Within patients undergoing endoscopic investigation following a positive bowel screening test an incidence of between 0-0.5% has been reported[19]. A recent review has reported a significantly increased risk of colorectal cancer (20%) in serrated polyposis syndrome with a colorectal cancer risk of 15% at time of

diagnosis[20]. These tumours are associated with right sided disease and BRAF mutations[21].

1.3 Inflammation and Cancer

The host immune system is a complex system representing the body's method of protecting itself from pathogens (non-self organisms including bacteria, fungi and viruses) and responding to injury. It can also detect abnormal cells including cancer cells. The immune system can be broadly divided into the innate (non-specific) and adaptive (acquired) immune system and furthermore, inflammatory responses may be local to the tumour microenvironment or systemic. The immune system comprises of a number of involved organs and structures including lymphatics, bone marrow, spleen, liver and circulating components.

Hanahan and Weinberg first described the six hallmarks of cancer: (1) Evading apoptosis, (2) Self-sufficiency in growth signals, (3) Insensitivity to anti-growth signals, (4) Tissue invasion and metastasis, (5) Limitless replicative potential and (6) Sustained angiogenesis[22]. In 2009, Colotta and colleagues[23] described cancer-related inflammation to be the seventh hallmark of cancer although an association between inflammation and cancer has been recognised from as early as 1863 when Rudolph Virchow recorded the presence of leukocytes in tumours[24]. Indeed, the inflammatory response has since been described as the tip of the cancer iceberg[25].

The relationship between inflammation and cancer is complex and carries both pro- and anti-tumour effects[26]. It is widely recognised that a chronically inflamed state is associated with an increased risk of cancer development and this is apparent within a number of disease processes including inflammatory bowel disease (colorectal cancer) and hepatitis (hepatocellular carcinoma). It is now recognised that tumours can drive an inflammatory response and this

inflammatory response has been associated with adverse outcomes[27]. Attenuation of this inflammatory response may be a way of improving outcomes in patients with cancer, however, to date the effect of this on outcomes remains unclear[28].

1.3.1 Innate Immune System

Anatomical barriers – epithelium lined surfaces including the skin, gastrointestinal tract and respiratory tract are the body's first line of defence against pathogens providing both a physical and physiological/chemical barrier (saliva, sweat, gastrointestinal secretions). A breach of these barriers activates the innate (non-specific) immune system.

The innate immune system is ancient in evolutionary terms and shared with plants, animals and insects. This innate immune system comprises of both cellular components including phagocytes (neutrophils and macrophages), granulocytes (basophils, eosinophils and mast cells) and natural killer cells (NK) and circulating humoral factors known as the compliment cascade. This response is driven through the production of chemokines and cytokines in response to either tissue injury or contact with a pathogen. In the early phase of the innate immune response, pro-inflammatory cytokines including Interleukin-1 (IL-1), Interleukin-6 (IL-6) and Tumour Necrosis Factor (TNF) predominate resulting in increased blood flow and vascular permeability at the site of infection/injury in addition to the recruitment of cells to engulf microbes[29,30]. Subsequently, anti-inflammatory mediators including Interleukin-10 (IL-10) encourage restoration of

normal tissue. Typically, activation of the innate immune system drives activation of the adaptive immune system.

1.3.2 Adaptive Immune System

The innate immune system described above activates the adaptive immune system – the part of the immune system that has memory of previous antigen exposure and can therefore produce a specific response against this. The adaptive immune response is triggered when antigen-presenting cells (dendritic cells) recognise foreign antigens. It is driven predominantly by lymphocytes and includes both humoral immunity and cellular immunity.

Humoral immunity is mediated via B lymphocytes that mature in the bone marrow and provide protection against extracellular pathogens. Recognition of a specific antigen through the B cell receptor results in activation of B cells to produce antibodies to these antigens, triggers the complement cascade and stimulates phagocytosis through further activation of the innate immune system.

Cellular immunity is mediated via T lymphocytes (lymphocytes that mature in the thymus) and protects against intracellular pathogens. T cells are activated when non-self antigens bind to the T cell receptors (TCR). Several types of T cells are involved including cytotoxic T cells (CD8+) that produce cytotoxins, helper T cells (CD4+) that mediate the immune response, memory T cells (CD45R0+) and regulatory T cells (FOXP3+) that limit and suppress the immune response[29].

1.3.3 Local Inflammatory Response

Tumours, including those of colorectal origin, consist of tumour cells contained within a tumour microenvironment. This microenvironment is complex and contains stroma, blood vessels, lymphatics, mesenchymal, inflammatory cells and the invasive margin (the border separating host tissue from malignant cells)[25]. Tumour growth is dependent on the interaction between tumour cells and the microenvironment. In 1986, Jass reported an association between a strong lymphocytic inflammatory infiltrate and favourable 5-year survival[31] in rectal cancer. Conversely, a strong local infiltrate by cells of the innate immune response (including neutrophils and macrophages) has been reported to have adverse outcomes[32]. The local inflammatory response has been stratified using a number of methods including the Galon Immunoscore[33], the Klintrup-Makinen grade[34] and the Glasgow Microenvironment Score (GMS)[35].

1.3.4 Systemic Inflammatory Response

Tissue injury may occur through a variety of methods including infection, trauma and cancer. This stimulates a systemic inflammatory response that, in its acute phase, aims to recognise and eliminate pathogens and stimulate tissue repair with restoration of homeostasis and subsequent resolution of the inflammatory response. Chronic inflammation results if the acute inflammatory reaction fails to restore tissue homeostasis and it is now recognised that this chronic response aids tumour progression.

IL-6, a proinflammatory cytokine first identified in 1980[36], is rapidly synthesised and released from macrophages in response to tissue injury. IL-6 causes activation of the Janus kinase signal transducer and activation of transcription 3 (JAK-STAT3) pathway[37]. It has been shown to stimulate growth activity within bone marrow, in particular the formation of neutrophils, and stimulates the production of acute phase proteins, including C-reactive protein, within the liver[38].

A number of scores and ratios have been developed to stratify the systemic inflammatory response either in the preoperative or postoperative environment. These typically utilise either the differential white cell count (neutrophils, lymphocytes, monocytes, platelets) or acute phase proteins (albumin and c-reactive protein). Many of these markers to stratify the systemic inflammatory response are widely available and routinely performed in the clinical setting. Regardless of the method of stratification, an elevated systemic inflammatory response has been shown to have adverse outcomes in patients undergoing treatment with curative intent for colorectal cancer[39-42]. These are described subsequently. To date, it remains unclear whether there is a role for stratification of the systemic inflammatory response through the use of both differential white cell count and acute phase protein based markers. Furthermore, although of interest within an academic environment, to date, the use of these preoperative blood based scores has had little clinical impact on patient care in patients diagnosed with colorectal cancer. There may be clinical utility for using the systemic inflammatory response in addition to TNM Stage in predicting outcomes. However, it seems likely that the potential role for modulating the systemic inflammatory response is of greater clinical importance. Such modulation of the preoperative response may carry prognostic

benefit both in terms of short-term and long-term outcomes. Alternatively, it may be that patients with a raised systemic inflammatory response may benefit from neoadjuvant/adjuvant therapy given the adverse outcomes seen within this high-risk subgroup.

1.3.4.1 Measurement of the Systemic Inflammatory Response – Acute Phase Proteins

Acute phase proteins are proteins where the plasma concentration alters by at least 25% during inflammatory disorders and are termed positive acute phase proteins or negative acute phase proteins depending on whether their concentration rises or falls[43].

C-reactive protein (CRP) is one such positive acute phase protein. This is a homopentameric plasma protein produced by the liver within 24-48 hours after tissue injury that is produced in response to IL-6 and is a key component of the innate immune system. It recognises pathogens and damaged cells and is able to mediate their elimination through recruitment of the compliment cascade and of phagocytic cells[44]. Within the clinical environment, CRP is readily measured and widely available and has been shown to have clinical utility in both the pre- and postoperative settings.

Albumin is a negative acute phase protein, produced by the liver. It decreases in the inflammatory state due to increased demand of amino acids for acute protein synthesis.

In the preoperative setting, the most widely used acute phase protein based score/ratio is the modified Glasgow Prognostic Score (mGPS)[41]. This score is stratified either 0/1/2 based on preoperative CRP and albumin thresholds as shown in Table 1-1. The modified Glasgow Prognostic Score has been shown to predict outcomes in patients undergoing surgery with curative intent for colorectal cancer[39] and in a range of other tumour types[42].

Table 1-1 Stratification of the systemic inflammatory response using the modified Glasgow Prognostic Score

mGPS	CRP/Albumin thresholds
0	CRP≤10mg/L
1	CRP>10mg/L and albumin≥35g/L
2	CRP>10mg/L And Albumin<35g/L

1.3.4.2 Measurement of the Systemic Inflammatory Response – Differential White Cell Count

Leukocytes (white cells) are a group of inflammatory cells including neutrophils, lymphocytes, monocytes, basophils and eosinophils. Neutrophils, previously described as the foot soldiers of the innate immune system, are the first leukocytes to be recruited to the site of injury and engulf and destroy pathogens by phagocytosis or the formation of neutrophil extracellular traps (NETs) and through recruitment of other cell types including monocytes[45].

The most widely used differential white cell count based score/ratio is the neutrophil/lymphocyte ratio (NLR)[40]. Similar to mGPS, the neutrophil-lymphocyte ratio has been shown to be prognostic in a range of tumour types

including colorectal cancer. No clear normal/abnormal threshold has been defined for the neutrophil-lymphocyte ratio however a recent review has shown 3 and 5 to be the most common thresholds used[42]. Other scores/ratios utilising the differential white cell count are in existence including the platelet lymphocyte ratio/score (PLR/PLS) and the lymphocyte monocyte ratio (LMR).

1.3.4.3 The Postoperative Systemic Inflammatory Response

Injury to the body, including surgery, stimulates a systemic inflammatory response and within the postoperative clinical setting, elevated inflammatory markers are an expected finding. The magnitude of rise in these inflammatory markers has been shown to be correlated with the stress of surgery[46]. An elevated postoperative systemic inflammatory response has been shown to be associated with both postoperative morbidity and mortality[47] and moreover with long-term oncological outcomes[48]. The administration of glucocorticoids on induction of anaesthesia is often used to reduce postoperative nausea and vomiting however has also been shown, within observational studies, to regulate the magnitude of the postoperative systemic inflammatory response and furthermore reduce postoperative complications[49]. However, to date, the effect of glucocorticoids given at induction of anaesthesia on the postoperative systemic inflammatory response has yet to be investigated within the context of a clinical trial.

Within the postoperative environment, the postoperative systemic inflammatory response may be stratified using the postoperative Glasgow Prognostic Score

(poGPS)[47]. This is similar to mGPS however the CRP and albumin thresholds are 150mg/l and 25g/l respectively as opposed to 10mg/l and 35g/l.

1.4 Risk Factors

There are multiple risk factors associated with the development of colorectal cancer. These include non-modifiable risk factors including age, sex and hereditary factors and modifiable risk factors including diet, smoking and physical activity.

1.4.1 Age

Increasing age represents the most significant risk factor for developing colorectal cancer. This is the result of an increasing cumulative lifetime exposure to risk factors and an increased likelihood of developing genetic mutations. Studies have shown that 95% of colorectal cancers are diagnosed in individuals aged over 50 years[50]. However, recent research suggests that there is an increasing proportion of colorectal cancers in the under 50s age group. This younger population is typically diagnosed at a more advanced disease stage. The association of younger age at diagnosis and prognosis after adjustment for disease stage remains unclear[51,52].

1.4.2 Sex

Colorectal cancer is common in both males and females however a higher incidence is noted in males - Globocan 2020[1] reported that although there was significant variation in the incidence of colon and rectal cancer between nations, the age-standardised incidence rate remained higher in males than females across all countries in both colon and rectal cancer. Male sex is associated with adverse overall and cancer-specific survival[53].

A recent review reported an association between female sex and increased incidence of right-sided colon cancer[54]. Studies have shown an association between male sex and the development of early onset colorectal cancer (age<50)[55].

1.4.3 Height

The Third Expert Report (2018) of the World Cancer Research Fund has classified adult attained height as "convincingly increases risk" for colorectal cancer[56]. The rationale for this is likely to be multifactorial. In part, taller people have a longer colon and more cells therefore there may be greater potential for mutations/exposure related DNA damage. Furthermore, adult attained height is related to greater exposure to growth hormone/insulin like growth factors and these are associated with an increased risk of colorectal cancer[57].

1.4.4 Diet

Previous literature has reported an association between colorectal cancer incidence and dietary factors as outlined below.

1.4.4.1 Red and Processed Meat

The Third Expert Report (2018) of the World Cancer Research Fund has classified red and processed meat as "probably increases risk"/"convincingly increases risk" respectively for colorectal cancer[56]. The EPIC study reported red and processed meat consumption to be a risk factor for colorectal cancer[58]. This was dose dependent – Hazard Ratio (HR) 1.55 per 100g increase in consumption[59]. The underlying reasons for this are likely to be multifactorial including the

effect of haem iron ingestion resulting in increased N-nitroso compounds (recognised carcinogens)[60], the production of hydrocarbons as a result of cooking meat at high temperatures[61] and the direct effect of iron resulting in DNA damage[62].

1.4.4.2 Fibre

The Third Expert Report (2018) of the World Cancer Research Fund has classified whole grains and foods containing dietary fibre as "probably decreases risk" of colorectal cancer[56]. This association was first described in 1971 by Burkitt on the basis of international variation in the incidence of colorectal cancer. This is in part thought to be due to an association between high fibre intake and decreased colonic transit time with a resultant reduction in exposure of the colorectal mucosa to carcinogens. More recently, a UK Biobank based prospective study reported a 4% reduction in the risk of colorectal cancer within the quintile of patients with highest fibre intake[63]. A further cohort study – the EPIC study[58] - of 519,978 individuals across ten European countries similarly found an association between high dietary fibre intake and reduced incidence of colorectal cancer, in particular tumours of the left colon. Within the last 10-20 years several systematic reviews and meta-analyses have reported an association between higher dietary fibre intake and reduced incidence of colorectal adenomas and/or carcinoma[64-68] although these predominantly include observational studies. A previous Cochrane Review of randomised controlled trials was unable to draw definitive conclusions with regard to the association between fibre intake and the prevention of recurrent adenomas or carcinomas within patients with a known history of adenomatous polyps[69].

1.4.4.3 Calcium and Vitamin D

In the Third Expert Report (2018) of the World Cancer Research Fund, Vitamin D has been suggested to decrease the risk of colorectal cancer. The EPIC study reported a protective effect of calcium and Vitamin D (and Vitamin C/E) in colon cancer although the effect was less evident in rectal cancer. The evidence regarding Vitamin D has been summarised in several meta-analyses[70,71]. Jenab and colleagues, reported, within 1248 patients with colorectal cancer matched 1:1 with disease-free controls, an inverse relationship between circulating Vitamin D concentration (25-hydroxy-vitamin-d (25-(OH)D) and risk of colorectal cancer within a European population[72]. This is thought to be due to a direct effect of Vitamin D on cell growth[73]. However, a randomised control trial of 2259 patients with previous colorectal adenomatous polyps did not find a reduction in the risk of recurrent adenomatous polyps through Vitamin D3 or calcium supplementation[74]. A further trial by Crockett and colleagues found as a late effect (6-10 years after introduction of calcium/Vitamin d supplementation) an increased number of serrated polyps in a cohort of 2058 patients with previous polyps receiving calcium/Vitamin d supplementation[75].

1.4.4.4 Alcohol

In the Third Expert Report (2018) of the World Cancer Research Fund[56], alcohol (two or more alcoholic drinks per day (approximately 30 grams of alcohol)) has been described as “convincingly increased the risk of colorectal cancer”. This is

in keeping with the results of the EPIC study[76]. This risk has been shown to be dose dependent with an 8% increased risk per 10 grams of alcohol intake per day[63]. The mechanism for this is likely to be multifactorial. Alcohol consumption has been reported to be associated with increased oxidative stress and release of carcinogens. Furthermore, alcohol, when metabolised by alcohol dehydrogenase within the liver forms a breakdown product called acetaldehyde[77]. Following ingestion of alcohol, high acetaldehyde concentrations within the colon have been reported and this has been shown to be carcinogenic[78]. More recently, alcohol has been shown to alter the gut microbiota and this appears to increase colorectal cancer risk[79].

1.4.5 Lifestyle Factors

1.4.5.1 Smoking

A number of studies have reported an association between smoking, both active and passive[80,81], and a significantly increased incidence of adenomatous polyps and colorectal cancer. This risk has been shown to correlate with pack year history however this risk has been shown to reduce following smoking cessation[82]. Smoking is associated with adverse short-term and long-term outcomes[83,84] in patients undergoing treatment for colorectal cancer.

1.4.5.2 Physical Activity

The Third Expert Report (2018) of the World Cancer Research Fund has classified physical activity as "convincingly decreases the risk" of colorectal cancer[56]. The EPIC study, including more than 400,000 participants reported an inverse relationship between physical activity and cancer risk within the proximal colon but no significant association within the distal colon or rectum[85]. This association remained despite adjustment for BMI and energy intake. The present literature analysing the association between colorectal cancer risk and physical activity has been summarised in a recent review[86]. The reasons for this association are likely to be multifactorial and include gastrointestinal transit time[87,88], the association with body composition (which may not be identified by adjustment for BMI)[89] and modulation of the immune response[90,91].

1.4.5.3 Obesity

The Third Expert Report (2018) of the World Cancer Research Fund has classified obesity ("body fatness") as "convincingly increases the risk" of colorectal cancer. This is predominantly based on body mass index but also includes waist circumference and waist-to-hip ratio. As described by Moghaddam and colleagues, central obesity is of particular risk with a dose-response relationship being described between waist circumference and colorectal cancer risk[92]. Obesity is related to a number of other factors including diet, physical activity and socio-economic deprivation however remains independently associated with colorectal cancer risk. However, adipocytes (fat cells) are not merely a store of energy. They produce cytokines and pro-inflammatory mediators including IL-6

and tumour necrosis factor alpha that are associated with an increased risk of cancer[93].

1.4.6 Co-morbidity

1.4.6.1 Inflammatory Bowel Disease

Inflammatory bowel disease, particularly ulcerative colitis, is strongly associated with an increased risk of developing colorectal cancer with a 2-6 times increased incidence of colorectal cancer compared to the general population[94,95]. This increased risk is due to the presence of chronic inflammation within the colon/rectum and is associated with a younger age at diagnosis and adverse outcomes[96]. In patients with ulcerative colitis, the probability of developing colorectal cancer is closely associated with the number of years since diagnosis[97].

1.4.6.2 Diabetes Mellitus

Diabetes Mellitus has been reported to be associated with a significantly increased risk of colorectal cancer compared to the general population[98-100]. Furthermore, patients with diabetes undergoing potentially curative surgery for colorectal cancer have been reported to have adverse short-term[101,102] and long-term[103,104] outcomes. Type 2 Diabetes Mellitus is strongly associated with obesity and that may be a significant confounding factor. However, hyperglycaemia due

to insulin resistance is one feature of metabolic syndrome, closely linked to the systemic inflammatory response.

1.4.7 Hereditary Colorectal Cancer

80% of new cases of colorectal cancer are sporadic with the remaining 20% considered either hereditary or familial. Hereditary colorectal cancer is the result of recognised polyposis or non-polyposis syndromes including hereditary non-polyposis colorectal cancer (HNPCC, also termed Lynch Syndrome) or familial adenomatous polyposis (FAP). These hereditary cases account for approximately 3-5% of cases of colorectal cancer. The remaining cases are familial – cases with a family history and likely inherited mutations but not classified amongst the hereditary syndromes. It is likely that these familial cases are also associated with particular lifestyle choices that may predispose to colorectal cancer.

1.4.7.1 Familial Adenomatous Polyposis

Familial adenomatous polyposis (FAP) syndrome includes classical FAP, attenuated FAP and MUTYH (mutY DNA glycosylase)-associated polyposis.

Classical FAP is a hereditary, autosomal dominant condition which has an incidence of between 1 in 13,000 and 1 in 18,000 live births[105] and is associated with <1% of cases of colorectal cancer. 10-30% of patients identified as having FAP do not have a family history[106]. FAP is caused by a mutation of the adenomatous polyposis coli (APC) gene on chromosome 5q21[107] resulting in complete gene non-function. It is characterised by the presence of at least one

hundred adenomatous polyps within the lower gastrointestinal tract. Extracolonic manifestations of FAP include a high incidence of gastric and duodenal cancers, desmoid tumours, skin manifestations and head and neck manifestations[108]. Based on recent guidelines from the British Society of Gastroenterology (BSG)[109], individuals with classical FAP should have a regular (every 1-3 years) colonoscopy starting from the age of 12-14 and regular upper gastrointestinal endoscopy from the age of 25. Patients with polyps>10mm in diameter, high grade dysplasia or a significant increase in polyp burden between examinations should be considered for surgical resection, typically either total colectomy and ileorectal anastomosis or proctocolectomy and ileoanal pouch formation. Without treatment, the majority of patients with FAP will develop colorectal cancer by the age of 40[110] with the majority of tumours being left-sided.

Attenuated FAP is when the APC gene remains functional, albeit impaired. Attenuated FAP typically presents later with fewer than 100 polyps and causes fewer symptoms than classical FAP. Lifetime risk of colorectal cancer is less than in classical FAP however remains high.

MUTYH-associated polyposis is an autosomal recessive condition that in a similar manner to classical-FAP is associated with the development of hundreds of colonic polyps and should be considered in such cases where an alteration in the FAP gene is not identified. It is caused by a mutation in the MYH (or MUTHY) gene. MUTYH-associated polyposis typically presents later than FAP – mean age at presentation between 46 and 51. Risk of colorectal cancer remains high at between 70% and 80% of affected individuals[111]. Differentiation of MUTYH-associated polyposis and FAP is important to establish family risk.

1.4.7.2 Hereditary Non-Polyposis Colorectal Cancer

Hereditary non-polyposis colorectal cancer (HNPCC), also known as Lynch syndrome was first described by Aldred Warthin in 1913[112] and accounts for 3% of all cases of colorectal cancer[113]. It is an autosomal dominant condition that results in mismatch repair (MMR) deficiency as previously described. Although colorectal cancer is the most common malignancy associated with Lynch syndrome, other cancers including uterine, renal and gastric cancer are also common[114]. Patients with known Lynch syndrome should consider taking daily aspirin to reduce the risk of colorectal cancer[115].

Colorectal cancers resulting from Lynch syndrome are typically found in younger patients (aged between 40 and 60) and are proximal, poorly differentiated, may be of mucinous or signet cell type and are associated with a raised local inflammatory response. The Amsterdam II criteria[116] and the Revised Bethesda Guidelines[117] (shown in Table 1-2) identify high risk patients who should be tested for Lynch syndrome.

Table 1-2 Amsterdam II Criteria and Revised Bethesda guidelines for testing for HNPCC

Amsterdam II Criteria
1) Three or more relatives with histologically verified Lynch syndrome- associated cancer, one of whom is a first degree relative of the other two
2) Cancer involving at least two generations
3) One or more cancer cases diagnosed <50 years of age
Revised Bethesda guidelines
1) Diagnosis of colorectal or endometrial cancer in a patient <50 years of age
2) Presence of synchronous/metachronous colorectal cancers or Lynch syndrome associated tumours, regardless of patient age
3) Colorectal cancer with MSI-H histology diagnosed in a patient <60 years of age
4) Diagnosis of colorectal cancer in one or more first-degree relatives with a Lynch syndrome-related tumour, with one of the diagnoses occurring <50 years of age
5) Colorectal cancer diagnosed in two or more first or second-degree relatives with HNPCC-related tumours, regardless of age

1.4.7.3 Hamartomatous Polyposis Syndromes

The Hamartomatous polyp was first described in 1957 by Horrilleno and colleagues[118]. Several autosomal-dominant inherited syndromes have since been described that are associated with development of these polyps including juvenile polyposis, Peutz-Jehers syndrome and hereditary mixed polyposis syndrome[119]. This rare group of syndromes accounts for less than 1% of hereditary colorectal cancer.

1.5 Routes to Presentation

The route to diagnosis of cancer has been thoroughly described by Elliss-Brookes and colleagues[120]. Colorectal cancer may be diagnosed either electively, as an emergency or through a bowel cancer screening programme. In reality this classification is somewhat simplified – elective and emergency presentations of colorectal cancer, as opposed to representing two distinct entities, are perhaps better considered to be at alternate ends of a spectrum. Similarly, patients diagnosed through screening, although typically considered asymptomatic may have decided to participate in screening due to a recent onset of lower GI symptoms.

1.5.1 Elective

The majority of new cases of colorectal cancer are diagnosed within the elective setting predominantly as a result of a patient presenting to their General Practitioner with either lower gastrointestinal or systemic symptoms (subsequently described) or, less commonly, due to an incidental finding on imaging carried out for alternative purposes. These patients will typically be referred by their General Practitioner to a colorectal or gastroenterology clinic or direct to test (as described subsequently).

1.5.2 Emergency

Emergency presentations of colorectal cancer can be broadly defined as patients requiring an unplanned admission to hospital for urgent investigation and treatment of acute symptoms. Within the literature, this definition may vary somewhat with some studies only considering those cases an emergency that

require definitive treatment within a set time period of presentation (typically 72 hours).

Emergency presentations are typically considered to result from either obstruction, perforation or significant lower gastrointestinal bleeding and have been reported to be associated with adverse short-term[121-126] and long-term[126-130] outcomes in comparison to elective presentations. Emergency presentations have been shown to have a more advanced disease stage at diagnosis compared to elective presentations and although the observed disparity in outcomes may be partly attributable to this, emergency presentation has been shown to remain associated with adverse outcomes even after adjustment for disease stage.

The proportion of colorectal cancer presenting emergently has been reported to vary between 10% and 30%[131-133]. In recent years there has been a reported reduction in the proportion of patients presenting emergently[134-136]. The reason for this is likely to be multifactorial including the widespread introduction of bowel cancer screening programmes, more thorough investigation of anaemia or lower gastrointestinal symptoms and increased patient awareness of seeking advice for lower gastrointestinal symptoms. Nonetheless, large bowel obstruction, likely to be predominantly due to colorectal cancer, remains the fourth most common indication for emergency laparotomy within the United Kingdom[137].

1.5.3 Screening

In 1966, Wilson and Jungner[138] described multiple factors that must be considered when establishing a screening service, both in terms of the health condition screened for and the population in whom to screen. Bowel cancer is recognised to be one such condition that can be adequately screened for with the potential to improve patient outcomes by diagnosing patients at an earlier disease stage.

Bowel cancer screening programmes have now been widely introduced in the Developed World as summarised by two recent reviews[139,140]. The majority of such programmes utilise faecal blood testing (either guaiac acid faecal occult blood testing (gFOBT) or faecal immunochemical testing (FIT)). Additionally, some programmes carrying out periodic lower gastrointestinal endoscopy.

Within Scotland, a population-based screening programme was introduced in 2007. All individuals aged between 50 and 74 are invited to participate in screening on a biennial basis. Individuals aged 75+ are not routinely invited however remain eligible to participate.

Between 2007 and 2017 screening tests were sent out in the form of guaiac-based faecal occult blood tests (gFOBT). Each test consisted of six stool specimens (2 samples from three separate occasions). Individuals with a negative test (zero positive specimens) were re-invited for screening in a further two years. Individuals with a strongly positive test (5-6 positive specimens) were invited to attend for colonoscopy. Individuals with a weakly positive (borderline) test (1-4 positive specimens) were asked to complete a faecal immunochemical test (FIT) with those patients with a positive test being invited for colonoscopy.

Since 2017, the screening test changed from gFOBT to FIT testing. Patients are now invited to complete a FIT test on a biennial basis. Patients with positive tests progress to colonoscopy and individuals with negative tests are reinvited to the subsequent round of screening.

Screening programmes are not without limitations. Although screening programmes have been widely introduced in developed nations, uptake to screening has shown to be suboptimal with uptake in many cases <50% of the eligible population[141]. Screening uptake has been shown to be particularly poor within more deprived populations who, due to lifestyle factors, are of increased risk and may derive the greatest benefit[142]. Furthermore, false negative tests may prove falsely reassuring to patients and result in the underreporting of significant symptoms. False positive tests result in unnecessary invasive investigations and can become a burden on healthcare resources.

1.6 Symptoms and Signs

1.6.1 Symptoms

The clinical presentation of colorectal cancer is predominantly dependent on tumour location. Right-sided tumours (proximal to the splenic flexure) typically present with iron deficiency anaemia (asymptomatic or symptomatic), bowel obstruction or an abdominal mass. Left-sided colonic (distal to the splenic flexure) or rectal tumours are more likely to present with rectal bleeding or an alteration in bowel habit. Rectal cancers may additionally present with tenesmus (feeling of incomplete evacuation). More advanced/metastatic disease may present with other systemic symptoms including weight loss, jaundice and lethargy. Notably however, the majority of colorectal cancers will present with more than one of these symptoms for example alteration in bowel habit and rectal bleeding. Indeed, Thompson and Colleagues[143] reported that an alteration in bowel habit without rectal bleeding carries a positive predictive value of 2.5% whereas a combination of altered bowel habit and rectal bleeding carries a positive predictive value of 19.7%.

1.6.2 Signs

The majority of patients presenting with colorectal cancer will not have any obvious signs on routine clinical examination. Occasionally there may be evidence of either an abdominal or rectal mass. In those patients presenting emergently there may be signs of acute complications of a tumour including abdominal distension, obstructive bowel sounds, peritonitis or blood on digital

rectal examination. In more advanced disease there may be systemic signs including cachexia, hepatomegaly, jaundice or ascites.

1.7 Investigations, Diagnosis and Staging

The investigation of (suspected) colorectal cancer can include laboratory, radiological and endoscopic investigations aiming to firstly confirm histologically the underlying diagnosis of cancer and secondly to stage the tumour. In elective presentations these investigations are undertaken preoperatively, however in emergency presentations (for example obstruction or perforation) histological diagnosis and the completion of staging may take place subsequent to emergency surgery.

1.7.1 Laboratory Tests

1.7.1.1 Routine Blood Tests

Although no specific blood test is capable of diagnosing colorectal cancer, a full blood count may show a microscopic (iron deficient) anaemia raising suspicion for blood loss within the gastrointestinal tract. Inflammatory markers may offer prognostic information as described previously. Renal function and liver function tests may, if abnormal, raise suspicion of metastatic disease and assist in providing an assessment of the overall health of the patient.

1.7.1.2 Carcinoembryonic Antigen

Carcinoembryonic antigen (CEA), first identified in 1965[144] is a glycoprotein that can be tested serologically. It is normally produced by gastrointestinal mucosa

during foetal development however is not produced in significant quantities in adults. CEA may be raised in individuals with colorectal cancer. Neither sensitive nor specific, the preoperative utility of CEA in patients with colorectal cancer is limited[145]. Nonetheless, a raised preoperative CEA has been reported to be a poor prognostic factor and, indeed, routine preoperative sampling is recommended in several clinical guidelines[146,147]. CEA is predominantly used in the postoperative follow-up period with the aim of early detection of recurrent/metastatic disease and is typically checked at 3-6 monthly intervals following curative treatment[148,149] prompting further investigation if raised.

1.7.1.3 Quantitative Faecal Immunochemical Testing

Quantitative faecal immunochemical testing (QFIT) is a non-invasive test that is able to detect microscopic quantities of blood in faeces using antibodies to haemoglobin. This test has been utilised within bowel screening programmes now predominantly superseding guaiac faecal occult blood testing (gFOBT) – a test that reacts with the pseudoperoxidase component of the haem molecules. More recently this test has had increased utility in the clinical environment, in part due to increased pressures on endoscopy services throughout the Covid-19 pandemic, both in terms of prioritising patients with red-flag symptoms for colonoscopy and in low-risk patients avoiding the need for endoscopic investigation. Indeed, it has been shown that the combination of a normal QFIT test and a normal haemoglobin excludes colorectal cancer in 99.96% of cases[150].

1.7.2 Investigations for Diagnosis

1.7.2.1 Lower Gastrointestinal Endoscopy

Lower gastrointestinal endoscopy is the gold standard method of diagnosing colorectal cancer. Typically, this is a full colonoscopy (from anal verge to caecum/terminal ileum) however in some cases a more limited examination, a flexible sigmoidoscopy (from anal verge to sigmoid/descending colon) may be performed.

Endoscopy allows complete visualisation of the colonic and rectal mucosa from the anal verge to the point of insertion. Furthermore, it allows lesions to be biopsied providing a histological diagnosis and may allow complete endoscopic resection of early-stage polyp cancers. Colonoscopy, while having the benefit of visualising the entire colon without the use of ionising radiation, requires full mechanical bowel preparation and often necessitates the administration of intravenous analgesia/sedation. Lower GI endoscopy is considered safe however carries a 1:1000 risk of colonic perforation or bleeding[151]. Flexible sigmoidoscopy is often performed using an enema as bowel preparation and does not usually require analgesia or sedation. However, this more limited colonic assessment will only identify approximately 70% of pathology (remaining 30% situated in the more proximal colon). Patients diagnosed with colorectal cancer should undergo imaging of the entire colon preoperatively to exclude the presence of synchronous tumours (approximately 3.5% of cases[152]) however in some cases this will be impossible due to a large impassable tumour. Nonetheless as defined by the Joint Advisory Group on GI Endoscopy (JAG), a minimum colonoscopy

completion rate (caecal intubation rate) of 90% and desirable rate of 95% exists for endoscopy providers within the United Kingdom[151].

1.7.2.2 Computed Tomography Colonography

Standard Computed Tomography (CT) imaging, while useful for identifying extra-colonic pathology and used routinely for cancer staging, is not sensitive in identifying abnormalities within hollow organs including the colon. A previous study by Klang and colleagues reported that colorectal cancer may be missed on 20% of CT scans[153].

CT colonography is an alternative to standard endoscopic examination that has been shown to be highly sensitive in identifying colorectal cancer[154]. Clinical indications and methodology for CT colonography has been comprehensively summarised by Scalise and colleagues[155]. For optimal imaging, patients require a clean and distended colon. To achieve this, they receive bowel preparation prior to the procedure and an air or carbon dioxide enema throughout the procedure to achieve colonic distension. Additionally, oral contrast (for example gastrograffin) may be given to tag residual stool. Intravenous contrast is not essential for the imaging of colorectal lesions however does improve imaging of other abdominal viscera[156]. Antispasmodic agents (for example buscopan) may be given to reduce abdominal discomfort and improve image quality. CT imaging is performed both in supine and prone positions to optimise colonic imaging. Minimal prep CT colonography is available for patients unable to tolerate full bowel preparation and can be carried out only with administration of oral contrast however is less sensitive than with full bowel preparation.

CT colonography is advantageous over colonoscopy as it has a lower risk of perforation than colonoscopy (approximately 0.04%)[157,158] and may be better tolerated by elderly or frail patients. CT colonography is also useful in patients where full colonic endoscopic examination is not possible either due to discomfort, looping or tight angulation or in patients in whom stricturing pathology is encountered precluding examination of the more proximal colon. Furthermore, CT colonography is able to identify both intra- and extra-colonic pathology. However, unlike colonoscopy, if colorectal pathology is identified on CT colonography a subsequent colonoscopy is likely be required for either polypectomy or biopsy to obtain a tissue diagnosis. Furthermore, residual faecal material may reduce the sensitivity/specificity of this procedure and this procedure involves the administration of ionizing radiation.

1.7.2.3 Colon Capsule Endoscopy

Recently, colon capsule endoscopy (CCE) has been introduced as an alternative to colonoscopy. This investigation requires the patient to swallow a camera containing capsule that transmits images to an externally worn recorder. CCE is beneficial in that it is minimally invasive however still requires the administration of oral bowel preparation. Similar to CT colonography, it carries the significant disadvantage of being unable to obtain a tissue diagnosis or perform polypectomy should pathology be encountered. It has been shown to be safe and effective in the detection of polyps and colorectal cancer when a complete examination is achieved.[159,160] However, completion rates have been reported to be as low as 57%[159-161]. CCE has the disadvantage of requiring manual review of the images taken however work is ongoing to automate this process.

Further research using real-world data is required to investigate whether this mode of imaging is effective or whether it is limited by the incomplete examination rate.

1.7.2.4 Barium Enema

Double contrast barium enema was previously used as a less invasive method of investigation of the colon than endoscopic evaluation, however has now been superseded by CT colonography and is now rarely performed. It is carried out through the rectal administration of double contrast – air and barium - with x-rays being subsequently obtained for abdominal imaging.

1.7.3 Investigations for Staging

1.7.3.1 Computed Tomography

Computed Tomography (CT) imaging of the thorax, abdomen and pelvis should be routinely carried out in all patients to assess for the presence of distant metastatic disease[149]. Typically, this is carried out following the administration of intravenous contrast unless contraindicated due to renal failure or previous contrast reactions. In such situations CT imaging may be carried out without intravenous contrast however this reduces the sensitivity of imaging. Ideally complete CT staging is performed preoperatively, however in emergency presentations some patients may require completion of staging (in particular of the thorax) following emergency surgery.

1.7.3.2 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is routinely carried out in rectal but not colonic cancer. Its utility is in local tumour staging and has been shown to be superior to CT imaging for this. This includes assessment of tumour and nodal staging, assessment of the circumferential resection margin and assessment for extramural venous invasion and is the primary modality of investigation to evaluate treatment decisions, particularly around the need for neoadjuvant chemotherapy and radiotherapy. Some centres may additionally use endoluminal ultrasound scan for the purposes of local staging however access to this is limited and it is not routinely required.

In select cases, MRI has additional utility in evaluation of the liver, either for further characterisation of equivocal lesions identified on staging CT scans or to provide a more detailed assessment of liver metastasis where a liver resection would be considered[162].

1.8 Management

The treatment aim and modality in patients with colorectal cancer depends on tumour stage and location (colonic versus rectal) in addition to patient factors including age, fitness and patient wishes. Treatment options include resectional surgery (predominantly with curative intent), palliative surgery (for example defunctioning or bypass procedures), neoadjuvant (preoperative) chemotherapy or radiotherapy, adjuvant (postoperative) chemotherapy or radiotherapy or palliative chemotherapy or radiotherapy. More recently, immunotherapy has become a treatment modality, predominantly within the palliative setting.

1.8.1 Multidisciplinary Management

The Scottish Intercollegiate Guideline Network (SIGN) and the National Institute for Clinical Excellence (NICE) guidelines[149,163] state that effective management of colorectal cancer requires a multidisciplinary approach. Studies have reported improved surgical and oncological outcomes with multidisciplinary team (MDT) decision making[164]. This team should consist of surgeons, oncologists, pathologists, radiologists and nurses. Involvement of a wider team may be required including hepatic or thoracic surgeons, palliative care specialists and geneticists. This should be carried out at initiation of treatment and following either neoadjuvant treatment or surgical resection to determine the need for further treatment.

1.8.2 Neoadjuvant Therapy

1.8.2.1 Rectal Cancer

Due to the narrow confines of the pelvis, rectal cancer has a significantly higher rate of local recurrence compared to colon cancer. Neoadjuvant radiotherapy +/- chemotherapy can be given to reduce this risk. Preoperative therapy is not routinely used in patients with early rectal cancer (T1-2N0M0) but should be offered in patients with T1-2N1-2M0 or T3-4NanyM0 disease or in margin threatening disease.

In patients without circumferential margin threatening disease, neoadjuvant therapy is usually given as short course radiotherapy (25 Gray in five fractions) but can also be given as long-course chemoradiotherapy. This has been shown to reduce local recurrence risk when compared to surgery alone (5% versus 11% local recurrence risk)[165] and has been shown to be more effective than postoperative radiotherapy at reducing recurrence risk[166]. No clear difference in outcomes of short-course radiotherapy versus long-course chemotherapy have been reported in non-margin threatening rectal cancer. Neoadjuvant therapy within non-margin threatening disease should be offered to people with TanyN1-2M0 disease or T3-4N0M0 disease.

In patients with circumferential margin threatening disease (from either primary tumour or involved lymph nodes) long-course neoadjuvant chemoradiotherapy can be given to downstage the tumour and facilitate surgical resection with clear margins within the total mesorectal excision (TME) plane. In some cases, this may also downstage tumours to allow for sphincter-preserving surgery. This is typically given as 45 Gray in 25 daily fractions over 5 weeks with concomitant

radio sensitising chemotherapy (for example capecitabine or 5-flurouracil) with a subsequent interval period (typically around 6-8 weeks) prior to surgery.

It is now recognised that in some patients, there may be a complete clinical and pathological tumour response to neoadjuvant therapy. After careful discussion with the patient, it may therefore be possible to avoid resectional surgery within these patients, however close follow-up is required to monitor and intervene early in the event of recurrent disease.

1.8.2.2 Colon Cancer

Neoadjuvant therapy has not traditionally been used in colon cancer. It is however recognised that the risk of local recurrence in advanced colon cancer is high – approximately 20%-30%. In the latest NICE guidance[149], a recommendation has been given to consider neoadjuvant chemotherapy in patients with cT4 colon cancer. At present, evidence around neoadjuvant chemotherapy in colon cancer is limited and further evidence is required before a firm recommendation on this can be given. The current data regarding neoadjuvant therapy in locally advanced colon cancer is summarised in a recent review[167]. The FOxTROT study – an international randomised controlled trial of 1052 patients evaluating neoadjuvant chemotherapy in colon cancer - reported neoadjuvant therapy to be safe, well tolerated and was associated with histological downstaging and a significantly reduced rate of incomplete resections[168]. However, no significant different in recurrence rates were seen at two years and longer-term follow-up data is not yet available.

1.8.3 Surgery

Resectional surgery remains the mainstay of treatment with curative intent for patients with colorectal cancer. Surgery has three aims: resection of the tumour with clear margins encompassing a margin of normal tissue, enbloc resection of draining lymph nodes to remove potential lymph node metastasis and allow for full pathological staging and, where possible, to restore intestinal continuity through anastomosing the two ends of bowel together. This can be performed either with sutures or a stapling device with no significant difference in outcome from the method used[169].

In the majority of cases, tumours should be resected with a 5cm longitudinal margin proximally and distally however, a 1cm margin is acceptable in low rectal cancer. The majority of patients undergoing surgery will be undergoing potentially curative surgery for non-metastatic disease although some patients may have potentially resectable lung or liver metastases where the aim of treatment remains curative.

Historically, colorectal cancer surgery was performed by true “general” surgeons who would perform a wide range of operations. More recently however, surgical subspecialisation has become commonplace resulting in a smaller number of surgeons performing a larger number of procedures annually with resultant improvements in patient outcomes[170].

1.8.3.1 Operation Type

The surgery performed will depend on the location of the primary tumour. Options include: right hemicolectomy (caecal, ascending colon and hepatic flexure tumours), extended right hemicolectomy (transverse colon or splenic flexure tumours), left hemicolectomy (descending colon tumours), sigmoid colectomy (sigmoid colon tumour), anterior resection (rectal cancer where preservation of the sphincter complex is achievable) or abdominoperineal resection (where preservation of the sphincter complex is not possible). Synchronous tumours and tumours on a background of inflammatory bowel disease may require a subtotal colectomy or panproctocolectomy.

1.8.3.2 Operative Technique

Traditionally, colorectal resections have been performed using open surgery however more recently minimally invasive techniques, predominantly laparoscopic surgery but more recently robotic surgery have become increasingly commonplace. The use of minimally invasive surgery has been reported to be associated with shorter length of stay, a lower postoperative systemic inflammatory response and no adverse oncological outcomes compared to traditional open surgery[171,172].

1.8.3.3 Restoration of Intestinal Continuity

Following resection of the primary tumour, the operating surgeon must make a decision on whether to: (1) restore intestinal continuity with a primary anastomosis, (2) restore intestinal continuity with a primary anastomosis but defunction this with a temporary stoma or (3) create a temporary or permanent stoma. Anastomotic leak is a feared complication associated with significant morbidity and mortality and the decision to form a stoma as opposed to making a primary anastomosis is predominantly due to concern over an unacceptably high risk of leakage and the consequences thereof. A number of tumour, host, and technical factors are associated with increased risk of anastomotic leak as summarised in a previous review. These include tumour factors (distal tumours, tumours larger than 3cm, advanced stage, emergency presentations), host factors (smoking, obesity, poor nutrition, immunosuppression) and intraoperative factors (prolonged surgery, intraoperative blood loss)[173]. Distal tumours are recognised to be associated with increased risk of anastomotic leakage and following low anterior resection with a primary anastomosis a defunctioning loop ileostomy may be performed to reduce the likelihood and severity of anastomotic leakage[174]. Patients undergoing emergency surgery are more likely to have a stoma with view to potential reversal and restoration of continuity as a staged procedure within the elective setting.

1.8.3.4 Special Considerations - Rectal Cancer

Within rectal cancer surgery, consideration must be given as to whether sphincter sparing surgery is possible without compromising oncological resection

margins. If sphincter sparing surgery is possible, an anterior resection is typically the surgery of choice. If it is not possible to achieve an oncologically adequate resection while sparing the sphincter complex an abdominoperineal resection is the operation of choice (excision of rectum and anus with closure of the perineum).

First described by Heald in 1979[175], total mesorectal excision (TME) involves removing the rectal specimen with the mesorectum intact. It has been shown to reduce local recurrence and improve survival in patients undergoing rectal resections and is now considered the holy grail of rectal cancer surgery. Resection within the TME plane should be routinely carried out in patients undergoing resectional surgery of the mid- or lower rectum. In addition to improving oncological outcomes, dissection within this plane preserves the autonomic nerves within the pelvis maintaining postoperative sexual and bladder function. It is however recognised that a significant proportion of patients (up to 40%) undergoing a low anterior resection may experience disordered bowel function[176]. This is known as low anterior resection syndrome (LARS) and symptoms include faecal urgency, incontinence and altered stool consistency.

Patients undergoing abdominoperineal resections have been reported within large cohort studies to have a higher rate of local recurrence than patients undergoing anterior resection and this is likely a result of higher rates of circumferential resection margin involvement and intraoperative tumour perforation. As a result, SIGN[163] have recommended that in patients undergoing abdominoperineal resection, an extralevator approach is recommended and this has been shown to have better outcomes[177-179]. However, this technique results

in a large perineal defect that may require plastic surgery input for closure with a pedicled flap.

1.8.3.5 Special Considerations – Local Excision

In some cases, local excision, either endoscopically or using transanal minimally invasive surgery (TAMIS) may be appropriate. While there are benefits to this approach, the local management of colorectal cancer requires careful discussion with the patient and close clinical, radiological and endoscopic follow-up to monitor for evidence of recurrence with timely formal resectional surgery should this be the case.

As defined in the recent SIGN guidelines, colonic polyp cancers may be completely removed at colonoscopy. Assuming these cancers are completely excised (1mm margin), are well-differentiated and do not show evidence of lymphovascular invasion, close follow-up without proceeding to formal colonic resection is reasonable. Patients must be made aware that while it is impossible to accurately tell whether or not there is lymph node involvement this is extremely rare in the case of a T1 polyp cancer.

1.8.3.6 Special Considerations - Metastatic Disease

The majority of patients with metastatic colorectal cancer at time of diagnosis will not be candidates for curative treatment. However, a subset of patients with liver or lung metastases may be considered for resectional surgery of both the primary tumour and metastatic disease with curative intent, albeit recurrence rates remain high. In some cases, ablation rather than resection of

the metastatic disease may also be possible. To date, there is no consensus on whether or not metastatic disease should be performed simultaneously or whether a staged approach should be undertaken.

1.8.3.7 Enhanced Recovery After Surgery

The enhanced recovery after surgery pathway (ERAS), first introduced in 1997, is a multimodal perioperative care pathway that aims to promote early recovery for patients undergoing major surgery. It is now commonplace within a number of specialties including colorectal, pancreatic and upper gastrointestinal surgery.

The enhanced recovery after surgery pathway includes a number of preoperative, intraoperative and postoperative measures that have been summarised within a recent review. These measures aim to reduce perioperative stress, maintain postoperative physiological function and accelerate recovery after surgery[180] and address issues including preoperative fasting and carbohydrate loading, the maintenance of normothermia intraoperatively, minimally invasive surgery, the avoidance of intraperitoneal drains and early return to oral intake and mobilisation withing the postoperative period. However, although the ERAS pathway aims to reduce the stress response to surgery, a previous review did not find clear evidence of this in terms of a reduction in the postoperative systemic inflammatory response, with the exception of the use of minimally invasive surgery[171]. Improved postoperative outcomes have however been reported following the introduction of ERAS measures[181].

1.8.4 Adjuvant Therapy

Adjuvant chemotherapy for colorectal cancer is considered for high risk TNM Stage II or TNM Stage III disease to reduce the risk of recurrent/metastatic disease. Chemotherapy is typically given as combination therapy, combining oxaliplatin with a thymidlytate synthase inhibitor for example capecitabine (XEPOX) or 5-flurouracili/folinic acid (FOLFOX). This combination therapy has been shown to be more effective than oral capecitabine alone[182] however does carry with it more treatment toxicity therefore in some patients (for example the elderly) single agent therapy with oral capecitabine may be more appropriate. Adjuvant therapy was previously given for 6 months however more recently, non-inferiority of 3 months versus 6 months of adjuvant chemotherapy has been reported[183].

TNM Stage II colorectal cancer is subdivided into low-risk and high-risk based on a number of clinicopathological variables. While those tumours deemed low-risk typically do not require adjuvant chemotherapy, tumours deemed high-risk should be considered for adjuvant treatment. However, within TNM Stage II colorectal cancer the overall benefit from adjuvant therapy is small and this requires careful balance of benefits and risks including patient age and co-morbidity. High risk clinicopathological features include emergency presentation, T4 disease, <12 nodes in the resection specimen, poorly differentiated tumours and the presence of margin involvement or extramural venous invasion[184]. The effect of adjuvant chemotherapy in TNM Stage II disease remains uncertain however both the QUASAR trial[185] and a recent meta-

analysis[186] reported improved survival with adjuvant chemotherapy in selected cases therefore this is recommended in several recent guidelines[147,184,187].

In TNM Stage III disease, adjuvant chemotherapy has been shown to reduce the risk of recurrence[188-190] following surgical resection with curative intent assuming benefits outweigh risks (for example, elderly or significant co-morbidities).

Within rectal cancer, adjuvant radiotherapy may be considered in the event of an unexpected positive margin if the patient has not received preoperative radiotherapy, however outcomes are worse when compared to neoadjuvant radiotherapy.

1.8.5 Follow-Up

Within the West of Scotland, regional guidelines exist for the follow-up of patients after treatment with curative intent for colorectal cancer. The follow-up protocol includes: routine outpatient clinic assessment, interval CEA testing and interval CT imaging to assess for evidence of recurrent or metastatic disease. Additionally, patients undergo follow-up colonoscopy to monitor for further lesions. The West of Scotland follow-up protocol is shown in Figure 1-3.

Appendix 1

Guidelines for the management of Follow-up for Colorectal Cancer

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

Given that there is no firm evidence base to support any single follow up strategy, these guidelines should not supersede clinical judgement in the management of individual patients.

West of Scotland Cancer Network
Final – Published Colorectal Cancer MCN Regional Follow-up Guidelines v2.0 18/04/2016

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Figure 1-3 Follow-up guidelines for colorectal cancer in the West of Scotland. Credit – West of Scotland Cancer Network

1.8.6 Palliative Therapy

In patients with non-resectable metastatic disease, inoperable disease or patients unfit for resectional surgery, palliative chemotherapy may be considered to slow disease progression and reduce symptoms. A careful balance has to be considered between improved prognosis versus the side effects experienced through chemotherapy. Furthermore, if a patient is unfit for resectional surgery they may be unfit for chemotherapy. Palliative radiotherapy, typically for pain or bleeding may be considered in rectal cancer[191]. In patients who develop mechanical obstruction due to their primary tumour, non-resectional palliative surgical options may be considered including stenting, defunctioning stoma or bypass procedures.

1.9 Pathology Reporting and Staging

1.9.1 Staging

Tumour staging is perhaps the most important factor to evaluate in a patient diagnosed with cancer. Staging is the most important prognostic factor in a patient presenting with colorectal cancer and determines the treatment that is likely to be undertaken. This includes evaluation of the degree of infiltration of the colonic wall, the presence of locoregional lymph node involvement and the presence of distant metastatic disease.

1.9.1.1 Dukes' Staging

In 1932, Cuthbert Esquire Dukes described a method of staging rectal cancer[192] that has subsequently been used for colon cancer – "Dukes' Staging". This staging system was originally intended for use in rectal cancer and initially graded from A to C. Since this method was first devised a number of modifications have been suggested, the most recent model being shown in Table 1-3. However, Dukes' staging has now been superseded by the TNM Classification and as outlined by the Royal College of Pathologists in 2018, Dukes' Staging should no longer be routinely recorded in colorectal cancer[193].

Table 1-3 Dukes' Staging of Colorectal Cancer

Stage	Tumour	Nodes	Distant Metastases
Dukes' A			
	A tumour involving the mucosa or submucosa only	No lymph nodes involved	No distant metastases

Dukes' B			
B1	Tumour extends to the muscularis propria	No lymph nodes involved	No distant metastases
B2	Tumour extends through muscularis propria	No lymph nodes involved	No distant metastases
Dukes' C			
C1	Tumour extends to the muscularis propria	Lymph nodes involved	No distant metastases
C2	Tumour extends through the muscularis propria	Lymph nodes involved	No distant metastases
Dukes' D			
	Any	Any	Distant metastases present

1.9.1.2 TNM Staging

The TNM Classification (tumour, node, metastases) was developed by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC). Although other factors are important, this staging system is the predominant factor used to make treatment decisions and to predict prognosis.

Preliminary radiological staging is ideally performed prior to resectional surgery however, particularly in the emergency setting, this may be completed postoperatively. As described previously, this involves a CT scan of the chest, abdomen and pelvis and in the case of rectal cancer, MRI scan for local disease staging. Final staging is performed based on the pathological specimen after resectional surgery.

TNM staging provides an overall tumour stage (I/II/III/IV) on the basis of the primary tumour (T Stage), the regional lymph node status (N Stage) and the

presence of distant metastases (M Stage). Since its initial formation, the TNM Staging System has gone through a number of modifications, the most recent version being the 8th edition. The criteria of each T Stage, N Stage and M Stage is shown in Table 1-4. These can be combined into an overall AJCC tumour stage as shown in Table 1-5.

Prefixes may be used in addition to TNM Staging. The prefix “c” indicates that this is based on radiological staging. The prefix “p” indicates that this is based on pathological staging. The prefix “y” indicates that neoadjuvant therapy has been administered. The prefix “r” should be used if the tumour is recurrent and the prefix “a” should be used if derived from an autopsy specimen.

Table 1-4 TNM Classification 8th Edition

Primary tumour (pT)		
pTX		Primary tumour cannot be assessed
pT0		No evidence of primary tumour
pT1		Tumour invades submucosa
pT2		Tumour invades muscularis propria
pT3		Tumour invades into subserosa or into non-peritonealised pericolic or perirectal tissues
pT4		
	pT4a	Tumour perforated visceral peritoneum
	pT4b	Tumour directly invades other organs or structures
Nodal staging (pN)		
pNx		Regional lymph nodes cannot be assessed
pN0		No regional lymph node metastatic disease
pN1		Metastatic disease in 1-3 regional lymph nodes
	pN1a	Metastasis in 1 regional lymph node
	pN1b	Metastasis in 2-3 regional lymph nodes
	pN1c	Tumour deposits (satellites) in the subserosa or non-peritonealised pericolic or perirectal soft tissue without regional lymph node metastatic disease
pN2		Metastatic disease in 4+ regional lymph nodes
	pN2a	Metastases in 4-6 regional lymph nodes
	pN2b	Metastasis in 7 or more regional lymph nodes
Distant metastasis (pM)		
pM0		No distant metastatic disease
pM1		
	pM1a	Metastasis confirmed to one organ without peritoneal metastasis
	pM1b	Metastasis in more than one organ
	pM1c	Metastasis to the peritoneum with or without other organ involvement

Table 1-5 – Classification of T Stage, N Stage and M Stage into overall AJCC tumour stage

AJCC Stage	T	N	M
0	Tis	0	0
I	T1 or T2	0	0
II	T3 or T4	0	0
IIa	T3	0	0
IIb	T4a	0	0
IIc	T4b	0	0
III	Tany	N1 or N2	M0
IIIa	T1 or T2	N1 or N1c	M0
	Or		
	T1	N2a	M0
IIIb	T3 or T4a	N1/N1c	M0
	Or		
	T2 or T3	N2a	M0
	Or		
	T1 or T2	N2b	M0
IIIc	T4a	N2a	M0
	Or		
	T3 or T4a	N2b	M0
	Or		
	N4b	N1 or N2	M0
IV	Any	Any	M1
IVA	Any	Any	M1a
IVB	Any	Any	M1b
IVC	Any	Any	M1c

1.9.2 Macroscopic Core Items

1.9.2.1 Site of Tumour

The tumour site is typically recorded by the surgeon prior to the specimen being sent to the laboratory. If the specimen straddles two sites, the site with the greatest tumour bulk should be recorded. The rectosigmoid junction is

considered the area where the three taeniae coli fuse to form the longitudinal rectal wall muscle. If distinction between sigmoid and rectum is not possible, the site should be reported as rectosigmoid junction.

1.9.2.2 Maximum Tumour Diameter

As defined by the Royal College of Pathologists dataset for histological reporting of colorectal cancer, maximum tumour diameter is the maximum tumour diameter (not thickness) measured from the luminal aspect of the bowel.

1.9.2.3 Distance of Tumour to Nearest Longitudinal Margin

As defined by the Royal College of Pathologists dataset for histological reporting of colorectal cancer, this is the measurement to the nearest longitudinal margin of the specimen. If the tumour is greater than 30mm to the nearest longitudinal margin, the margin can be assumed not to be involved. However, if the tumour is within 30mm of the nearest longitudinal margin or if there are a number of high-risk features (including signet ring carcinomas, tumours with extensive vascular or lymphatic permeation or undifferentiated cancers) the margins should be examined histologically.

1.9.2.4 Tumour Perforation

As defined by the Royal College of Pathologists dataset for histological reporting of colorectal cancer, tumour perforation is a macroscopically visible defect through the tumour resulting in the bowel lumen being in communication with the external surface of the resection specimen. It may be spontaneous or iatrogenic. This is distinct from a proximal perforation away from the tumour site and is recognised to be an adverse prognostic feature[194,195]. Tumours with a perforation are considered pT4a.

1.9.2.5 Relation of Tumour to Peritoneal Reflection (Rectal Cancer)

As defined by Royal College of Pathologists dataset for histological reporting of colorectal cancer, rectal tumours should have their relationship to the peritoneal reflection at the anterior aspect of the specimen classified as: entirely above the peritoneal reflection, at the level of the peritoneal reflection or entirely below the level of the peritoneal reflection. Tumours situated below the level of the peritoneal reflection are associated with higher local recurrence rates[196].

1.9.2.6 Plane of Mesorectal Excision

As described previously, rectal resections should be carried out at the level of the mesorectal plane. Breach of the mesorectum is associated with increased risk of local recurrence. As defined by the Royal College of Pathologists dataset

for histological reporting of colorectal cancer, three planes of excision are described: mesorectal (smooth mesorectum with no violation of fascial covering), intramesorectal (moderate bulk to the mesorectum with minor irregularity of the mesorectal surface) and muscularis propria (substantial areas where mesorectal tissue is missing with cuts/tears down to muscularis propria).

1.9.2.7 Plane of Resection of the Sphincters (Abdominoperineal Resection)

In patients undergoing abdominoperineal resection, the Royal Collage of Pathologists dataset has defined the plane of excision of levators/sphincters as either extralevator, sphincteric or intrasphincteric. In an extralevator resection, the plane lies external to the levator ani muscles which are removed en bloc creating a more cylindrical specimen. A sphincteric plane is considered a plane where no levator muscles (or only a small cuff) are attached to the specimen and the resection margin is formed by the surface of the sphincter muscles. There is likely to be some waisting of the specimen. An intrasphincteric plane is described as where the surgeon has inadvertently entered the sphincter muscle, deeper into the submucosa, or the presence of a perforation at any point below the peritoneal reflection.

1.9.2.8 Distance from Dentate Line (Abdominoperineal Resection)

In patients undergoing an abdominoperineal excision, the distance from the distal aspect of the tumour to the dentate line is given as a crude estimation of the appropriateness of abdominoperineal (AP) resection.

1.9.3 Microscopic Core Items

1.9.3.1 Tumour Type

The majority of colorectal cancers are adenocarcinomas. However, as defined by the World Health Organisation 2019 Classification[197], there are other tumour types including: mucinous carcinomas, signet ring cell carcinomas, squamous carcinomas, neuroendocrine tumours and undifferentiated carcinomas. All colorectal cancer should be tested for microsatellite instability for the purpose of detecting Lynch syndrome.

1.9.3.2 Differentiation

As defined by the Royal College of Pathologists dataset for histological reporting of colorectal cancer, tumours should be defined as either poorly differentiated (high grade) or moderately-well differentiated (low grade) based on tumour architecture and gland or tubule formation. Poorly differentiated tumours are associated with adverse outcomes[198].

1.9.3.3 Local Invasion (T Stage)

The maximum degree of local invasion into the bowel wall (T Stage) should be recorded as described previously in the TNM Staging Section. The maximum distance of tumour spread beyond the bowel wall should be reported. Involvement of the peritoneal surface is defined by the Royal College of

Pathologists as “tumour breaching the serosa with tumour cells visible either on the peritoneal surface, free in the peritoneal cavity or separated from the peritoneal surface by inflammatory cells only”.

1.9.3.4 Preoperative Therapy Response

Typically, neoadjuvant treatment has been limited to rectal cancers however more recently a role has been developed in the use of neoadjuvant chemotherapy in colon cancer. Response to neoadjuvant therapy has been stratified using a tumour regression score as shown in Table 1-6. Patients with a marked or complete response to neoadjuvant therapy have been reported to have better oncological outcomes[199,200], albeit previous studies have been predominantly limited to rectal cancer only. Evidence of response within regional lymph nodes or other potentially metastatic sites should also be recorded.

Table 1-6 – Tumour regression score

Tumour regression score	Description
0 – Complete response	No viable cancer cells
1 – Near complete response	Single cells or rate small groups of cancer cells
2 – Partial response	Residual cancer with evident tumour regression but more than single cells or rare small groups of cancer cells
3 – Poor or no response	Extensive residual cancer with no evident tumour regression (poor or no response)

1.9.3.5 Involvement of Margins (Longitudinal and Circumferential)

As defined by the Royal College of Pathologists dataset for histological reporting of colorectal cancer, if longitudinal margins are examined histologically the

presence or absence of tumour should be recorded. In rectal cancers, the circumferential resection margin should also be recorded and if it is <1mm the margin is considered to be involved. Margin involvement is associated with adverse outcomes in particular local recurrence[201] and may be an indication for adjuvant therapy. Margin status can be defined as R0 (clear margins), R1 (microscopic margin involvement) or R2 (macroscopic margin involvement).

1.9.3.6 Lymph Node Status

As defined by the Royal College of Pathologists dataset for histological reporting of colorectal cancer, all lymph nodes should be histologically examined. The total number of retrieved lymph nodes, the total number of involved lymph nodes and the involvement of the lymph node closest to the main vascular tie should be recorded. Furthermore, if neoadjuvant therapy has been administered, evidence of regression within nodal tissue should be recorded. An involved node is considered as any lymph node with a deposit >0.2mm. Single tumour cells or groups <0.2mm in maximum dimension are considered tumour negative. Nodal staging is described within the TNM Staging section.

1.9.3.7 Tumour Deposits

As defined by Royal College of Pathologists dataset for histological reporting of colorectal cancer, tumour deposits are discrete macroscopic or microscopic nodules of cancer, separate from the primary tumour. They are located in the mesocolon/mesorectum however are distinct from the primary tumour and not

related to lymph nodes/vascular/neural structures. They should be classified by presence (yes/no) and the number of deposits (1/2/3/4/>5) and are associated with adverse outcomes[202].

1.9.3.8 Venous, Lymphatic and Perineural Invasion

Venous, lymphatic and perineural invasion may be described as intramural (intramuscular or submucosal) or extramural (beyond the muscularis propria). Venous invasion has been widely reported and recognised to be an adverse prognostic feature particularly in the case of extramural venous invasion but also intramural venous invasion[203]. As described by Talbot, venous invasion can be considered as tumour present within an extramural endothelium lined space that is either surrounded by a rim of muscle or contains red blood cells[204].

More recently, perineural invasion (tumour cells invading nerves and spreading along nerve sheaths) has been associated with adverse outcomes[205] and the Royal College of Pathologists now recommend that the deepest level of venous, lymphatic and perineural invasion should be recorded. If involved, venous, lymphatic and perineural invasion should be recorded as V1/2, L1 and Pn1 respectively in addition to the deepest level of spread (intramural/extramural).

1.9.3.9 Histologically Confirmed Distant Metastatic Disease

The presence and site of histologically confirmed distant metastatic disease should be recorded. Metastatic disease in lymph nodes distant from the tumour

(for example para-aortic or external iliac nodes) should be regarded as distant metastatic disease.

1.9.3.10 Separate Abnormalities

As defined by Royal College of Pathologists dataset for histological reporting of colorectal cancer, separate abnormalities including inflammatory bowel disease, polyps, diverticulosis or evidence of polyposis syndromes should be recorded.

1.9.3.11 Non-Core Items

Other items that may be recorded include the nature of the advancing margin, tumour budding, peritumoral inflammation and tumour stromal percentage.

1.10 Outcomes

1.10.1 Short-Term Outcomes

Surgery, the mainstay of curative treatment in colorectal cancer, is associated with significant postoperative morbidity. As described by Dindo and colleagues, a postoperative complication is anything that causes the patient to deviate from the expected postoperative course. Short-term outcomes (postoperative morbidity and mortality) may be classified based on either type of complication (infective versus non infective, surgical site infection versus non-surgical site infection) or by severity. The Clavien-Dindo classification[206,207] is a validated and replicable measure of classifying postoperative complications for severity and is routinely utilised within the clinical setting as shown in Table 1-7.

Postoperative complications are recognised to have multiple adverse effects on the patient. In the short-term, complications result in a prolonged length of hospital stay and a significant economic burden on healthcare service. In the long-term they have been shown to adversely impact oncological outcomes, quality of life and long-term survival following surgery[47,48].

Table 1-7 – Clavien-Dindo Classification of postoperative complications

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Antiemetics, analgesics, antipyretics and intravenous fluids/electrolytes may be administered. This grade includes wound infections opened at the bedside.
Grade II	Complications requiring pharmacological treatment outwith those allowed for Grade I complications
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anaesthesia
Grade IIIb	Intervention under general anaesthesia
Grade IV	Life threatening complications requiring ICU management
Grade IVa	Single organ dysfunction
Grade IVb	Multiorgan dysfunction
Grade V	Death

1.10.2 Long-Term Outcomes

The prediction of prognosis in colorectal cancer is predominantly determined by disease stage, however it is now recognised that other tumour and host factors previously described have a significant impact on prognosis independent of TNM Stage. As shown in Table 1-8, 5-year overall survival in patients diagnosed with colorectal cancer within the United Kingdom from 2013-2017 was 92%/84%/65%/10% for TNM I/II/III/IV colorectal cancer respectively. When compared to the European average, outcomes within the United Kingdom are below average in comparison to the rest of Europe. It is unclear why this is the case but may relate to differences in cancer biology, stage at diagnosis, screening participation or treatment received[5]. As shown in Figure 1-4, between 1971 and 2019 age standardised (AS) mortality rates have decreased by 45%.

Table 1-8 5-year survival adjusted by tumour stage – adapted from Cancer Research UK

TNM Stage		All Persons	Males	Females
I		92%	91%	93%
II		84%	84%	85%
III		65%	64%	66%
IV		10%	10%	10%
Unstageable		42%	42%	41%

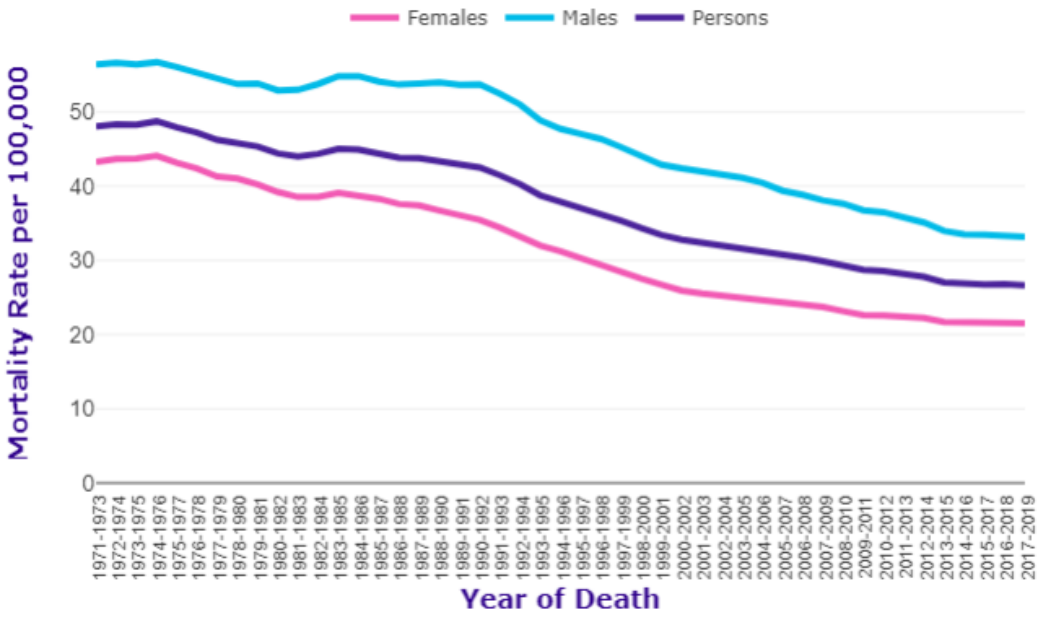


Figure 1-4 Bowel Cancer, European Age-Standardised Mortality Rates per 100,000 persons population, UK, 1971-2019. Credit: Cancer Research UK

1.11 Managed Clinical Network Data – Scotland

Within Scotland, National Cancer Managed Clinical Networks (MCNs) have been established with the aim of delivering high quality patient care. Three such networks have been established: WoSCAN (West of Scotland Cancer Network), NOSCAN (North Scotland Cancer Network) and SCAN (South East Cancer Network). These networks are groups of health professionals from primary, secondary and tertiary care not limited by existing professional or NHS trust boundaries.

The predominate dataset used within this thesis is a cohort of patients diagnosed with colorectal cancer between 2011 and 2014 from the West of Scotland Managed Clinical Network. After approval from the Public Benefit and Privacy Panel (PBPP) for Scotland, the electronic Data Research and Innovation Service (eDRIS) team (Public Health Scotland) were able to identify all patients diagnosed with colorectal cancer in the West of Scotland (NHS Greater Glasgow and Clyde, NHS Ayrshire and Arran, NHS Forth Valley, NHS Lanarkshire) based on the ICD-10 codes: C18, C19 and C20. Through data linkage performed by eDRIS, this patient cohort was linked to the Scottish Bowel Screening Programme (SBoSP) dataset, National Records of Scotland deaths data, the Prescribing Information System for Scotland (PIS). This database was checked for missing data and inconsistencies and through an electronic records search these were corrected where possible.

Additional data points including laboratory results, BMI, smoking status, co-morbidities, ethnicity and postoperative complications were obtained from electronic records. Deprivation was stratified using the Scottish Index of Multiple Deprivation (SIMD) 2012[208] and thus provided the most accurate SIMD at time of

diagnosis. Patients were considered to have received adjuvant chemotherapy if this had been started regardless of the duration of treatment received. Treatment intent had been defined as either curative or palliative as determined by the MDT at time of treatment and as such, patients with microscopically (but not macroscopically) involved margins were considered curative.

Deaths data was updated until the end of 2018. The primary and secondary (if applicable) causes of death were taken from Section 1a and Section 1b of the death certificate respectively. Deaths were calculated from the date of surgery until date of death unless the population studied included patients who did not undergo surgery in which case deaths were calculated from the date of diagnosis until date of death. This has been specified in the individual methods sections. Cancer related deaths were defined as colon and/or rectal cancer being either the primary or secondary cause of death on the death certificate. All patients were followed up for a minimum of 48 months from diagnosis and 42 months from surgery. It is therefore recognised that depending on the algorithm used the number of cancer deaths may vary.

1.13 Summary and Aims

Colorectal cancer remains the fourth most common cancer and second most common cause of cancer related death in the United Kingdom. Worldwide, there are approximately 1.8 million new cases of colorectal cancer annually. Disease stage (TNM Stage) at diagnosis is the most significant factor that determines management and predicts long-term oncological outcomes however a number of other factors have also been reported to be independently associated with short-term and long-term outcomes. Resectional surgery remains the mainstay of curative treatment for colorectal cancer but is associated with significant morbidity. Even after potentially curative resectional surgery with/without chemotherapy/radiotherapy a significant proportion of patients will eventually succumb from their disease.

Although the majority of patients are diagnosed with and undergo investigations and treatment for colorectal cancer on an elective basis, a significant proportion continue to present with acute symptoms requiring investigation and treatment on an emergency basis. Emergency presentations are widely reported to be associated with adverse short-term and long-term outcomes even after adjustment for other clinicopathological factors including disease stage. Although the widespread introduction of bowel screening programmes has had some effect on reducing emergency presentations, large bowel obstruction (likely to be predominantly the result of colorectal cancer) remains one of the most common indications for emergency laparotomy within the United Kingdom.

A number of clinicopathological factors (tumour, host, perioperative and other factors) have been reported to differ between elective and emergency

presentations of colorectal cancer. Many of these factors will be associated with adverse outcomes. It therefore seems likely that it is a combination of these factors, as opposed to emergency presentation per se, that result in the adverse outcomes seen in emergency compared to elective presentations of colorectal cancer. The identification of those factors that underpin the adverse outcomes seen in patients presenting emergently with colorectal cancer may help to identify strategies to improve short-term and long-term outcomes within this high-risk group of patients. Furthermore, while some of these factors (for example the systemic inflammatory response) may be more common within emergency patients, the identification of these factors may also allow for strategies to improve outcomes within patients undergoing elective diagnosis, investigation and treatment.

The aim of the present thesis was to:

1) Summarise the previous literature with regard to the association between tumour and host factors and mode of presentation in patients with colorectal cancer– a systematic review and meta-analysis.

2) Examine the association between mode of presentation and short-term/long-term outcomes of all patients diagnosed with colorectal cancer within the West of Scotland.

3) Examine the association between tumour and host factors, mode of presentation and short-term/long-term survival in patients undergoing resectional surgery with curative intent for colon cancer.

4) Examine the association between co-morbidity, mode of presentation and short-term/long-term survival in patients undergoing resectional surgery with curative intent for colon cancer.

5) Examine the role for assessing the preoperative systemic inflammatory response using both a differential white cell count based score and acute phase protein-based score in patients undergoing curative surgery for colon cancer and to assess the association between mode of presentation, the preoperative systemic inflammatory response and short-term/long-term survival.

6) Examine the association between CT-derived body composition and mode of presentation in patients undergoing curative resectional surgery for colon cancer and the subsequent effect of this on short-term/long-term survival.

7) Examine the route to diagnosis of colorectal cancer in a population with an established bowel screening programme.

8) Examine the association between common genetic mutations and mode of presentation in patients undergoing curative resectional surgery for colon cancer and the effect of these on long-term survival.

9) Establish attitudes towards the use of single dose perioperative steroids in patients undergoing curative resectional surgery for colorectal cancer and to determine whether there is equipoise for conducting a randomised controlled trial to examine the role of perioperative steroids in reducing the postoperative systemic inflammatory response and improving

postoperative short-term/long-term outcomes in patients undergoing curative surgery for colorectal cancer.

2 Chapter 2 – Determinants of Emergency Presentation in Patients with Colorectal Cancer – a Systematic Review and Meta-Analysis

2.1 Introduction

As described within Chapter 1, colorectal cancer remains highly prevalent and is associated with significant morbidity and mortality. There are multiple modalities of presentation of colorectal cancer however these can be broadly classified into elective or emergency[120].

Emergency presentations of colorectal cancer are associated with adverse short-term and long-term outcomes in comparison to elective presentations. While factors including more advanced disease stage[130,209] and higher ASA classification[210] at presentation may contribute to this, recent research suggests that emergency presentation remains a poor prognostic factor following potentially curative treatment for colorectal cancer even after adjustment for other clinicopathological factors including disease stage[211,212].

It seems likely that the adverse outcomes observed in emergency compared to elective presentations of colorectal cancer are due to disparities in tumour, host and other factors between each mode of presentation rather than being due to emergency presentation per se. To improve long-term outcomes within this high-risk group of patients it is essential to firstly determine how elective and emergency presentations differ both in terms of tumour factors and host factors and subsequently to determine which of these factors have the most significant effect on short-term and long-term outcomes. For common clinicopathological

factors the association between these factors and mode of presentation has been previously studied. For more novel clinicopathological factors, the association with mode of presentation may yet to be studied. To date, the existing literature comparing clinicopathological factors and mode of presentation has not been comprehensively summarised.

The present study takes the form of a systematic review and meta-analysis and aims to comprehensively review thirty years of literature analysing the association between clinicopathological factors and mode of presentation of colorectal cancer to identify those factors that differ between elective and emergency presentations.

2.2 Methods

This systematic review and meta-analysis of published literature was carried out according to a pre-defined protocol. The primary outcome was to analyse the differences between tumour factors and host factors and mode of presentation of colorectal cancer.

Studies published between January 1990 and August 2018 were identified through an electronic search of the US National Library of Medicine (MEDLINE) and the Cochrane Database of Systematic Reviews. Selected other studies were identified through a manual bibliography search. The following search strategy was used: (colon OR rectum OR rectal OR colorectal) AND (cancer OR carcinoma OR adenocarcinoma OR neoplasm OR malign OR tumour) AND (emergency OR acute OR urgent OR non-elective) AND (surgery OR surgical OR operation OR resection OR procedure).

On completion of the online search, the title and abstract of each identified study was examined for relevance with full text being obtained for all potentially relevant studies. This was undertaken by an individual researcher with discussion with a senior author where required. Studies were included regardless of design, with both trials and observational studies being eligible for inclusion. Studies that were not in English, studies where the full text was not available, studies that included patients undergoing colorectal resection for pathology other than cancer or patients undergoing colonic stenting were excluded. The present study involved a wide literature search to capture as much of the pre-existing literature as possible however small studies (deemed those with less than 50 patients within the emergency group) were excluded to reduce the risk of bias. A small number of additional studies were identified

through a manual research of the reference list of included papers. In those instances where multiple studies were available using the same patient population only the most recent study was included. If populations varied the most inclusive study was used. Those studies that did not provide comparison between elective and emergency patients were excluded from this review. This is shown in the PRISMA flow diagram (Figure 2-1).

Provided that there were 3 or more studies for a particular factor, a meta-analysis of tumour/host factors was performed. Studies included either reported the numbers of emergency and elective patients and the number of patients with the factor of interest analysed or reported percentages in a way that allowed these numbers to be calculated. The Cochrane Handbook for Systematic Reviews[213] has been used to guide the reporting of results within the present study and the PRISMA-P checklist was used to confirm appropriate reporting of this study.

2.2.1 Statistical Analysis

All statistical analyses were performed using Review Manager (RevMan) Version 5.3, The Cochrane Collaboration. For all comparisons an unadjusted odds ratio was used. Where possible, total sample sizes and events were taken from the raw data presented in each study. If events were reported as a percentage of total sample size, the event size was calculated from this percentage. 95% confidence intervals were used throughout and a p-value of <0.05 was considered significant. Forest plots were used for graphical display of results. The degrees of heterogeneity were defined as non-significant between 0% and

30%, moderate between 30% and 50%, substantial between 50% and 75% and considerable between 75% and 100%

2.3 Results

2.3.1 Literature Search

Studies were selected as demonstrated in the PRISMA diagram (Figure 2-1). The initial search strategy identified 7,609 studies whose titles and abstracts were reviewed. Studies were excluded that were published prior to 1990 (n=600), not available in English (n=1,035), primarily compared colonic stenting (n=141), did not have an available full paper (n=648) or were either not relevant to this topic or included pathologies other than colorectal cancer (n=5,034). This led to the review of 151 full papers. Of these a further 97 were excluded as they included less than 50 patients (n=23), did not provide a comparison between elective and emergency patients (n=30), included pathologies other than colorectal cancer (n=13), were articles (n=1), duplicate studies (n=4) or were not relevant (n=26). The remaining 54 studies were included in this review.

2.3.2 Tumour Factors

2.3.2.1 Tumour Location

20 studies examined the association between tumour location and mode of presentation in 97,788 patients (Table 2-1). Within this review, tumours of the right colon, hepatic flexure and transverse colon were considered right-sided. Tumours of the splenic flexure, left colon and sigmoid colon have been considered left-sided. Rectosigmoid and rectal tumours have been considered rectal.

11 studies [123,126,128-130,214-220] examined the association between colonic/rectal location and mode of presentation in 62,867 patients. On meta-analysis

including all of these studies (Figure 2-2) there was an association between emergency presentation and colonic location (OR 2.45, 95%CI 2.33-2.57, p<0.001, I^2=94%).

19 studies[123,126,128,130,210,214-227] examined the association between colonic location (left/right) and mode of presentation in 95,911 patients. On meta-analysis including 15 studies of 61,738 patients (Figure 2-3) no significant association was reported between emergency presentation and colonic location (OR 0.98, 95%CI 0.94-1.01, p=0.22, I^2=77%).

2.3.2.2 Tumour Size

1 study[130] examined the association between tumour size and mode of presentation in 1,672 patients (Table 2-2) and reported an association between emergency presentation and larger tumour diameter (p=0.011).

2.3.2.3 Overall Staging

22 studies[126,128,130,136,209,214,216,218,221,222,225-236] examined the association between overall tumour stage (TNM/Dukes' Staging) and mode of presentation in 30,382 patients (Table 2-3). On meta-analysis including 21 studies of 28,956 patients (Figure 2-4) there was an association between emergency presentation and more advanced (Dukes' C-D/TNM 3-4 (lymph node or distal metastatic disease)) overall tumour stage (OR 2.05, 95%CI 1.94-2.18, p<0.001, I^2=81%).

2.3.2.4 Tumour Stage (T Stage)

11 studies[122,129,130,210,214,219,221,224,225,232,237] examined the association between T Stage and mode of presentation in 40,130 patients (Table 2-4). On meta-analysis including all of these studies (Figure 2-5) there was a significant association between emergency presentation and T4 disease (OR 2.56, 95%CI 2.31-2.84, $p<0.001$, $I^2=80\%$).

2.3.2.5 Nodal Stage (N Stage)

9 studies[122,214,219,221,222,224,225,228,237] examined the association between N Stage and mode of presentation in 7,254 patients (Table 2-5). On meta-analysis including 8 studies of 6,988 patients (Figure 2-6) there was an association between emergency presentation and node positive disease (OR 1.59, 95%CI 1.38-1.83, $p<0.001$, $I^2=77\%$).

2.3.2.6 Metastatic disease (M stage)

7 studies[126,130,219,221,222,229,237] examined the association between M Stage and mode of presentation in 8,703 patients (Table 2-6). On meta-analysis including all of these studies (Figure 2-7) there was an association between emergency presentation and metastatic disease (OR 1.75, 95%CI 1.55-1.99, $p<0.001$, $I^{2=}78\%$).

2.3.2.7 Tumour Circumference

1 study[222] examined the association between luminal tumour circumference and mode of presentation in 150 patients (Table 2-7) and reported an association

between emergency presentation and tumour circumference of greater than two thirds of the luminal circumference (p=0.009).

2.3.2.8 Tumour Type

4 studies[130,131,214,218] examined the association between tumour type and mode of presentation in 84,791 patients (Table 2-8). One study[131] of 81,825 patients found an inverse association between emergency presentation and simple adenocarcinomas (83% vs 85%) and an association between emergency presentation and proportion of mucinous/signet type tumours (12% vs 11%) however it was unclear whether this was of statistical significance. 2 studies [130,218] of 1,992 patients reported no significant association between emergency presentation and histological tumour type.

2.3.2.9 Lymphovascular Invasion

3 studies[225,226,228] examined the association between lymphovascular invasion and mode of presentation in 2,019 patients (Table 2-9). On meta-analysis including all of these studies (Figure 2-8) there was an association between emergency presentation and lymphovascular invasion (OR 1.76, 95%CI 1.39-2.23, p<0.001, I^2=79%).

2.3.2.10 Vascular Invasion

6 studies [129,214,224,226,230,237] examined the association between vascular invasion and mode of presentation in 5,825 patients (Table 2-10). On meta-analysis including all of these studies (Figure 2-9) there was an association between

emergency presentation and vascular invasion (OR 1.92, 95%CI 1.62-2.27, p<0.001, I^2=70%).

2.3.2.11 Tumour Perforation

1 study[230] examined the association between tumour perforation and the mode of presentation in 707 patients (Table 2-11) and reported an association between emergency presentation and microscopic perforation (p=0.010).

2.3.2.12 Perineural Invasion

3 studies[214,226,237] examined the association between perineural invasion and mode of presentation in 3,210 patients (Table 2-12). On meta-analysis including all of these studies (Figure 2-10) there was an association between emergency presentation and perineural invasion (OR 1.89, 95%CI 1.49-2.41, p<0.001, I^2=0%).

2.3.2.13 Tumour Desmoplasia, Necrosis and Budding

1 study[214] examined the association between tumour desmoplasia (Table 2-13), necrosis (Table 2-14) and budding (Table 2-15) and mode of presentation in 974 patients. Tumour desmoplasia was associated with emergency presentations (OR 2.11, p=0.03). No significant association was reported between emergency presentation and either tumour necrosis or tumour budding (p=0.33 and p=0.28 respectively).

2.3.2.14 Tumour Differentiation/Grade

13 studies[122,129-131,214,218,220,222,224-226,228,230] examined the association between tumour differentiation/grade and mode of presentation in 80,626 patients (Table 2-16). On meta-analysis including all of these studies (Figure 2-11) there was an association between emergency presentation and high grade/poorly differentiated tumours (OR 1.24, 95%CI 1.19-1.28, $p<0.001$, $I^2=59\%$).

2.3.3 Host Factors

2.3.3.1 Sex

24 studies[122,124,127-132,209,210,216,218,219,221,222,224,226,228,231,235,237-240] examined the association between patient sex and mode of presentation in 1,001,307 (Table 2-17). On meta-analysis that included all of these studies (Figure 2-12) there was an association between emergency presentation and female sex (OR 1.08, 95%CI 1.07-1.09, $p<0.001$, $I^2=98\%$).

2.3.3.2 Age

29 studies [122,124,126,127,129,130,136,209,210,215,217,218,221,222,224,226,228-231,233-235,237-239,241-243] examined the association between age and mode of presentation in 909,131 patients (Table 2-18). Due to heterogeneity of data it was not possible to perform a meta-analysis of this factor.

11 studies of 514,205 patients did not find a significant association between emergency presentation and age. This included a large study[124] from the USA of

507,750 patients that compared the proportion of patients aged over 65 who presented either electively or as an emergency.

18 studies of 394,926 patients found an association between emergency presentation and older age. This included 1 study[127] from the UK of 286,591 patients ($p<0.001$). 10 studies[126,127,209,210,215,217,230,238,241,243] subcategorised age into <70/70+ (n=1), <75/75+ (n=6) and <80/80+ (n=3) in 386,618 patients. 9 studies of 386,430 patients found an association between emergency presentation and older age.

2.3.3.3 Ethnicity

4 studies[127,131,237,243] examined the association between ethnicity and mode of presentation in 149,991 patients (Table 2-19). 3 of these studies were from the USA and 1 was from the UK. Two studies compared white vs African-American individuals, 1 study classified patients as either White, Black or Asian and the final study classified patients as ethnic minority (yes/no) however did not provide further description of ethnic minority status. On meta-analysis including all of these studies (Figure 2-13) there was an association between emergency presentation and ethnic minority status (OR 1.58, 95%CI 1.51-1.65, I^2=81%).

2.3.3.4 Body Mass Index

3 studies[228,237,244] examined the association between Body Mass Index (BMI) and mode of presentation in 1,700 patients (Table 2-20). 2 studies[237,244] of 1,071 patients reported no significant association between emergency presentation

and median BMI. 1 study[228] of 455 patients reported an association between a BMI <25 or >40 and emergency presentation (p=0.001).

2.3.3.5 Distance to Hospital

1 study[245] examined the association between distance to hospital and mode of presentation in 380 patients (Table 2-21) – no significant association was found.

2.3.3.6 Socio-economic Status

14 studies [127,131,209,215,216,228,230,231,238,239,245-248] examined the association between socio-economic status and mode of presentation in 433,364 (Table 2-22). Due to heterogeneity of data it was not possible to perform a meta-analysis of this factor.

6 studies[127,131,209,215,231,246] of 426,348 patients reported an association between emergency presentation and socio-economic deprivation. This included a study of 284,235 patients from the UK that classified patients into Index of Multiple Deprivation (IMD). quintiles - emergency surgery was more likely in the most deprived quintile (Quintile 1→ Quintile 5 OR 1.64, 95%CI 1.50-1.80).

2.3.3.7 Comorbid Status

ASA Classification

3 studies[210,233,236] examined the association between ASA classification and mode of presentation in 31,359 patients (Table 2-23). On meta-analysis including all of these studies (Figure 2-14) there was an association between emergency presentation and ASA ≥3 (OR 1.83, 95% CI 1.72-1.94, p<0.001, I^2=48%).

Other Assessments of Comorbidity

11 studies[121,124,130,132,210,216,218,229,237,243,249] examined the association between co-morbid status and mode of presentation in 724,136 patients (Table 2-24). Co-morbidities were compared using a variety of methods that included Charlson Score, Comorbidities (Yes/No) or the presence of specific co-morbidities including diabetes, cardiovascular or respiratory disease. Due to heterogeneity of data it was not possible to perform a meta-analysis of this factor.

2 studies of 538,939 patients[124,210] reported an association between emergency presentation and less co-morbid status. This included a study[124] of 508,032 patients that reported a Charlson Score ≥2 in 8.6% of emergency patients and 9.2% of elective patients (p≤0.001). A further study[210] of 30,907 patients reported a Charlson score of ≥2 in 24% of emergency patients and 26% of elective patients (level of statistical significance not provided).

7 studies[121,130,215,216,218,243,249] of 183,286 patients reported an association between emergency presentation and more co-morbid status.

2.3.3.8 Preoperative Systemic Inflammatory Response

2 studies[233,250] examined the association between preoperative systemic inflammatory response and mode of presentation in 1,246 patients (Table 2-25).

1 study[250] of 581 patients examined the association between both the modified Glasgow Prognostic Score (mGPS) and the neutrophil-lymphocyte ratio (NLR) and reported that on univariate analysis both mGPS and NLR were associated with emergency presentation (OR 7.71, p<0.001 and OR 4.94, p<0.001 respectively).

1 study[233] of 106 patients examined the association between median preoperative C-reactive protein (CRP) and mode of presentation and reported a higher median preoperative CRP in emergency presentations (Emergency – median 2.5mg/L (range 1.3-5), Elective – median 0.6mg/L (range 0.3-17), p<0.05).

2.3.3.9 Seasonal Variability

1 study[222] examined the association between seasonal variability and mode of presentation (Table 2-26) and reported an association between emergency presentation and presentation during the summer months (June-August) in comparison to the winter months (December-February) - 36% vs 23% p=0.05.

2.3.4 Other Factors

1 study[251] examined the association between haemoglobin and weight loss and mode of presentation in 372 patients (Table 2-27). Low haemoglobin levels and weight loss were both associated with emergency presentation (both P≤0.001).

1 study[233] examined the association between CEA, TNF A, IL1 and IL6 and mode of presentation in 106 patients (Table 2-28) and reported a significantly higher

CEA, IL1 and IL6 in the emergency cohort. No significant difference was reported in TNF A levels.

2.4 Discussion

The present systematic review and meta-analysis confirms multiple differences in tumour, host and other factors between elective and emergency presentations of colorectal cancer. It may therefore be a combination of these factors that are associated with the poorer short-term and long-term outcomes reported in emergency presentations of colorectal cancer[211,212] rather than emergency presentation per se.

In particular, tumour location (colon vs rectum), tumour stage, lymphovascular/perineural invasion, tumour differentiation, ethnicity and ASA classification differed significantly on meta-analysis between the elective and emergency cohorts as summarised in Figure 2-15. Although not analysed in the meta-analysis due to study heterogeneity/<3 studies, other factors that differed between elective and emergency presentations include age, socio-economic status and the preoperative systemic inflammatory response. Many of these factors have been reported to be associated with oncological outcomes in colorectal cancer[42,47,232,252,253] and it therefore cannot be assumed that the negative effect of emergency presentation is solely due to more advanced disease. More recently, factors including body composition[254], frailty[255] and perioperative blood transfusion[256] have been reported to be associated with poorer long-term outcomes following curative resection for colorectal cancer and would be of interest for inclusion in future studies comparing elective and emergency presentations. The present review found that, on meta-analysis, ethnic minority status was associated with emergency presentation. However, given that the included studies were either from the USA or UK, non-Caucasian was essentially considered the ethnic minority group. No studies compared the

effect of ethnic minority status in a country where Caucasian was the minority group and this would be an interesting area of future research.

Emergency presentations of colorectal cancer remain associated with poorer long-term outcomes than elective presentations, even after adjustment for TNM stage. Indeed, within TNM Stage II colorectal cancer, emergency presentation is considered to be a high-risk factor requiring consideration for adjuvant chemotherapy[147,184,257]. Further research would allow for both adjusted analysis of factors associated with emergency presentation and the subsequent effect of these on long-term outcomes both within the overall patient population and within stage-specific disease.

Over the last two decades, colorectal cancer screening programmes have become widespread throughout the developed world. While participation in screening programmes has resulted in a significant reduction in the proportion of patients presenting emergently[135] many patients continue to present with acute symptoms requiring emergency investigation and treatment. The present review included literature from both a screening and pre-screening era. It has been shown that factors including age, sex, socio-economic status and tumour stage and site[134] differ between unscreened patients and those patients who have either participated in or been diagnosed through screening. No studies have been identified to date comparing emergency presentations between those patients who did/did not participate in screening and this would be of interest in future work.

The present study has several limitations. Due to the nature of this study, a significant degree of heterogeneity was present both in terms of inclusion criteria and reported outcomes within individual studies. Therefore, it was not

possible to compare adjusted data hence the use of unadjusted data within the present review. Factors within the present study including age and BMI have not been included within meta-analysis due to data heterogeneity and the continuous nature of these variables. Consideration was given to conducting meta-regression however in keeping with guidance[213] this could not be carried out due to the small number of studies suitable for such analysis. While the present review identified a large number of studies comparing elective and emergency presentations of colorectal cancer, very few studies subclassify emergency presentations into their presenting diagnoses, predominantly obstruction, perforation and bleeding. It therefore remains uncertain how factors and outcomes vary between different emergency presentations. One would hypothesise that patients presenting with perforation may have significantly different characteristics and outcomes than those presenting with an otherwise uncomplicated large bowel obstruction. The optimal management of patients presenting as an emergency with large bowel obstruction remains uncertain. While the majority of patients undergo emergency colonic resection, some clinicians opt for primary colonic stenting in the emergency setting with subsequent elective resectional surgery. This in an important question which remains unanswered however lies outside the scope of the present review[258-260]. The present review focussed on factors at time of presentation (tumour and host factors), however other factors including surgeon subspecialisation, surgeon/hospital volume, surgical approach (open versus minimally invasive) and adjuvant chemotherapy administration may also be associated with mode of presentation and patient outcomes. Further investigation of these factors would be of interest in future work. A wide timeframe of literature (1990-2018) was included within this review. Although this may introduce potential for bias due to changing healthcare culture (earlier reporting of symptoms and more

extensive investigation of symptoms) or changing healthcare practices (including the introduction of screening and surgical subspecialisation), the present review aimed to provide a comprehensive overview of the literature to facilitate subsequent, more detailed, prospective investigation in the time period 2011-2014.

It is commonplace within Systematic Reviews and Meta-Analyses to present risk of bias and quality of included studies using a variety of measures[213]. However, the nature of the present review does not analyse the effect of an intervention on outcomes and therefore such measures are not applicable to the present review. Furthermore, with reference to specific factors, the small number of studies precluded meaningful analysis of the overall quality of studies and risk of bias. Nonetheless, within the included tables, major factors that may introduce bias for example disease stage, colon/rectum, type of treatment in included studies were described. The protocol for this systematic review and meta-analysis was not prospectively published or registered (Prospero). When this review commenced, Prospero was not as widely used as it is now. Prospero does not accept registration of reviews that have already commenced hence it was not possible to register this review retrospectively. Indeed, prior research has reported that less than 50% of Systematic Reviews are registered and the status of reviews registered are inaccurate in up to 85% of cases[261,262]. As such, although Prospero has the potential to be a useful resource, it is currently incomplete. Nevertheless, a search of Prospero did not find any other similar studies currently in progress therefore the lack of Prospero registration is unlikely to be a significant limitation of this study. The literature review was carried out by a single researcher with the assistance of the supervisor. Although it may have been optimal for a second researcher to repeat the literature search

the search was broad and a large number of studies were included therefore the impact of this is likely to be minimal.

In summary, the present study has identified multiple factors that differ between elective and emergency presentations of colorectal cancer as reported within the past 30 years of literature. This literature review paves the way to determining which tumour and host factors are independently significant with mode of presentation and which have the most significant effects on short-term and long-term outcomes therefore explaining the poorer outcomes reported within emergency presentations. Defining these factors would help to determine those patients that have the worst short-term and long-term outcomes and therefore identify strategies within the perioperative and adjuvant settings to improve outcomes for these high-risk patients.

2.5 Tables

Table 2-1 Association between tumour location (colonic vs rectal and colonic location) and mode of presentation

Study	n – El (n - Em)	Country Years	Location Stage	Cohort	Comparison	Outcome	P-Value
Sucullu[221] 2015	186 (66)	Turkey 2004-2013	Colon TNM I-IV	Curative resections	Colon location	No sig dif	0.818
Ghazi[214] 2013	837 (123)	Sweden 2004-2006	Colorectal TNM I-IV	All resections	Colon/rectum	Association between colonic and Em	<0.001
					Colon location	Association between left-sided and Em	-
Rabeneck[215] 2006	33617 (7739)	Canada 1996-2001	Colorectal TNM I-IV	All cases	Colon/rectum	Association between colonic and Em	<0.001
					Colon location	44% of elective left side vs 43% Em	-
Yang[130] 2011	1459 (215)	China 1998-2005	Colorectal TNM I-IV	All surgery	Colon/rectum	Association between colonic and Em	<0.001
					Colon location	Association between > left-sided and Em	<0.001
Askari[216] 2015	1648 (263)	UK 2004-2014	Colorectal TNM I-IV	All surgery	Colon/rectum	Association between colonic and Em	<0.001
Anderson[217] 1992	363 (207)	UK 1974-1979	Colorectal TNM I-IV	All cases	Colon/rectum	Association between colonic and Em	-
					Colon location	Association between left-sided and Em	-
Gunnarsson[222] 2011	89 (90)	Sweden 1996-2005	Colon TNM I-IV	All resections	Colon location	Association between left-sided and Em	0.04
Mik[223] 2017	414 (63)	Poland 2009-2012	Colon TNM I-IV	All resections	Colon location	Association between left-sided and Em	0.006
Biondo[224] 2005	207 (59)	Spain 1996-1998	Colon TNM I-III	Curative resections	Colon location	No sig dif	1
Bayar[218] 2016	230 (90)	Turkey 2009-2013	Colorectal TNM I-IV	All surgery	Colon/rectum	Association between colonic and Em	-
					Colon location	Association between left-sided and Em	-

McArdle[126] 2004	2214 (986)	UK 1991-1994	Colorectal TNM I-IV	All resections	Colon/rectum	Association between colonic and Em	-
					Colon location	Association between left-sided and Em	-
Oliphant[129] 2014	1626 (251)	UK 2001-2004	Colorectal TNM I-II	Curative resections	Colon/rectum	Association between colonic and Em	<0.001
Hogan[225] 2015	342 (97)	Ireland 2000-2010	Colon TNM I-IV	Curative resections	Colon location	Rectosigmoid Em<El SF and desc Em>El	0.004
Kelly [123] 2012	4974 (2937)	Ireland 2002-2008	Colorectal TNM I-IV	All resections	Colon/rectum	Association between colonic and Em	X
					Colon location	Right Em>El	X
Bakker[210] 2016	24960 (5947)	Netherlands 2009-2013	Colon TNM I-IV	All resections	Colon location	Association between left-sided and Em	X
Boeding[219] 2018	1058 (178)	Netherlands 2004-2010	Colorectal TNM I-IV	All resections	Colon/rectum	Association between colonic and Em	<0.1
					Colon location	Association between left-sided and Em	-
Wanis[226] 2018	1022 (158)	Canada 2006-2015	Colon TNM I-III	Curative resections	Colon location	Association between left-sided and Em	X
Sjo[227] 2009	740 (170)	Norway 1993-2007	Colon TNM I-IV	All surgery	Colon location	No sig dif	0.12
Ho[128] 2010	1193 (223)	Australia 1984-2004	Colorectal TNM I-III	Curative resections	Colon/rectum	Association between colonic and Em	<0.001
					Colon location	Association between left-sided and Em	Significant
Weixler[220] 2016	663 (84)	Switzerland 1989-2013	Colorectal TNM I-IV	All resections	Colon/rectum	Association between colonic and Em	0.019
					Colon location	Association between left-sided and Em	-

Table 2-2 Association between tumour size and mode of presentation

Study	n – El (n - Em)	Country Years	Location Stage	Cohort	Comparison	Outcome	P-Value
Yang[130] 2011	1457 (215)	China 1998-2005	Colorectal TNM I-IV	All surgery	Tumour size <5cm less or >5cm	Association between >5cm tumours and Em	0.011

Table 2-3 Association between overall tumour staging (TNM/Dukes') and mode of presentation

Study	n - El (n - Em)	Country Years	Location Stage	Cohort	Comparison	Outcome	P-Value
Sucullu[221] 2015	186 (66)	Turkey 2004-2013	Colon TNM I-IV	All resections	TNM	Association between > TNM Stage and Em	<0.001
Ghazi[214] 2013	845 (129)	Sweden 2004-2006	Colorectal TNM I-IV	All resections	TNM	Association between > TNM Stage and Em	<0.0001
Yang[130] 2011	1475 (215)	China 1998-2005	Colorectal TNM I-IV	All surgery	TNM	Association between > TNM Stage and Em	0.016
Askari[216] 2015	1254 (195)	UK 2004-2014	Colorectal TNM I-IV	All surgery	TNM	Association between > TNM Stage and Em	<0.001
Gunnarsson[209] 2013	9286 (2808)	Sweden 1997-2006	Colon TNM I-IV	All cases	TNM	Association between > TNM Stage and Em	<0.001
Gunnarsson[222] 2011	403 (87)	Sweden 1997-2006	Colon TNM I-IV	All resections	TNM	Association between > TNM Stage and Em	<0.001
Mitchell[228] 2007	347 (108)	Canada 2002-2004	Colorectal TNM I-IV	All resections	TNM	Association between > TNM Stage and Em	<0.001
Nascimbeni[136] 2008	793 (106)	Italy 1975-1984	Colorectal TNM I-IV	All surgery	Dukes'	Association between > Dukes' Stage and Em	0.01
Gunnarsson[229] 2014	563 (251)	Sweden 2006-2008	Colon TNM I-IV	All surgery	TNM	Association between > TNM Stage and Em	<0.001
Roxburgh[230] 2013	686 (187)	UK 2001-2010	Colorectal TNM I-IV	All cases	TNM	Association between > TNM Stage and Em	<0.001
Borowski[231] 2016	860 (203)	UK 2009-2014	Colorectal TNM I-IV	All cases	TNM	Association between > TNM Stage and Em	<0.001
Barclay[232] 2015	432 (125)	Australia 2005-2010	Colorectal TNM I-IV	All resections	TNM	Association between > TNM Stage and Em	<0.001
Catena[233] 2009	106 (50)	Italy 1999-2001	Colon and high rectal TNM I-IV	All resections	Dukes'	Association between > Dukes' Stage and Em	<0.05
Bayar[218] 2016	320 (90)	Turkey 2009-2013	Colorectal TNM I-IV	All surgery	TNM	Association between > TNM Stage and Em	<0.001
McArdle[126] 2004	3200 (986)	UK 1991-1994	Colorectal TNM I-IV	All resections	Dukes'	Association between > Dukes' Stage and Em	<0.001
Hogan[225] 2015	56 (50)	Ireland 2000-2010	Colon TNM I-IV	Curative resections	TNM	Association between > TNM Stage and Em	<0.01

Kundes[234] 2016	207 (51)	Turkey 2012-2014	Colorectal TNM I-III	Curative resections	TNM	Association between > TNM Stage and Em	<0.0001
Wanis[226] 2018	1022 (158)	Canada 2006-2015	Colon TNM I-III	Curative resections	TNM	Association between > TNM Stage and Em	-
Beuran[235] 2018	325 (270)	Romania 2011-2016	Left colon TNM I-IV	All resections	TNM	Association between > TNM Stage and Em	-
Sjo[227] 2009	744 (176)	Norway 1993-2007	Colon TNM I-IV	All surgery	TNM	Association between > TNM Stage and Em	<0.01
Ho[128] 2010	1193 (233)	Australia 1984-2004	Colorectal TNM I-III	Curative resections	TNM	Association between > TNM Stage and Em	<0.01
Ming-Gao[236] 2014	261 (85)	China 2000-2010	Colorectal TNM I-IV	All surgery	Dukes'	Association between > Dukes' Stage and Em	<0.01

Table 2-4 Association between T stage and mode of presentation

Study	n - El (n - Em)	Country Years	Location Stage	Cohort	Comparison	Outcome	P-Value
Sucullu[221] 2015	186 (66)	Turkey 2004-2013	Colon TNM I-IV	Curative resections	T Stage 1/2/3/4	Association between > T Stage and Em	<0.001
Ghazi[214] 2013	845 (129)	Sweden 2004-2006	Colorectal TNM I-IV	All resections	T2	No sig dif	0.72
					T3	More T3 in Em vs El	0.03
					T4	More T4 in Em vs El	0.002
Yang[130] 2011	1457 (215)	China 1998-2005	Colorectal TNM I-IV	All surgery	T Stage 1/2/3/4	Association between >T Stage and Em	<0.0001
Barclay[232] 2015	432 (125)	Australia 2005-2010	Colorectal TNM I-IV	All resections	T Stage 1/2/3/4	Association between > T Stage and Em	<0.0001
Amri[237] 2015	969 (102)	USA 2004-2011	Colon TNM I-IV	All resections	T Stage 1-3/4	Association between > T Stage and Em	<0.001
Biondo[224] 2005	207 (59)	Spain 1996-1998	Colon TNM I-III	Curative resections	T Stage 1/2/3/4	Association between > T Stage and Em	0.014
Okuda[122] 2018	885 (94)	Japan 2007-2011	Colorectal TNM II-III	Curative resections	T Stage in TNM II	No sig difference	0.652
					T Stage in TNM III	Association between > T Stage and Em	<0.001
Oliphant[129] 2014	1544 (233)	UK 2001-2004	Colorectal TNM I-II	Curative resections	T Stage 1/2/3/4	Association between > T Stage and Em	<0.001
Hogan[225] 2015	342 (97)	Ireland 2000-2010	Colon TNM I-IV	Curative Resections	T1	Sig more el than em	0.017
					T2	Sig more el than em	0.008
					T3	No sig dif	0.495
					T4	Sig more em than el	0.009
Bakker[210] 2016	24960 (5947)	Netherlands 2009-2013	Colon TNM I-IV	All resections	T Stage 1-2/3/4	Association between > T4 disease and Em	-
Boeding[219] 2018	1058 (178)	Netherlands 2004-2010	Colorectal TNM I-IV	All resections	T Stage 1/2/3/4	Sig fewer T1/2 in Em than El	<0.01

Table 2-5 Association between N stage and mode of presentation

Study	n - El (n - Em)	Country Years	Location Stage	Cohort	Comparison	Outcome	P-Value
Sucullu[221] 2015	186 (66)	Turkey 2004-2013	Colon TNM I-IV	Curative resections	N 0/N1-2	Association between > N Stage and Em	0.002
Ghazi[214] 2013	845 (129)	Sweden 2004-2006	Colorectal TNM I-IV	All resections	N 0/1/2	Association between > N Stage and Em	<0.001
Yang[130] 2011	1457 (215)	China 1998-2005	Colorectal TNM I-IV	All surgery	N 0/1-2	No sig dif	0.868
					N 1/2	No sig dif	0.567
Mitchell[228] 2007	347 (108)	Canada 2002-2004	Colorectal TNM I-IV	All resections	N 0/1-2	No sig dif	0.38
Amri[237] 2015	969 (102)	USA 2004-2011	Colon TNM I-IV	All resections	N 0/1-2	Association between > N Stage and Em	<0.001
Biondo[224] 2006	207 (59)	Spain 1996-1998	Colon TNM I-III	Curative resections	N0/1-2	No sig dif	0.222
Okuda[122] 2018	885 (94)	Japan 2007-2011	Colorectal TNM II-III	All resections	N1/2 in TNM III	No sig dif	0.355
Hogan[225] 2015	342 (97)	Ireland 2000-2010	Colon TNM I-IV	Curative resections	N0 el vs em	N0 – more El than Em	0.016
					N1 el vs em	N1 – no sig dif	0.527
					N2 el vs em	N2 – more Em than El	<0.01
Boeding[219] 2018	991 (155)	Netherlands 2004-2010	Colorectal TNM I-IV	All resections	N0 el vs em	Assoc between <Em and N0	<0.01
					N1 el vs em	Assoc between >N1 and Em	0.02
					N2 el vs em	No sig dif	0.048

Table 2-6 Association between presence of metastatic disease and mode of presentation

Study	n – El (n - Em)	Country Years	Location Stage	Cohort	Comparison	Outcome	P-Value
Sucullu[221] 2015	186 (66)	Turkey 2004-2013	Colon TNM I-IV	Curative resections	Metastatic disease Yes/No	Association between > metastatic disease and Em	0.037
Yang[130] 2011	1457 (215)	China 1998-2005	Colorectal TNM I-IV	All surgery	Liver mets Yes/no	Association between > metastatic disease and Em	0.001
Gunnarsson[222] 2011	403 (87)	Sweden 1996-2005	Colon TNM I-IV	All resections	Metastatic disease Yes/No	Association between > metastatic disease and Em	-
Gunnarsson[229] 2014	568 (255)	Sweden 2006-2008	Colon TNM I-IV	All surgery	Metastatic disease Yes/No	Association between > metastatic disease and Em	-
Amri [237] 2015	969 (102)	USA 2004-2011	Colon TNM I-IV	All resections	Metastatic disease Yes/No	Association between > metastatic disease and Em	<0.001
McArdle[126] 2004	2214 (986)	UK 1991-1994	Colorectal TNM I-IV	All resections	Metastatic disease Yes/no	Association between > metastatic disease and Em	-
Boeding[219] 2018	1025 (170)	Netherlands 2004-2010	Colorectal TNM I-IV	All resections	Metastatic disease Yes/No	Association between > metastatic disease and Em	<0.01

Table 2-7 Association between luminal tumour circumference and mode of presentation

Study	n – El (n - Em)	Country Years	Location Stage	Cohort	Comparison	Outcome	P-Value
Gunnarsson[222] 2011	67 (83)	Sweden 1996-2005	Colon TNM I-IV	All resections	+/- 2/3 of luminal circumference	Association between circumference >2/3 and Em	0.009

Table 2-8 Association between tumour type and mode of presentation

Study	n – El (n - Em)	Country Years	Location Stage	Cohort	Comparison	Outcome	P-Value
Ghazi[214] 2012	845 (129)	Sweden 2004-2006	Colorectal TNM I-IV	All resections	Mucin type	No sig dif	>0.05
					Signet ring type	Association between > Signet ring and Em	0.001
Yang[130] 2011	1457 (215)	China 1998-2005	Colorectal TNM I-IV	All surgery	Adeno vs mucinous vs signet ring tumours	No sig dif	0.123
Pruitt[131] 2014	58158 (23667)	USA 1992-2005	Colorectal TNM I-IV	All cases	Adenocarcinoma vs mucinuous/signet ring vs other	Association between non-simple adeno and Em	-
Bayar[218] 2016	230 (90)	Turkey 2009-2013	Colorectal TNM I-IV	All surgery	Adeno vs mucinous vs signet cell vs insitu vs malignant epithlelial tumour	No sig dif	>0.05

Table 2-9 Association between the presence of lymphovascular invasion (LVI) and mode of presentation

Study	n – El (n - Em)	Country Years	Location Stage	Cohort	Comparison	Outcome	P-Value
Mitchell[228] 2007	347 (108)	Canada 2002-2004	Colorectal TNM I-IV	All resections	LVI (Pos/neg)	Association between LVI and Em	0.03
Hogan[225] 2015	342 (97)	Ireland 2000-2010	Colon TNM I-IV	Curative resections	LVI (Pos/neg)	Association between LVI and Em	<0.01
Wanis[226] 2018	969 (156)	Canada 2006-2015	Colon TNM I-III	Curative resections	LVI (Pos/neg)	Association between LVI and Em	-

Table 2-10 Association between the presence of vascular invasion and mode of presentation

Study	n – El (n - Em)	Country Years	Location Stage	Cohort	Comparison	Outcome	P-Value
Ghazi[214] 2013	845 (129)	Sweden 2004-2006	Colorectal TNM I-IV	All resections	Vascular invasion	Association between > Vascular Invasion and Em	<0.001
Roxburgh[230] 2013	555 (113)	UK 2001-2010	Colorectal TNM I-IV	cases	EMVI	Association between > Vascular Invasion and Em	<0.001
Amri[237] 2015	969 (102)	USA 2004-2011	Colon TNM I-IV	All resections	EMVI	Association between > Vascular Invasion and Em	0.021
Biondo[224] 2005	207 (59)	Spain 1996-1998	Colorectal TNM I-III	Curative resections	Vascular invasion	No sig dif	0.092
Oliphant[129] 2014	1460 (226)	UK 2001-2004	Colorectal TNM I-II	Curative resections	EMVI	Association between > Vascular Invasion and Em	0.001
Wanis[226] 2018	1004 (156)	Canada 2006-2015	Colon TNM I-III	Curative resections	Venous invasion	Association between > Vascular Invasion and Em	x

Table 2-11 Association between tumour perforation and mode of presentation

Study	n – El (n - Em)	Country Years	Location Stage	Cohort	Comparison	Outcome	P-Value
Roxburgh[230] 2013	557 (150)	UK 2001-2010	Colorectal TNM I-IV	All cases	Tumour perforation	Association between > tumour perforation and Em	0.010

Table 2-12 Association between perineural invasion and mode of presentation

Study	n – El (n - Em)	Country Years	Location Stage	Cohort	Comparison	Outcome	P-Value
Ghazi[214] 2013	845 (129)	Sweden 2004-2006	Colorectal TNM I-IV	All resections	Perineural invasion	Association between > perineural invasion and Em	0.001
Amri[237] 2015	969 (102)	USA 2004-2011	Colon TNM I-IV	All resections	Perineural invasion	Association between > perineural invasion and Em	0.005
Wanis[226] 2018	1008 (157)	Canada 2006-2015	Colon TNM I-III	Curative resections	Perineural invasion	Association between > perineural invasion and Em	-

Table 2-13 Association between tumour desmoplasia and mode of presentation

Study	n – El (n - Em)	Country Years	Location Stage	Cohort	Comparison	Outcome	P-Value
Ghazi[214] 2013	845 (129)	Sweden 2004-2006	Colorectal TNM I-IV	All resections	Tumour desmoplasia	Association between > desmoplasia and Em	0.03

Table 2-14 Association between tumour necrosis and mode of presentation

Study	n – El (n - Em)	Country Years	Location Stage	Cohort	Comparison	Outcome	P-Value
Ghazi[214] 2013	845 (129)	Sweden 2004-2006	Colorectal TNM I-IV	All resections	Tumour necrosis	No significant different between El and Em	0.33

Table 2-15 Association between tumour budding and mode of presentation

Study	n – El (n - Em)	Country Years	Location Stage	Cohort	Comparison	Outcome	P-Value
Ghazi[214] 2013	845 (129)	Sweden 2004-2006	Colorectal TNM I-IV	All resections	Tumour budding	No significant difference between El and Em	0.28

Table 2-16 Association between tumour grade/differentiation and mode of presentation

Study	n – El (n - Em)	Country Years	Location Stage	Cohort	Comparison	Outcome	P-Value
Ghazi[214] 2013	845 (129)	Sweden 2004-2006	Colorectal TNM I-IV	All resections	Mod-Well vs Poorly dif	No sig dif	0.21
Yang[130] 2011	1457 (215)	China 1998-2005	Colorectal TNM I-IV	All surgery	Well vs Mod vs Poorly dif	No sig dif	0.396
Gunnarsson[222] 2011	585 (97)	Sweden 1996-2005	Colon TNM I-IV	All resections	Low vs medium vs high grade	No sig dif	0.4
Mitchell[228] 2007	338 (105)	Canada 2002-2004	Colorectal TNM I-IV	All resections	Well vs Mod vs Poorly dif	No sig dif	0.71
Roxburgh[230] 2013	557 (113)	UK 2001-2010	Colorectal TNN I-IV	All cases	Well-mod vs poorly dif	Association between poorly dif and Em	0.020
Pruitt[131] 2014	50773 (20278)	USA 1992-1995	Colorectal TNM I-IV	All cases	Low vs high grade	Association between High Grade and Em	<0.001
Biondo[224] 2005	194 (57)	Spain 1996-1998	Colorectal TNM I-III	Curative resections	Well vs Mod vs Undif	No sig dif	0.660
Bayar[218] 2016	230 (90)	Turkey 2009-2013	Colorectal TNM I-IV	All surgery	Well vs Mod vs Poorly dif	Association between >dif and Em	<0.001
Okuda[122] 2018	449 (48)	Japan 2007-2011	Colorectal TNM II-III	Curative resections	Mod-well vs poorly dif TNM II	No sig dif	1.000
					Mod-well vs poorly dif TNM III	No sig dif	0.787
Oliphant[129] 2014	1530 (228)	UK 2001-2004	Colorectal TNM I-II	Curative resections	Well-mod vs poorly dif	No sig dif	0.103
Hogan[225] 2015	342 (97)	Ireland 2000-2010	Colon TNM I-IV	Curative resections	Well dif em vs el	Assoc between <well dif and Em	0.003
					Mod dif em vs el	No sig dif	0.141
					Poorly dif em vs el	No sig dif	0.164
Wanis[226] 2018	1002 (156)	Canada 2006-2015	Colon TNM I-III	Curative resections	Poor/undif vs mod/well dif	No sig dif	-
Weixler[220] 2016	634 (77)	Switzerland 1989-2013	Colorectal TNM I-IV	All resections	G1 vs G2vs G3	No sig dif	0.180

Table 2-17 Association between sex and mode of presentation

Study	n – El (n- Em)	Country Years	Location Stage	Cohort	Comparison	Outcome	P-Value
Sucullu[221] 2015	186 (66)	Turkey 2004-2013	Colon TNM I-IV	Curative resections	M vs F	Association between >F and Em	0.740
Crozier[238] 2009	133 (55)	UK 1999-2006	Colon TNM I-III	Curative resections	M vs F	No sig dif	0.268
Scott[239] 1995	633 (272)	UK 1982-1992	Colorectal TNM I-III	All cases	M vs F	No sig dif	N.S.
Shah[124] 2013	457845 (54400)	USA 2003-2007	Colorectal TNM I-IV	All surgery	M vs F	Assoc between >M and Em	0.017
Yang[130] 2011	1457 (215)	China 1998-2005	Colorectal TNM I-IV	All surgery	M vs F	No sig dif	0.407
Askari[216] 2015	1648 (263)	UK 2004-2014	Colorectal TNM I-IV	All surgery	M vs F	No sig dif	0.175
Gunnarsson[209] 2013	9437 (2856)	Sweden 1997-2006	Colon TNM I-IV	All cases	M vs F	No sig dif	0.125
Gunnarsson[222] 2011	488 (97)	Sweden 1996-2005	Colon TNM I-IV	All resections	M vs F	No sig dif	0.9
Mitchell[228] 2007	347 (108)	Canada 2002-2004	Colorectal TNM I-IV	All resections	M vs F	Association between >F and Em	0.004
Pruitt[131] 2014	59082 (24248)	USA 1992-2005	Colorectal TNM I-IV	All cases	M vs F	Association between >F and Em	<0.001
Borowski[231] 2016	916 (229)	UK 2009-2014	Colorectal TNM I-IV	All cases	M vs F	Association between >F and Em	0.039
Rabeneck[132] 2005	47564 (12106)	Canada 1993-2001	Colorectal TNM I-IV	All cases	M vs F	Association between >F and Em	<0.001
Schneider[240] 2013	137 (52)	UK 2002-2004	Colorectal TNM I-IV	All cases	M vs F	No sig dif	0.80
Amri[237] 2015	969 (102)	USA 2004-2011	Colon TNM I-IV	All resections	M vs F	No sig dif	0.51
Biondo[224] 2005	207 (59)	Spain 1996-1998	Colon TNM I-III	Curative resections	M vs F	No sig dif	0.760
Bayar[218] 2016	230 (90)	Turkey 2009-2013	Colorectal TNM I-IV	All surgery	M vs F	No sig dif	0.904
Okuda[122]	885	Japan	Colorectal	Curative resections	M vs F TNM II	No sig dif	0.211

2018	(94)	2007-2011	TNM II-III		M vs F TNM III	No sig dif	0.679
Oliphant[129] 2014	1626 (251)	UK 2001-2004	Colorectal TNM I-II	Curative resections	M vs F	No sig dif	0.103
Bakker[210] 2016	24960 (5947)	Netherlands 2009-2013	Colon TNM I-IV	All resections	M vs F	Association between >F and Em	-
Boeding[219] 2018	1058 (178)	Netherlands 2004-2015	Colorectal TNM I-IV	All resections	M vs F	No sig dif	0.54
Wanis[226] 2018	1022 (158)	Canada 2006-2015	Colon TNM I-III	Curative resections	M vs F	Association between >F and Em	-
Beuran[235] 2018	340 (275)	Romania 2011-2016	Left colon TNM I-IV	All resections	M vs F	No sig dif	>0.05
Ho[128] 2010	1200 (225)	Australia 1984-2004	Colorectal TNM I-III	Curative resections	M vs F	No sig dif	0.267
Askari[127] 2017	216873 (69718)	UK 1997-2012	Colorectal TNM I-IV	All surgery	M vs F	Association between >F and Em	<0.001

Table 2-18 Association between age and mode of presentation

Study	n – El (n- Em)	Country Years	Location Stage	Cohort	Comparison	Outcome	P-Value
Renzi[241] 2016	1158 (448)	UK 2005-2006	Colorectal TNM I-IV	All cases	Proportion 25-59/60-69/70-79/80+	Association between > age and Em	0.04
Sucullu[221] 2015	186 (66)	Turkey 2004-2013	Colon TNM I-IV	Curative resections	Mean age	No sig dif	0.3
Crozier[238] 2009	133 (55)	UK 1999-2006	Colon TNM I-III	Curative resections	Proportion <65/65-74/>75	No sig dif	0.204
Rabeneck[215] 2005	33617 (7739)	Canada 1996-2001	Colorectal TNM I-IV	All cases	Proportion 20-49/50-69/>70	Association between > age and Em	<0.001
Scott[239] 1995	633 (272)	UK 1982-1992	Colorectal TNM I-III	All cases	Median age	Association between > age and Em	0.04
MacDonald[242] 2011	1223 (395)	UK 2006-2008	Colorectal TNM I-IV	All resections	Mean age	Association between > age and Em	<0.05
Shah[124] 2013	453723 (54027)	USA 2003-2007	Colorectal TNM I-IV	All surgery	Proportion <65/65+	No sig dif	0.455
Yang[130] 2011	1672 (215)	China 1998-2005	Colorectal TNM I-IV	All surgery	Mean	No sig dif	0.140
					<40/41-64/65+	No sig dif	0.487
Anderson[217] 1992	363 (207)	UK 1974-1979	Colorectal TNM I-IV	All cases	Proportion <55/55-64/65-74/75+	Association between > age and Em	X
Gunnarsson[209] 2013	9437 (2856)	Sweden 1997-2006	Colon TNM I-IV	All cases	Proportion <69/70-79/>80	Association between > age and Em	<0.001
Gunnarsson[222] 2011	488 (97)	Sweden 1996-2005	Colon TNM I-IV	All resections	Mean age	Association between > age and Em	0.04
Mitchell[228] 2007	347 (108)	Canada 2002-2004	Colorectal TNM I-IV	All resections	Mean age (years)	Association between > age and Em	0.005
Nascimbeni[136] 2008	430 (41)	Italy 1975-1984	Colorectal TNM I-IV	All surgery	Mean age	Association between > age and Em	0.002
Gunnarsson[229] 2014	508 (263)	Sweden 2006-2008	Colon TNM I-IV	All surgery	Proportion >85 + Median age	No sig dif	0.35
Roxburgh[230] 2013	690 (187)	UK 2007-2010	Colorectal TNM I-IV	All cases	Proportion <65/65-75/>75	Association between > age and Em	<0.001
Borowski[231] 2016	916 (229)	UK 2009-2014	Colorectal TNM I-IV	All cases	Median age	No sig dif	-
Catena[233]	56	Italy	Colon/high rectal	All resections	Mean age	No sig dif	>0.05

2009	(50)	1991-2001	TNM I-IV				
Amri[237] 2015	969 (102)	USA 2004-2011	Colon TNM I-IV	All resections	Median age	No sig dif	0.24
Biondo[224] 2005	207 (59)	Spain 1996-1998	Colon TNM I-III	Curative resections	Mean age	No sig dif	0.900
Bayar[218] 2016	230 (90)	Turkey 2009-2013	Colorectal TNM I-IV	All surgery	Mean age	No sig dif	>0.05
Sikka[243] 2012	6938 (2092)	USA 1996-2000	Colorectal TNM I-IV	All cases	Proportion 66-69/70-74/75-79/80-84/>85	Association between > age and Em	X
Okuda[122] 2018	885 (94)	Japan 2007-2011	Colorectal TNM II-III	Curative resections	Median age TNM II	No sig dif	0.683
					Median age TNM III	No sig dif	0.058
McArdle[126] 2004	2214 (986)	UK 1991-1994	Colorectal TNM I-IV	All resections	Proportion <64/65-74/>75	Association between > age and Em	<0.001
Oliphant[129] 2014	1626 (251)	UK 2001-2004	Colorectal TNM I-III	Curative resections	Mean age	Association between > age and Em	0.023
Kundes[234] 2016	209 (51)	Turkey 2012-2014	Colorectal TNM I-II	Curative resections	Mean age	Association between > age and Em	0.02
Bakker[210] 2016	24960 (5947)	Netherlands 2009-2013	Colon TNM I-IV	All resections	Proportion <75/75+	Association between > age and Em	X
Wanis[226] 2018	1022 (158)	Canada 2006-2015	Colon TNM I-III	All resections	Mean age	Association between > age and Em	X
Beuran[235] 2018	340 (275)	Romania 2011-2016	Left colon TNM I-IV	All resections	Mean age	No sig dif	0.102
Askari[127] 2017	216873 (69718)	UK 1997-2012	Colorectal TNM I-IV	All surgery	Proportion 18-54/55-69/70/79/>79	Association between age <55 and >79 and Em	<0.001

Table 2-19 Association between ethnicity and mode of presentation

Study	n – El (n - Em)	Country Years	Location Stage	Cohort	Comparison	Outcome	P-Value
Pruitt[131] 2014	59082 (24248)	USA 1992-2005	Colorectal TNM I-IV	All cases	African Americans vs Whites	Association between > non-white and Em	<0.05
Amri[237] 2015	969 (102)	USA 2004-2011	Colon TNM I-IV	All resections	Ethnic minority yes vs no	No sig dif	0.23
Sikka[243] 2012	6938 (2092)	USA 1996-2000	Colorectal TNM I-IV	All cases	White vs African American	Association between > non-white and Em	<0.05
Askari[127] 2017	41048 (15512)	UK 1997-2012	Colorectal TNM I-IV	All surgery	White vs Black vs Asian	Association between > non-white and Em	<0.001

Table 2-20 Association between body mass index and mode of presentation

Study	n – El (n - Em)	Country Years	Location Stage	Cohort	Comparison	Outcome	P-Value
Costa[244] 2017	87 (87)	Italy 2006-2012	Colorectal TNM I-IV	All resections	Median BMI	No sig dif	0.09
Mitchell[228] 2007	347 (108)	Canada 2002-2004	Colorectal TNM I-IV	All resections	BMI (categories)	Association between BMI >40/<25 and Em	0.001
Amri[237] 2015	969 (102)	USA 2004-2011	Colon TNM I-IV	All resections	Median BMI	No sig dif	0.29

Table 2-21 Association between distance to hospital and mode of presentation

Study	n – El (n - Em)	Country Years	Location Stage	Cohort	Comparison	Outcome	P-Value
Blind[245] 2018	304 (76)	Sweden 2007-2010	Colon TNM I-IV	All surgery	Mean distance	No sig dif	0.433
					Distance quartiles	No sig dif	>0.05

Table 2-22 Association between socio-economic status and mode of presentation

Study	n – El (n - Em)	Country Years	Location Stage	Cohort	Comparison	Outcome	P-Value
Crozier[238] 2009	133 (55)	UK 1996-2006	Colon TNM I-III	Curative resections	Carstairs 1-2/3-5/6-7	No sig dif	0.142
Rabeneck[215] 2006	32779 (7378)	Canada 1996-2001	Colorectal TNM I-IV	All cases	Income quintile	Assoc between > deprivation and Em	<0.001
Scott[239] 1995	333 (117)	UK 1982-1992	Colorectal TNM I-III	All cases	Social class 1-2/4-7	No sig dif	>0.05
Askari[216] 2015	1607 (257)	UK 2004-2014	Colorectal TNM I-IV	All surgery	IMD quintile	No sig dif	0.444
Oliphant[246] 2013	3351 (945)	UK 2001-2004	Colorectal TNM I-IV	All surgery	SIMD quintile	Assoc between > deprivation and Em	0.033
Blind[245] 2018	304 (76)	Sweden 2007-2010	Colon TNM I-IV	All surgery	Average income High/low	No sig dif	0.122
A El[247] 2016	434 (99)	UK 2010-2014	Colorectal TNM I-IV	All cases	IMD quintile	No sig dif	0.10
Gunnarsson[209] 2013	9420 (2850)	Sweden 1997-2006	Colon TNM I-IV	All cases	Education	Assoc between > deprivation and Em	0.018
					Income quartile	Assoc between > deprivation and Em	<0.001
Mitchell[228] 2007	347 (108)	Canada 2002-2004	Colorectal TNM I-IV	All resections	Income quintile	No sig dif	0.82
					Education level	No sig dif	0.46
Hole[248] 2002	1545 (724)	UK 1991-1994	Colorectal TNM I-IV	All resections	Carstairs 1-2/3-5/6-7	No sig dif	0.80
Roxburgh[230] 2013	690 (187)	UK 2001-2010	Colorectal TNM I-IV	All cases	Carstairs 1-2/3-4/5-6	No sig dif	0.384
Pruitt[131] 2014	59082 (24248)	USA 1992-2005	Colorectal TNM I-IV	All cases	Neighbourhood poverty rate	Assoc between > deprivation and Em	<0.0001
Borowski[231] 2016	1145 (915)	UK 2009-2014	Colorectal TNM I-IV	All cases	LSOA quintiles	Assoc between > deprivation and Em	0.048
Askari[127] 2017	215097 (69138)	UK 1997-2012	Colorectal TNM I-IV	All surgery	IMD quintile	Assoc between > deprivation and Em	<0.001

Table 2-23 Association between ASA classification and mode of presentation

Study	n – El (n - Em)	Country Years	Location Stage	Cohort	Comparison	Outcome	P-Value
Catena[233] 2009	56 (50)	Italy 1999-2001	Colon and high rectal TNM I-IV	All resections	ASA classification (1/2/3/4)	Assoc between > ASA and Em	<0.05
Bakker[210] 2016	24960 (5947)	Netherlands 2009-2013	Colon TNM I-IV	All resections	ASA classification 1-2 vs 3+	Assoc between >ASA and Em	-
Ming-Gao[236] 2014	261 (85)	China 2000-2010	Colorectal TNM I-IV	All surgery	ASA classification	Assoc between >ASA and Em	<0.01

Table 2-24 Association between other assessments of co-morbidity and mode of presentation

Study	n – El (n - Em)	Country Years	Location Stage	Cohort	Comparison	Outcome	P-Value
Rabeneck[215] 2006	33617 (7739)	Canada 1996-2001	Colorectal TNM I-IV	All cases	Deyo score	Assoc between > comorbidity and Em	<0.001
Shah[124] 2013	454000 (54032)	USA 2003-2007	Colorectal TNM I-IV	All surgery	Charlson score	Assoc between < comorbidity and Em	0.000
Yang[130] 2011	1457 (215)	China 1998-2005	Colorectal TNM I-IV	All surgery	Number of comorbidities	Assoc between > comorbidity and Em	0.002
Askari[216] 2015	1647 (264)	UK 2004-2014	Colorectal TNM I-IV	All surgery	Charlson score Em vs El	Assoc between > comorbidity and Em	<0.001
Gunnarsson [229] 2014	577 (263)	Sweden 2006-2008	Colon TNM I-IV	All surgery	CV disease Diabetes Resp disease	No sig dif	0.34/0.12 /0.39
Wallace[249] 2014	64884 (17889)	UK 2007-2011	Colorectal TNM I-IV	All cases	Individual components of Charlson Score	Assoc between > comorbidity and Em	Not provided
Amri[237] 2015	969 (102)	USA 2004-2011	Colon TNM I-IV	All resections	Charlson score	No sig dif	0.62
					DM Type 2	No sig dif	0.96
					IBD	No sig dif	0.36
					Prev colorectal cancer	No sig dif	0.30
					Prev polyps	No sig dif	0.56
Bayar[218] 2016	230 (90)	Turkey 2009-2013	Colorectal TNM I-IV	All surgery	Yes/no	Assoc between >comorbidity and Em	<0.001
Sikka[243] 2012	6938 (2092)	USA 1996-2010	Colorectal TNM I-IV	All cases	Charlson score	Assoc between > comorbidity and Em	<0.05
Bakker[210] 2016	24960 (5947)	Netherlands 2009-2013	Colon TNM I-IV	All resections	Charlson score 0/1/2+	Assoc between < comorbidity and Em	Not provided
Neuman[121] 2013	31574 (14650)	USA 1992-2005	Colon TNM I-IV	All cases	Individual co-morbidities	Assoc between > comorbidity and Em	<0.001

Table 2-25 Association between the preoperative systemic inflammatory response and mode of presentation

Study	n – El (n - Em)	Country Years	Location Stage	Cohort	Comparison	Outcome	P-Value
Park[250] 2018	1077 (63)	UK/Japan 1997-2013 2005-2015	Colorectal TNM I-III	Curative resections	mGPS	Association between > mGPS and Em	<0.001
					NLR	Association between > NLR and Em	<0.001
Catena[233] 2009	56 50	Italy 1999-2001	Colon and high rectal TNM I-IV	All resections	Median CRP	Association between > CRP and Em	<0.05

Table 2-26 Association between time of year and mode of presentation

Study	n – El (n - Em)	Country Years	Location Stage	Cohort	Comparison	Outcome	P-Value
Gunnarsson[222] 2011	482 (97)	Sweden 1996-2005	Colon TNM I-IV	All resections	Seasonal change Em vs El	More Em cases in summer No sig association between El and seasons	0.05

Table 2-27 Association between haemoglobin and weight loss and mode of presentation

Study	n – El (n - Em)	Country Years	Location Stage	Cohort	Comparison	Outcome	P-Value
Cleary[251] 2007	310 (62)	UK 1998-2002	Colorectal TNM I-IV	All cases	Haemoglobin <13	Association between < Hb and Em	<0.001
					Weight loss	Association between > weight loss and Em	<0.001

Table 2-28 Association between CEA, TNF A, IL-1 and IL-6 and mode of presentation

Study	n – El (n -Em)	Country Years	Location Stage	Cohort	Comparison	Outcome	P-Value
Catena[233] 2009	56 (50)	Italy 1999-2001	Colon and high rectal TNM I-IV	All resections	Preop CEA	Assoc between >CEA and Em	<0.05
					Preop TNF A	No sig dif	Non sig
					Preop and postop IL1	Assoc between >IL1 and Em	<0.05
					Preop and postop IL6	Assoc between >IL6 and Em	<0.05

2.6 Figures

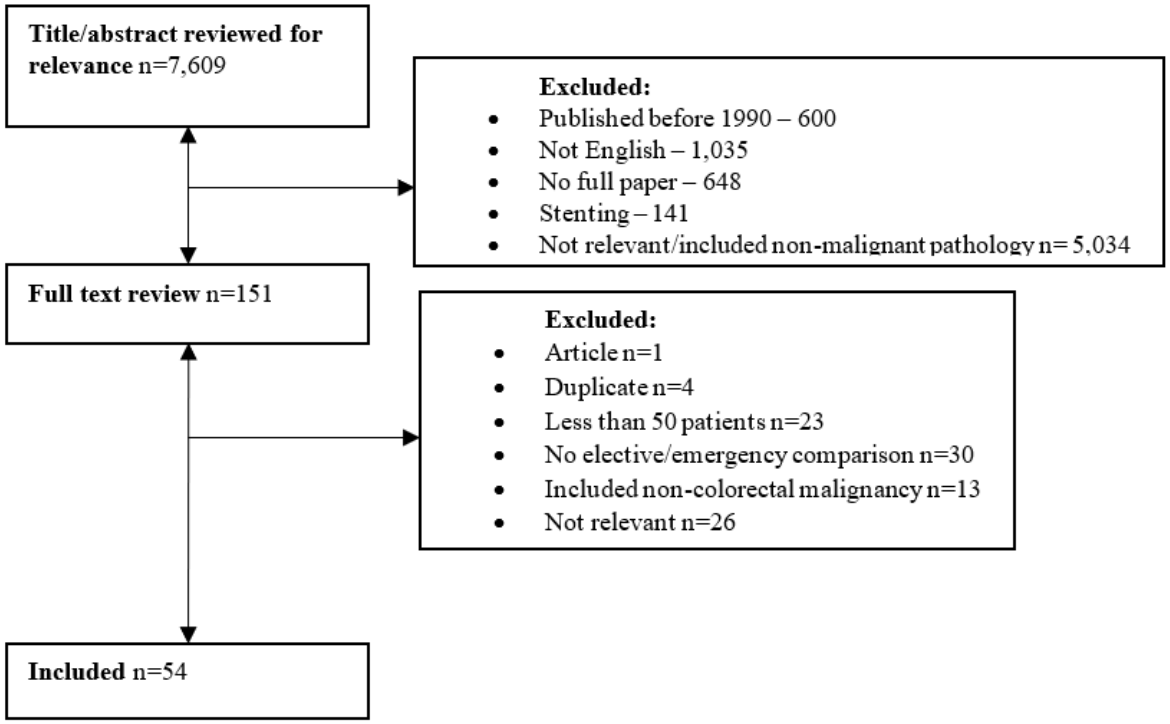


Figure 2-1 Prisma Statement

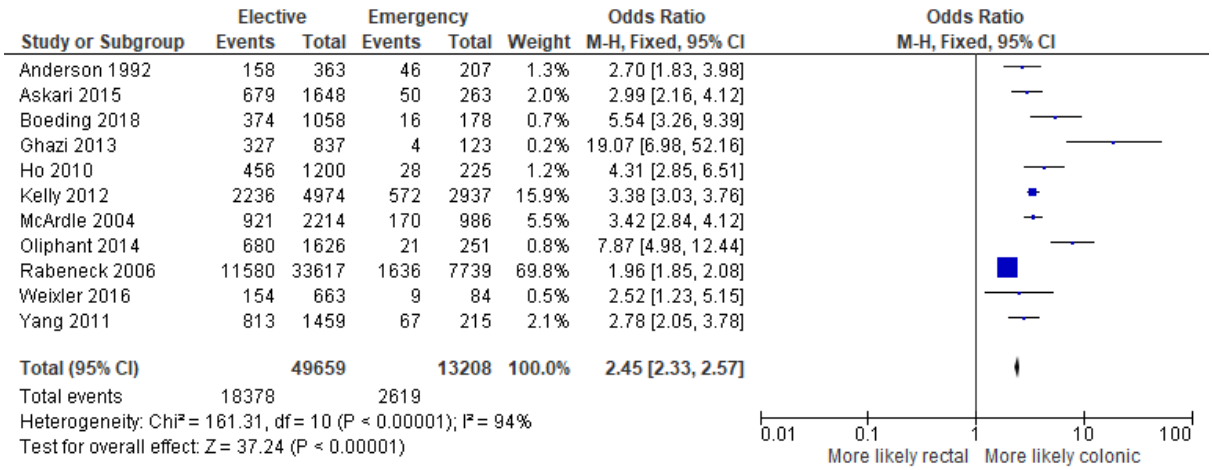


Figure 2-2 Association between tumour location (rectal vs colonic) and emergency presentation

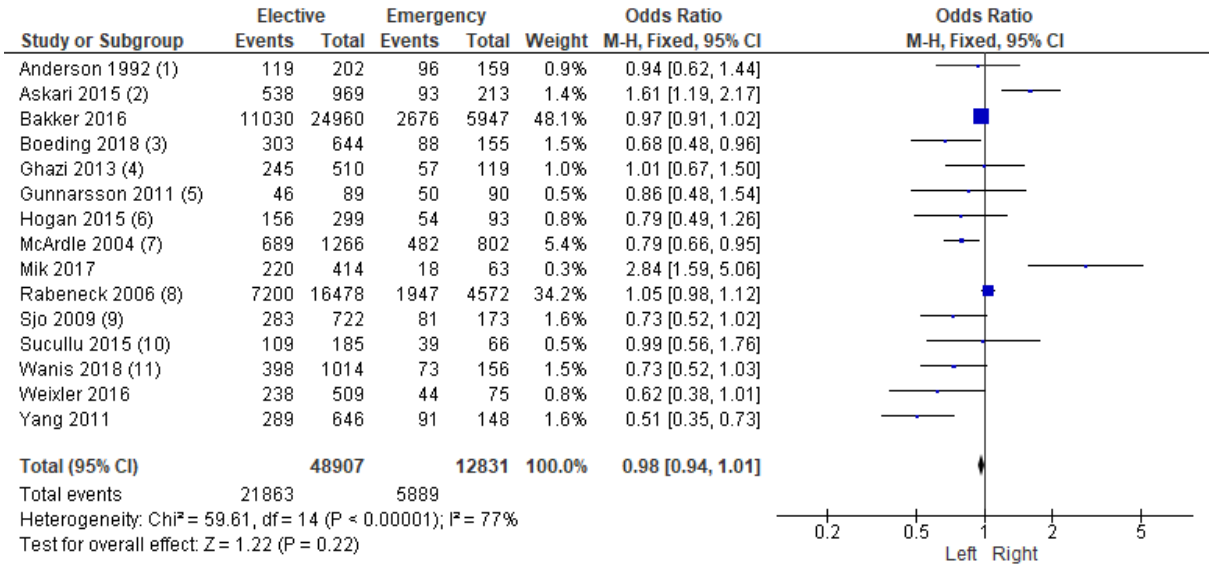


Figure 2-3 Association between colonic tumour location (right-sided versus left-sided) and emergency presentation

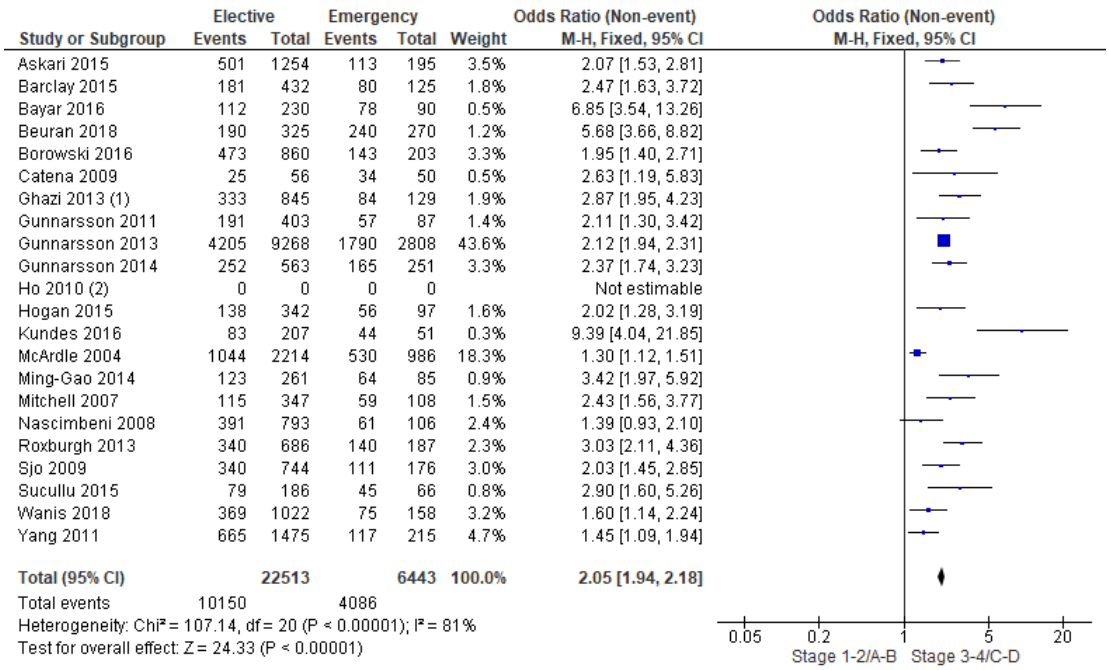


Figure 2-4 Association between overall tumour staging and emergency presentation

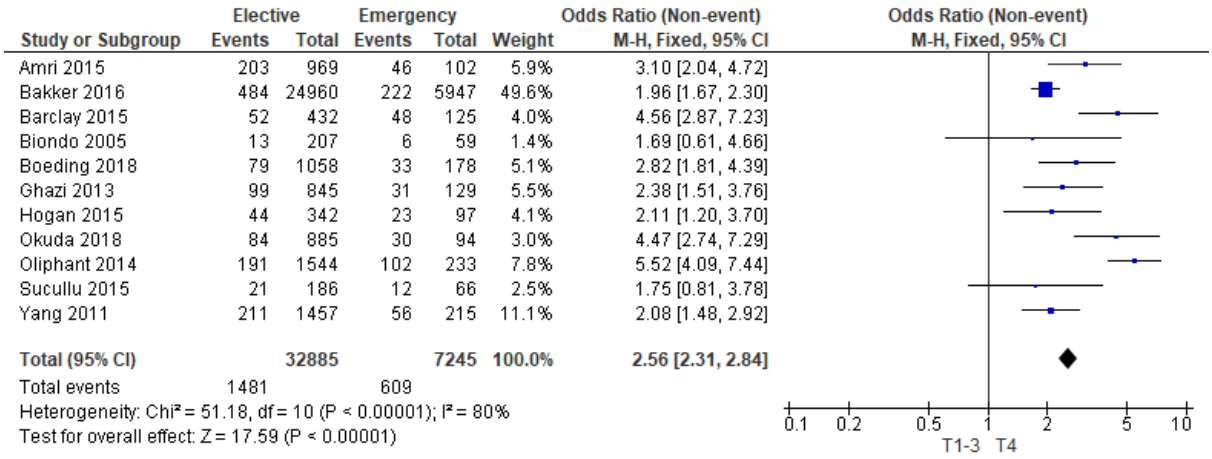


Figure 2-5 Association between T Stage and emergency presentation

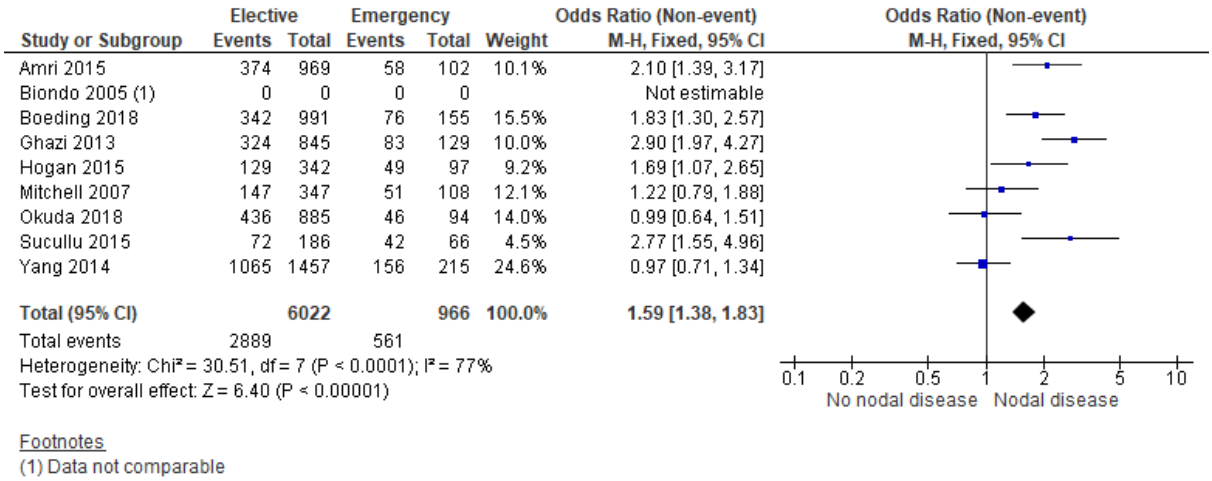


Figure 2-6 Association between N Stage and emergency presentation

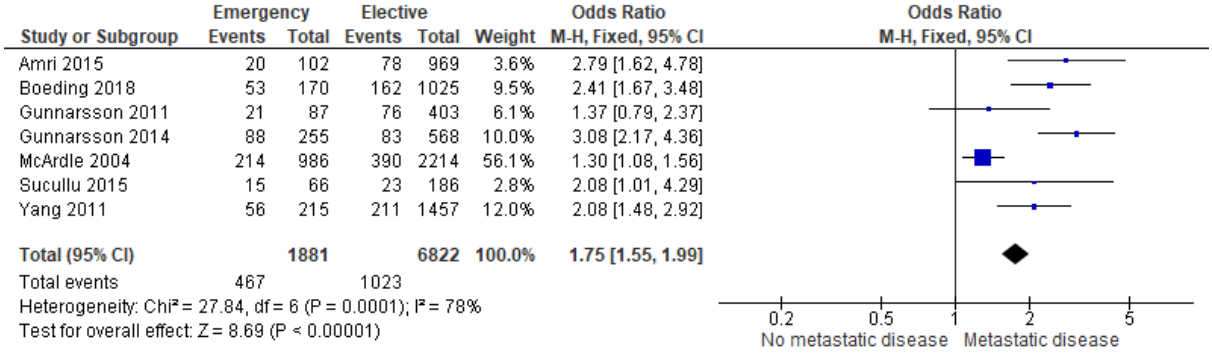


Figure 2-7 Association between M Stage and emergency presentation

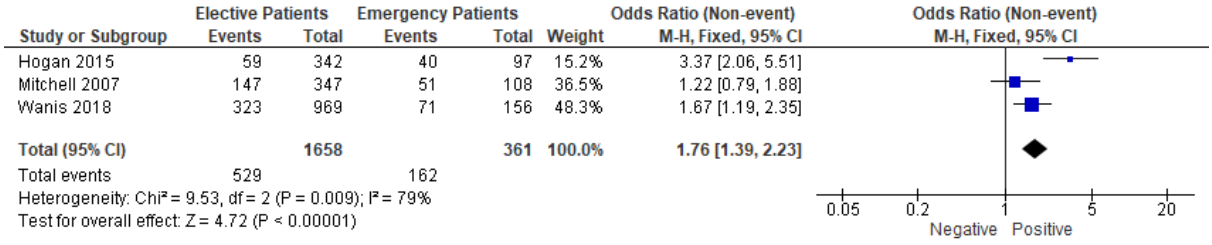


Figure 2-8 Association between the presence of lymphovascular invasion and emergency presentation

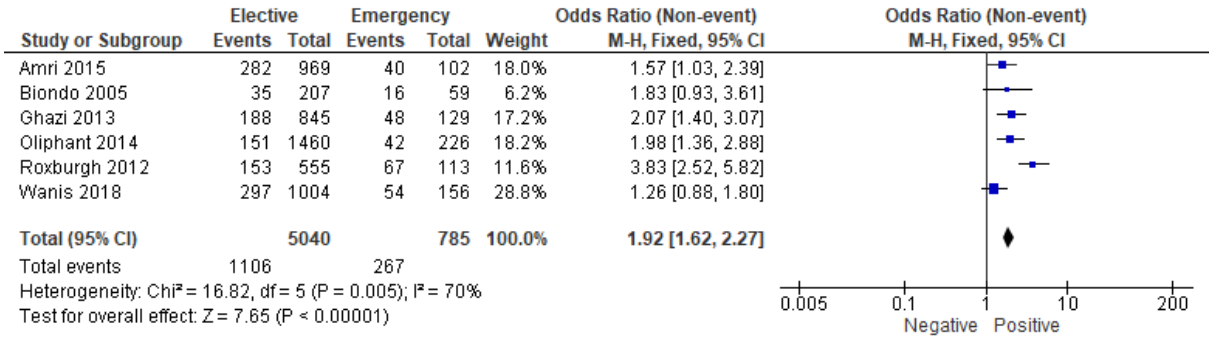


Figure 2-9 Association between the presence of vascular invasion and emergency presentation

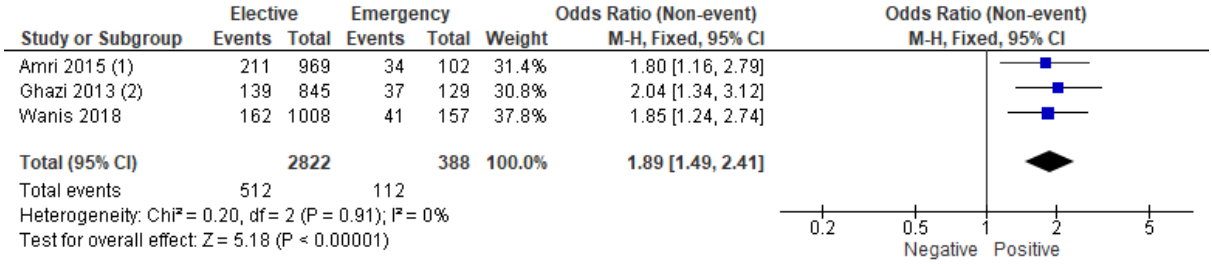


Figure 2-10 Association between the presence of perineural invasion and emergency presentation

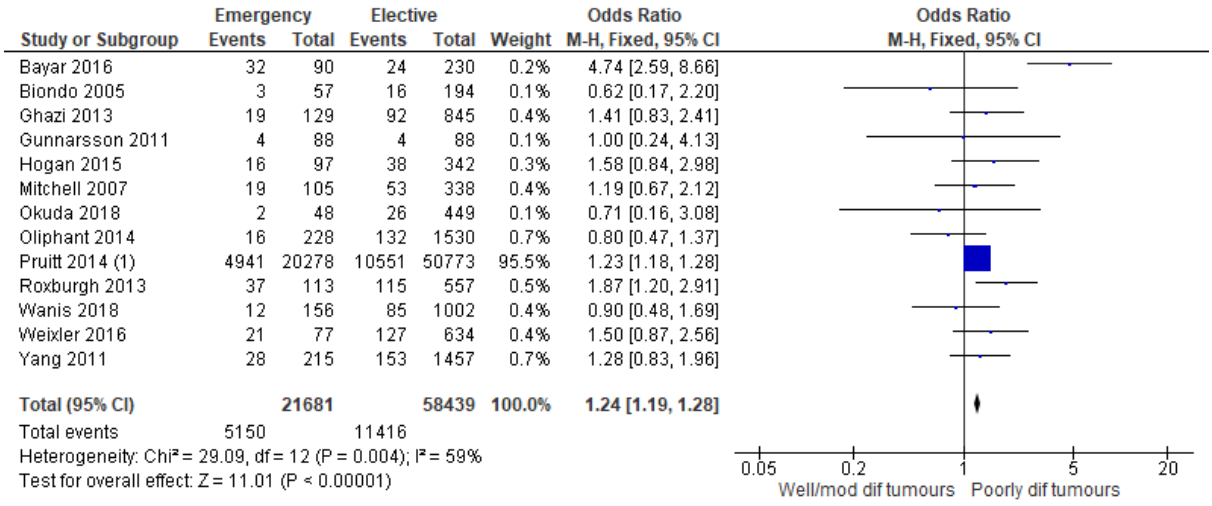


Figure 2-11 Association between tumour grade/differentiation and emergency presentation

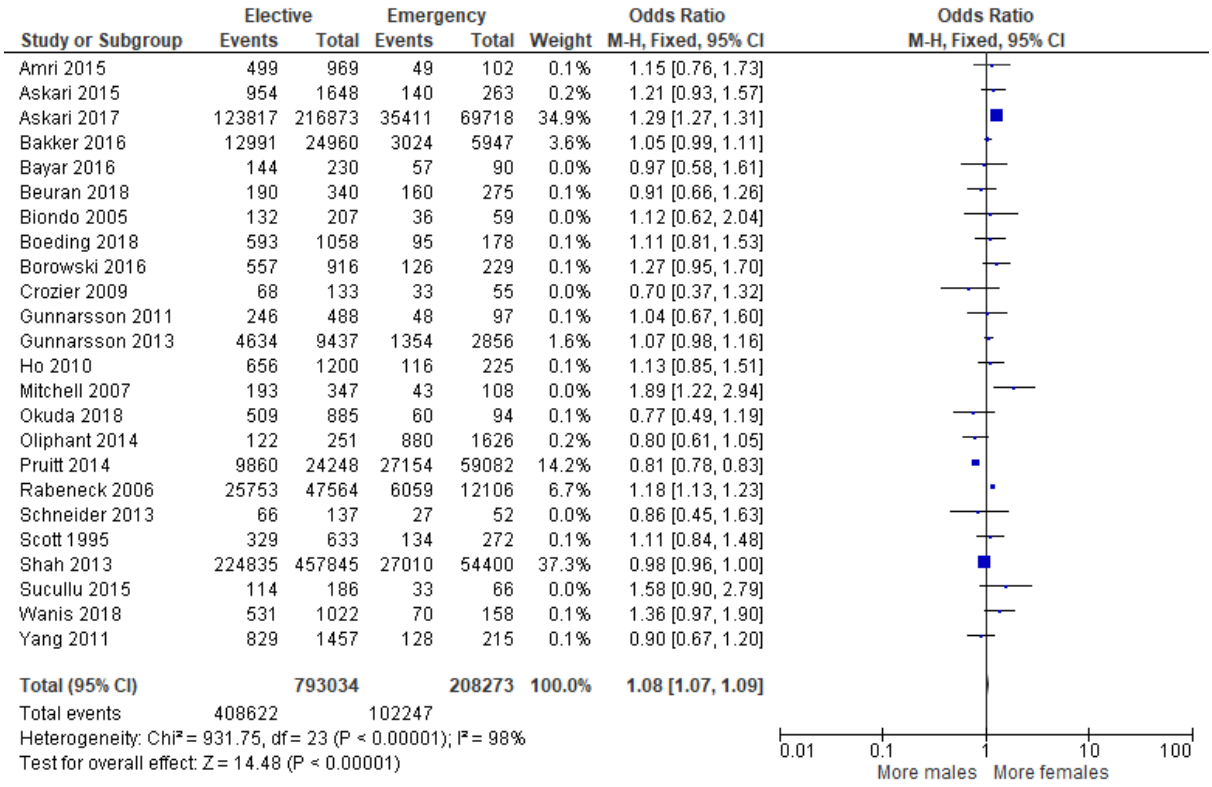


Figure 2-12 Association between sex and emergency presentation

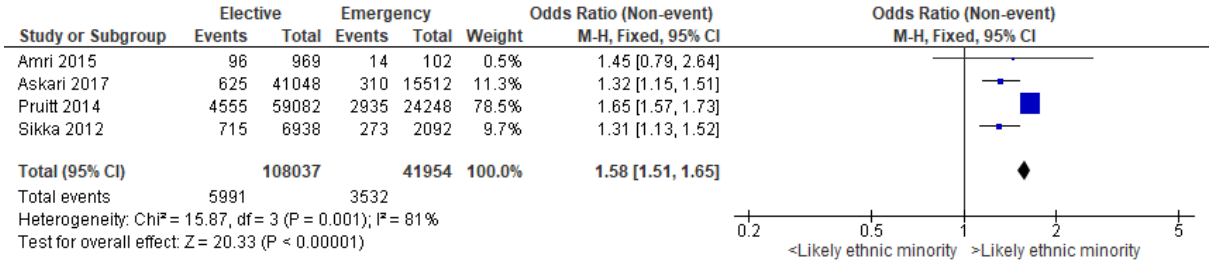


Figure 2-13 Association between ethnicity and emergency presentation

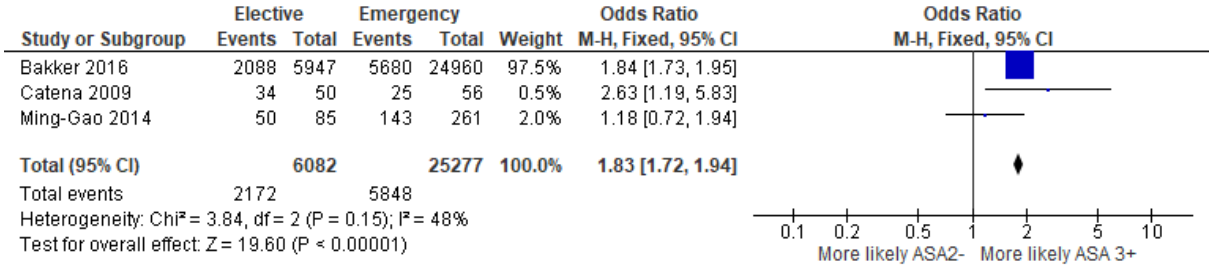


Figure 2-14 Association between ASA classification and emergency presentation

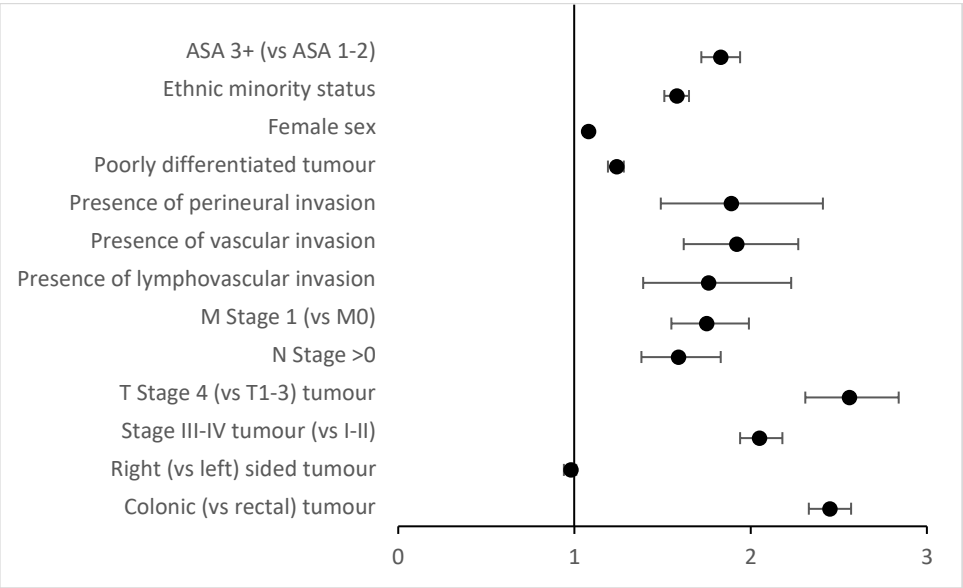


Figure 2-15 Summary of meta-analysis findings - association between clinicopathological characteristics and emergency presentation (odds ratios and 95% confidence intervals)

3 Chapter 3 - An Investigation Into the Basic Clinical and Demographic Characteristics of Colorectal Cancer Within the West of Scotland

3.1 Introduction

As described within Chapter 1, colorectal cancer is highly prevalent and remains a major cause of morbidity and mortality, even in patients undergoing treatment with curative intent for non-metastatic disease. The majority of cases of colorectal cancer present and undergo definitive treatment on an elective basis however a significant minority present and undergo investigation and treatment on an unplanned emergency basis. As reported within the systematic review and meta-analysis presented within Chapter 2 there is an association between colon cancer and emergency presentations[123,126,215].

A number of factors are likely to influence the mode of presentation of colorectal cancer. Four major models of healthcare system have been described[263] ranging from free at point of care services (for example the National Health Service within the United Kingdom) to pay-as-you-go systems (found within a number of less developed nations). An extension to standard healthcare – the introduction of population based screening programmes has been shown to have influenced the rate of emergency presentations of colorectal cancer[134] however a number of other factors are likely to exist including host factors, tumour factors, geographical and cultural factors, some of which have been identified within the literature review in Chapter 2.

Within the United Kingdom, the National Health Service (NHS) provides a free at point of care health service available to the entire population. As described within Chapter 1, within Scotland, a national bowel cancer screening programme was rolled out in 2007 and is routinely offered on a biennial basis to all adults from the age of 50 to 75 with the aim of increasing the proportion of the population diagnosed with early-stage disease on an elective basis.

A significant proportion of the studies comparing elective and emergency presentations of colorectal cancer identified in the literature review presented within Chapter 2 focussed on patients undergoing potentially curative resectional surgery for non-metastatic disease. Adverse short-term and long-term oncological outcomes have been reported for patients presenting emergently even after adjustment for disease stage[211,212]. However, it also seems likely that there is a disparity in the proportion of patients presenting with metastatic disease and subsequent influence on treatment types (palliative procedures/no procedures/resectional surgery) between patients presenting electively and emergently.

Colon and rectal cancer, traditionally considered a single disease process (colorectal cancer) are increasingly considered two distinct entities. This is largely in part due to differing disease biology, investigation (local preoperative staging in rectal cancer) and treatment strategies (neoadjuvant treatment within rectal cancer). Patients with colon cancer presenting with acute symptoms (including obstruction and abdominal pain) are more likely to undergo a definitive surgical procedure during index admission whereas patients with rectal cancer presenting with acute symptoms are more likely to undergo a temporising procedure (for example defunctioning colostomy) to allow further

staging, neoadjuvant treatment and finally definitive surgery on a planned, elective basis.

This thesis will predominantly investigate patients undergoing resectional surgery with curative intent for TNM I-III colon cancer. However, this chapter first describes the denominator – all patients within the West of Scotland diagnosed with colorectal cancer over a four-year period. This study describes the association between mode of presentation and tumour location, year of diagnosis, season of diagnosis and presenting symptoms. Subsequently it describes the association between mode of presentation and treatment type/aims. Finally, it describes within patients undergoing curative resectional surgery for TNM Stage I-III colon cancer, the association between mode of presentation and short-term and long-term outcomes.

3.2 Methods

The West of Scotland Colorectal Cancer Managed Clinical Network (MCN) maintains a prospectively collected dataset of all patients diagnosed with colorectal cancer in the West of Scotland and contains basic clinicopathological data. This covers four health boards (Ayrshire and Arran, Forth Valley, Lanarkshire and Greater Glasgow and Clyde) and includes almost half of the population of Scotland. Cancer registration data within Scotland is recognised to be of high quality[264,265]. These patients are usually followed up for a period of 3-5 years as described within Chapter 1 and receive treatment in line with national guidelines.

Patients diagnosed with colorectal cancer between January 2011 and December 2014 within the West of Scotland were identified from the MCN database. Emergency presentations were defined as unplanned admissions requiring investigation and definitive treatment within 72 hours of hospital admission. Patients who did not undergo any intervention for colorectal cancer were not defined as either elective or emergency presentations. All other patients were classified as elective presentations. Season of diagnosis was stratified Spring (March/April/May), Summer (June/July/August), Autumn (September/October/November) and Winter (December/January/February). Disease stage was classified using the TNM Classification of Malignant Tumours, Sixth Edition 2002[266]. Tumours proximal to the splenic flexure were considered right-sided. Tumours of the splenic flexure, descending or sigmoid colon were considered left-sided. Rectosigmoid and rectal tumours were considered rectal. Treatment intent (either curative or palliative) was the final assessment of treatment intent as agreed by the MDT. The type of procedure performed was based on the final definitive (or only) surgery performed and was classified as

either non-resectional (for example stoma or bypass), local excision (endoscopic excision) or formal colorectal resection. Where described within the results section as “any procedure” this includes, endoscopic resection, resectional surgery (both curative and non-curative), bypass surgery, surgery to defunction and stenting. Where only curative procedures or resectional procedures with curative intent have been included this has been described.

The cause of emergency presentation was identified from electronic patient records based on documentation from the index admission and radiology reports. The postoperative systemic inflammatory response, as described in Chapter 1 was classified using the postoperative Glasgow Prognostic Score (poGPS)[47]. Postoperative mortality was considered as a death of any cause within thirty postoperative days. Complications were categorised as overall complications, infective complications and non-infective complications. Infective complications were subcategorised as non-surgical site infections (SSIs) or surgical site infections which were then further subcategorised as: superficial SSIs (presence of pus either discharging spontaneously or requiring drainage or the use of antibiotics due to a diagnosis of cellulitis around the wound), deep SSI (intra-abdominal pus or infection requiring either drainage or antibiotic therapy) or anastomotic leakage (diagnosed either on imaging or laparotomy). Complications were categorised by severity using the Clavien-Dindo classification[207].

Survival was updated through data linkage to the National Records of Scotland (NRS) deaths data until the end of 2018. Oncological outcomes (3-year overall/cancer-specific survival) were calculated after exclusion of 30-day mortality. Overall survival was calculated from the date of surgery until date of death of any cause. Cancer-specific survival was calculated as the time from

date of surgery until date of death due to recurrent/metastatic colon cancer. A death was considered a result of colon cancer if this was the primary cause of death on the death certificate in accordance with rules set out by the World Health Organisation[267]. All patients were followed up for a minimum of three years following surgery.

Ethical approval was granted for this project from the Public Benefit and Privacy Panel (NHS Scotland) for Health and Social Care (PBPP).

3.2.1 Statistical Analysis

The relationship between categorical variables including the relationship between mode of presentation and clinicopathological characteristics and the relationship between presenting symptoms and tumour sidedness has been examined using the Chi squared test. Three-year overall and cancer-specific survival was carried out using the life table function of SPSS and results were displayed as percentage 3-year survival and percentage standard error. On survival analysis, statistical significance was calculated using the log rank test. Overall and cancer-specific survival has been shown graphically on Kaplan-Meier curves with 30-day mortality included.

Statistical analysis was carried out using IBM SPSS Statistics for Windows Version 28 (IBM Corporation, Armonk, New York, USA). A two-tailed p-value of <0.05 was considered significant throughout.

3.3 Results

6549 patients were diagnosed with colorectal cancer within the West of Scotland from January 2011 until December 2014. Of these, 5250 patients were classified as either elective or emergency presentations. The remaining 1299 patients did not have a mode of presentation classified as they did not undergo a procedure. Overall, 912 patients (17%) presented as emergency. 72% of patients (n=3782) were diagnosed with colon cancer and 28% (n=1468) were diagnosed with rectal cancer.

3.3.1 Association Between Tumour Location (Colonic/Rectal) and Mode of Presentation

As shown in Table 3-1, of 3782 patients with colon cancer, 858 underwent an emergency procedure (23%). Of 1468 patients with rectal cancer, 54 underwent an emergency procedure (4%). This association was statistically significant ($p<0.001$).

3.3.2 Association Between Basic Clinical and Demographic Factors and Mode of Presentation in Colon Cancer

As shown in Table 3-2, no significant association was seen between mode of presentation: year of diagnosis ($p=0.228$), health board of diagnosis ($p=0.168$) or season of diagnosis ($p=0.348$). Overall, 12% (414/3569) of patients had metastatic disease at diagnosis. 8% (210/2795) of elective patients had

metastatic disease at time of diagnosis in comparison to 26% (204/774) of emergency patients (p<0.001). Patients presenting emergently were more likely to undergo a non-resectional procedure (bypass/defunctioning stoma/stent) as opposed to either a local excision of tumour or a formal colorectal resection (p<0.001). Overall, 86% (3070/3577) of patients underwent a curative procedure. 92% (2574/2799) of elective patients underwent a curative procedure in comparison to 64% (496/778) of emergency patients (p<0.001). The association between mode of presentation and overall/cancer-specific survival (inclusive of 30-day mortality) in all patients with TNM I-IV colon cancer is shown graphically in Figures 3-1/3-2 respectively.

3.3.3 Causes of Emergency Presentation of Colorectal Cancer and Association With Tumour Site

As shown in Table 3-3, of 794 patients undergoing a procedure for an emergency presentation of colorectal cancer the reasons for emergency presentation were: obstruction (52%), perforation with or without obstruction (18%), abdominal pain (13%), intraabdominal sepsis (9%), lower gastrointestinal bleeding (3%), presumed appendicitis (2%) or other (3%). Patients with right-sided colon cancer were more likely to present with abdominal pain, intra-abdominal sepsis or presumed appendicitis whereas patients with left-sided colon cancer were more likely to present with obstruction or perforation and patients with rectal cancer were more likely to present with lower GI bleeding (p<0.001).

3.3.4 The Association Between Mode of Presentation and the Postoperative Systemic Inflammatory Response and Postoperative Morbidity and Mortality in Patients Undergoing Curative Surgery for TNM Stage I-III Colon Cancer

As shown in Table 3-4, of 2705 patients undergoing curative resectional surgery for TNM Stage I-III colon cancer, the overall postoperative mortality rate was 3% (n=76). Emergency presentation was associated with a higher postoperative mortality rate than elective presentation (8% versus 2%, $p<0.001$).

As shown in Table 3-5, in patients undergoing curative resectional surgery for TNM Stage I-III colon cancer, when the postoperative systemic inflammatory response was stratified using the postoperative Glasgow Prognostic Score (poGPS), 47%/32%/20% and 60%/22%/18% of patients had a poGPS of 0/1/2 on postoperative days 3 and 4 respectively. Emergency presentation was associated with a raised postoperative days 3 and 4 Glasgow Prognostic Score (both $p<0.001$).

The association between mode of presentation and postoperative morbidity was available for 2225 patients undergoing curative resectional surgery for colon cancer and is shown in Table 3-6. An association was seen between emergency presentation and any postoperative complication (56% versus 40%, $p<0.001$) and infective complications (45% versus 29%, $p<0.001$). Emergency presentations were associated with an increased proportion of surgical site infections (28% versus 20%, $p<0.001$), deep surgical site infections (10% versus 5%, $p<0.001$), respiratory tract infections (16% versus 9%, $p<0.001$) and cardiac complications

(7% versus 4%, p=0.013). A trend was seen between emergency presentations and increased non-infective complications (21% versus 17%, p=0.067) and anastomotic leaks (8% versus 6%, p=0.094). No association was seen between mode of presentation and superficial surgical site infections (p=0.151), urinary tract infections (p=0.281) or remote site infections (p=0.986). When categorised by overall Clavien-Dindo classification, emergency presentations were associated with a significantly higher proportion of Clavien-Dindo 3-5 complications than elective presentations (22% versus 10%, p<0.001).

3.3.5 The Association Between Mode of Presentation and Long-Term Oncological Outcomes in Patients Undergoing Curative Surgery for TNM Stage I-III Colon Cancer

The association between mode of presentation and 3-year overall/cancer-specific survival after exclusion of postoperative mortality is shown in Table 3-7. For all patients (TNM Stage I-III) 3-year overall and cancer specific survival was 82% and 88% respectively. When subclassified by TNM Stage, 3-year overall survival was 93%/85%/72% and 3-year cancer specific survival was 98%/92%/77% for TNM Stage I/II/III disease respectively. The association between mode of presentation and overall/cancer-specific survival (inclusive of 30-day mortality) in patients undergoing resectional surgery with curative intent for TNM I-III colon cancer is shown graphically in Figures 3-3/3-4 respectively.

For all patients (TNM Stage I-III) emergency presentation was associated with adverse 3-year overall survival (85% versus 65%, p<0.001) and cancer-specific

survival (91% versus 74%, p<0.001). For patients with TNM Stage I disease (n=553) emergency presentation was associated with adverse 3-year overall survival (94% versus 81%, p<0.001) but not cancer-specific survival (98% versus 93%, p=0.259). For patients with TNM Stage II disease (n=1123) emergency presentation was associated with adverse 3-year overall survival (87% versus 77%, p<0.001) and cancer-specific survival (94% versus 84%, p<0.001). For patients with TNM Stage III disease (n=953) emergency presentation was associated with adverse 3-year overall survival (75% versus 58%, p<0.001) and cancer-specific survival (81% versus 62%, p<0.001)

3.4 Discussion

The present results show that within a free at point of care health service (with an established bowel screening service), a significantly larger proportion of cases of colon cancer compared to rectal cancer present and undergo a definitive procedure on an emergency basis. No significant difference was observed between mode of presentation and year/season/health board of diagnosis. Patients presenting emergently were more likely to have metastatic disease at diagnosis and undergo a palliative or non-resectional procedure. Amongst emergency presentations, obstruction and perforation were the most common diagnoses on presentation however this varied dependent on tumour location (right/left/rectal). In patients undergoing potentially curative surgery for TNM Stage I-III colon cancer, emergency presentation was associated with an increased 30-day mortality, increased postoperative systemic inflammatory response, adverse short-term outcomes (in particular infective complications) and adverse 3-year overall/cancer-specific survival after adjustment for disease stage.

The present study was carried out within a free at point of care National Health Service with an established population bowel screening programme. This removes some of the biases/confounding factors that may be observed within other types of healthcare system. The association between colon cancer and emergency presentation is consistent with previous literature as reported within the literature review in Chapter 2. No significant association was observed between mode of presentation and year of diagnosis. The study period was relatively short (4 consecutive years) and there were no significant changes to either the health service or the bowel screening programme during the study

period therefore this observation was expected. The present results do not show any association between mode of presentation and season of diagnosis. A single study had reported an association between mode of presentation and season of diagnosis[222], in particular an increased emergency presentation rate during the summer months however no clear hypothesis could be given as to why this may be the case. No other studies had examined this association. The previous result may have been merely an anomaly however no firm conclusion can be made on this observation without further validation. Despite the free at point of care health service described above, the West of Scotland contain some of the most deprived areas of Scotland. This is recognised to impact on mode of presentation, interaction with screening and outcomes in colorectal cancer and would be an important area for further investigation within this population[246].

Consistent with the literature review reported within Chapter 2, emergency presentation was associated with an increased proportion of patients with metastatic disease at diagnosis and in keeping with this, a higher proportion of palliative/non-resectional procedures. Emergency presentations are widely considered to present with obstruction, perforation or bleeding and, indeed, some studies identified within Chapter 2 defined emergency presentation by this. Obstruction and perforation account for the majority of emergency presentations of colorectal cancer. Other presenting diagnoses – abdominal pain or intra-abdominal sepsis without evidence of obstruction or perforation are other leading causes of emergency presentation therefore it is imprecise to consider emergency presentations as only patients presenting with obstruction, perforation or bleeding. In patients with colon cancer, lower GI bleeding was a rare cause of emergency presentation (2%) however this proportion was significantly higher in patients with rectal cancer.

In patients undergoing curative resectional surgery for TNM Stage I-III colon cancer, emergency presentation was associated with higher postoperative mortality, an increased postoperative systemic inflammatory response (as measured by poGPS) and a higher proportion of short-term complications, in particular infective complications. This is in keeping with previous literature[47,121,122,233,268,269]. Interestingly, within the present study, no significant association between superficial surgical site infections and mode of presentation was found. This was unexpected and is described further in the limitations section below.

The present results show that within the subgroup of patients with TNM Stage I-III colon cancer undergoing resectional surgery with curative intent, emergency presentation remained associated with adverse long-term oncological outcomes (overall and cancer-specific survival) even after exclusion of postoperative deaths and adjustment for TNM Stage. This is consistent with published literature and validates our data. The reason for this is likely to be multifactorial and includes tumour factors, host factors, perioperative factors and postoperative factors. Furthermore, previous literature[47] also reported an association between the postoperative systemic inflammatory response, postoperative morbidity and long-term oncological outcomes and this is likely to be another factor underlying these differences. Further detailed research into all of these factors is required to better understand this disparity in outcomes.

Limitations of this study include the retrospective nature of certain aspects of data collection within this study, in particular postoperative Glasgow Prognostic Score and complication data. Postoperative blood results on Days 3 and 4 were only available if they had been routinely taken and as such there was missing

data for these areas. It seems likely that patients would have been more likely to have postoperative blood tests checked if there had been a clinical cause for concern and this may potentially introduce bias. Postoperative complication data was obtained retrospectively from patient records and again relies on the accuracy of complication reporting. It seems likely that major complications – anastomotic leaks, intraabdominal complications, return to theatre and significant cardiorespiratory complications would have been accurately reported. However, other, less significant complications, for example a postoperative wound infection requiring antibiotics or wound opening on the ward may be less likely to be accurately recorded. This may explain why no association between mode of presentation and superficial surgical site infection was reported within the present study. Within the present study, patients who did not undergo a procedure were not coded as either elective or emergency. Ideally the data would be coded in such a way that all patients had a designated mode of presentation. Furthermore, across datasets reported within the existing literature, there is no standardised way of classifying the mode of presentation. Within the present study, the dataset was coded so that patients with an unplanned admission requiring investigation and definitive treatment within 72 hours of presentation were considered emergencies and the rest were considered elective. In reality, it seems likely that there was a spectrum of cases as opposed to distinct elective and emergency cases. Adjuvant chemotherapy was not included within the present study. Further work is required in this area as the likelihood of: receiving chemotherapy, completing chemotherapy, need for dose reduction or delay to starting chemotherapy may differ between elective and emergency presentations of colon cancer (both high risk TNM Stage II and TNM Stage III disease) and this may contribute towards the adverse outcomes seen in emergency presentations.

In conclusion, the results of the present study confirm that there is a significant association between emergency presentation and colon cancer. Emergency presentations were associated with adverse short-term outcomes in terms of the postoperative systemic inflammatory response, postoperative morbidity and postoperative mortality. Furthermore, despite the present study utilising a free at point of care national health service with established bowel screening programme, emergency presentations of colon cancer were associated with adverse oncological outcomes even after adjustment for TNM Stage. This confirms the rationale to carry out further investigation within the present cohort into the differences (tumour, host and other factors) between elective and emergency presentations of colon cancer and the subsequent impact on survival.

3.5 Tables

Table 3-1 Association between mode of presentation and tumour location (any procedure, colon or rectum included)

	Total	Elective	Emergency	p
Cancer location	5250	4338 (83%)	912 (17%)	<0.001
Colon	3782 (72%)	2924 (67%)	858 (94%)	
Rectum	1468 (28%)	1414 (33%)	54 (6%)	

Table 3-2 Association between mode of presentation and basic clinical/demographic factors (any procedure, colon cancer only included)

Variable	Total	Elective	Emergency	p
Year of diagnosis	3577	2798 (78%)	779 (22%)	0.228
2011	947 (27%)	747 (27%)	200 (26%)	
2012	920 (26%)	733 (26%)	187 (24%)	
2013	824 (23%)	646 (23%)	178 (23%)	
2014	886 (25%)	672 (24%)	214 (28%)	
Healthboard	3576	2797 (78%)	779 (22%)	0.168
Greater Glasgow and Clyde	1949 (55%)	1541 (55%)	408 (52%)	
Ayrshire and Arran	558 (16%)	442 (16%)	116 (15%)	
Lanarkshire	687 (19%)	516 (18%)	171 (22%)	
Forth Valley	382 (11%)	298 (11%)	84 (11%)	
Season of diagnosis	3578	2799 (78%)	779 (22%)	0.348
Winter	802 (22%)	617 (22%)	185 (24%)	
Spring	903 (25%)	700 (25%)	203 (26%)	
Summer	960 (27%)	770 (28%)	190 (24%)	
Autumn	913 (26%)	712 (25%)	201 (26%)	
Metastatic disease at diagnosis	3569	2795 (78%)	774 (22%)	<0.001
No	3155 (88%)	2585 (93%)	570 (74%)	
Yes	414 (12%)	210 (8%)	204 (26%)	
Type of procedure	3578	2799 (78%)	779 (22%)	<0.001
No resection (bypass/stent/defunctioning)	226 (6%)	97 (4%)	129 (17%)	
Local excision only	214 (6%)	209 (8%)	5 (1%)	
Formal colorectal resection	3138 (88%)	2493 (89%)	645 (83%)	
Treatment intent	3577	2799 (78%)	778 (22%)	<0.001
Curative procedure	3070 (86%)	2574 (92%)	496 (64%)	
Palliative procedure	507 (14%)	225 (8%)	282 (36%)	

Table 3-3 Causes of emergency presentation of colorectal cancer and association with tumour site (any procedure, colon or rectal cancer included)

	Total	Right colon	Left colon	Rectal	P
Total	794	407 (51%)	339 (43%)	48 (6%)	<0.001
Obstruction	412 (52%)	192 (47%)	198 (58%)	22 (46%)	
Perforation (+/- obstruction)	143 (18%)	60 (15%)	76 (22%)	7 (15%)	
Abdominal pain	103 (13%)	68 (17%)	31 (9%)	4 (8%)	
Intra-abdominal sepsis	72 (9%)	46 (11%)	23 (7%)	3 (6%)	
Lower GI bleeding	23 (3%)	8 (2%)	5 (2%)	10 (21%)	
Presumed appendicitis	19 (2%)	19 (5%)	0	0	
Other	22 (3%)	14 (3%)	6 (2%)	2 (4%)	

Table 3-4 Association between mode of presentation and postoperative (30-day) mortality (curative resectional surgery, colon cancer only included)

Postoperative mortality	Total	Elective	Emergency	p
Total	2705	2263 (84%)	442 (16%)	<0.001
No	2629 (97%)	2220 (98%)	409 (93%)	
Yes	76 (3%)	43 (2%)	33 (8%)	

Table 3-5 Association between mode of presentation and postoperative systemic inflammatory response (curative resectional surgery, colon cancer only included)

	Total	Elective	Emergency	P
POD3 GPS	1733	1467 (85%)	266 (15%)	<0.001
0	820 (47%)	771 (53%)	49 (18%)	
1	561 (32%)	494 (34%)	67 (25%)	
2	352 (20%)	202 (14%)	150 (56%)	
POD 4 GPS	1535	1279 (83%)	256 (17%)	<0.001
0	924 (60%)	810 (63%)	114 (45%)	
1	340 (22%)	296 (23%)	44 (17%)	
2	271 (18%)	173 (14%)	98 (38%)	

Table 3-6 Association between mode of presentation and postoperative morbidity (curative resectional surgery, colon cancer only included)

	Total	Elective	Emergency	P
Any complication	2225	1889 (85%)	336 (15%)	<0.001
No	1272 (57%)	1125 (60%)	147 (44%)	
Yes	953 (43%)	764 (40%)	189 (56%)	
Infective complication	2225	1889 (85%)	336 (15%)	<0.001
No	1519 (68%)	1334 (71%)	185 (55%)	
Yes	706 (32%)	555 (29%)	151 (45%)	
Non-infective complication	2225	1889 (85%)	336 (15%)	0.067
No	1833 (82%)	1568 (83%)	265 (79%)	
Yes	392 (18%)	321 (17%)	71 (21%)	
Surgical site infection	2225	1889 (85%)	336 (15%)	<0.001
No	1764 (79%)	1521 (81%)	243 (72%)	
Yes	461 (21%)	368 (20%)	93 (28%)	
Superficial surgical site infections	2225	1889 (85%)	336 (15%)	0.151
No	1947 (88%)	1661 (88%)	286 (85%)	
Yes	278 (13%)	228 (12%)	50 (15%)	
Anastomotic leak	2225	1889 (85%)	336 (15%)	0.094
No	2085 (94%)	1777 (94%)	308 (92%)	
Yes	140 (6%)	112 (6%)	28 (8%)	
Deep surgical site infections	2225	1889 (85%)	336 (15%)	<0.001
No	2106 (95%)	1803 (95%)	303 (90%)	
Yes	119 (5%)	86 (5%)	33 (10%)	
Respiratory tract infection	2225	1889 (85%)	336 (15%)	<0.001
No	2000 (90%)	1719 (91%)	281 (84%)	
Yes	225 (10%)	170 (9%)	55 (16%)	
Urinary tract infection	2225	1889 (85%)	336 (15%)	0.281
No	2182 (98%)	1855 (98%)	327 (97%)	
Yes	43 (2%)	34 (2%)	9 (3%)	
Remote site infection	2225	1889 (85%)	336 (15%)	0.986
No	2185 (98%)	1855 (98%)	330 (98%)	
Yes	40 (2%)	34 (2%)	6 (2%)	
Cardiac complication	2225	1889 (85%)	336 (15%)	0.013
No	2129 (96%)	1816 (96%)	313 (93%)	
Yes	96 (4%)	73 (4%)	23 (7%)	
Clavien Dindo Grade	2225	1889 (85%)	336 (15%)	<0.001
0-2	1958 (88%)	1695 (90%)	263 (78%)	
3-5	267 (12%)	194 (10%)	73 (22%)	

Table 3-7 Association between mode of presentation and oncological outcomes in colon cancer after exclusion of 30-day mortality (curative resectional surgery, colon cancer only included)

	Total	Elective	Emergency	P
TNM I-III	2629	2220	409	
Overall survival	82% (SE 1%)	85% (SE 1%)	68% (SE 2%)	<0.001
Cancer Specific Survival	88% (SE 1%)	91% (SE 1%)	74% (SE 2%)	<0.001
TNM I	553	537	16	
Overall survival	93% (SE 1%)	94% (SE 1%)	81% (SE 10%)	<0.001
Cancer specific survival	98% (SE 1%)	98% (SE 1%)	93% (SE 7%)	0.259
TNM II	1123	916	207	
Overall survival	85% (SE 1%)	87% (SE 1%)	77% (SE 3%)	<0.001
Cancer specific survival	92% (SE 1%)	94% (SE 1%)	84% (SE 3%)	<0.001
TNM III	953	767	186	
Overall survival	72% (SE 1%)	75% (SE 2%)	58% (SE 4%)	<0.001
Cancer specific survival	77% (SE 1%)	81% (SE 1%)	62% (SE 4%)	<0.001

3.6 Figures

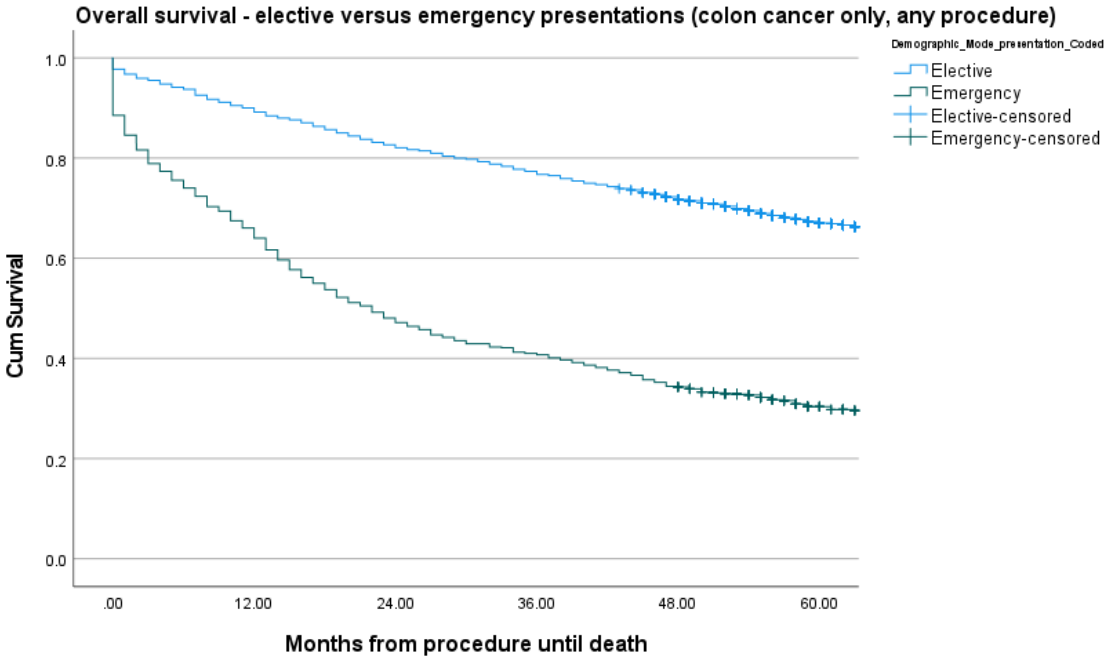


Figure 3-1 – Overall survival in elective versus emergency presentations of colon cancer (TNM I-IV, any surgery, colon only)

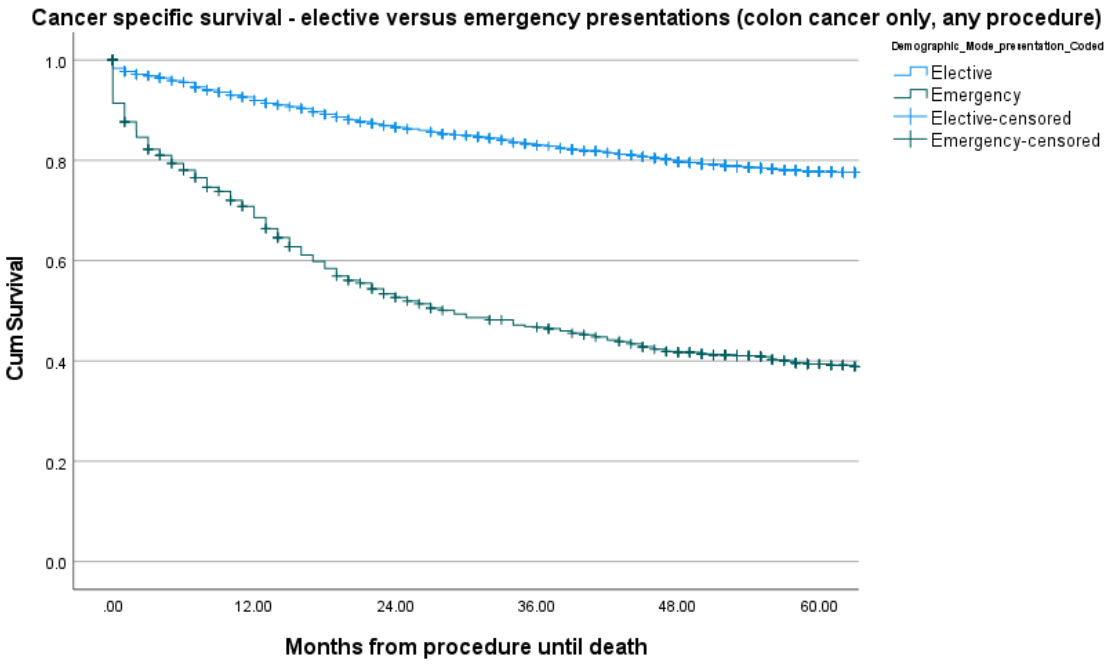


Figure 3-2 – Cancer-specific survival in elective versus emergency presentations of colon cancer (TNM I-IV, any surgery, colon only)

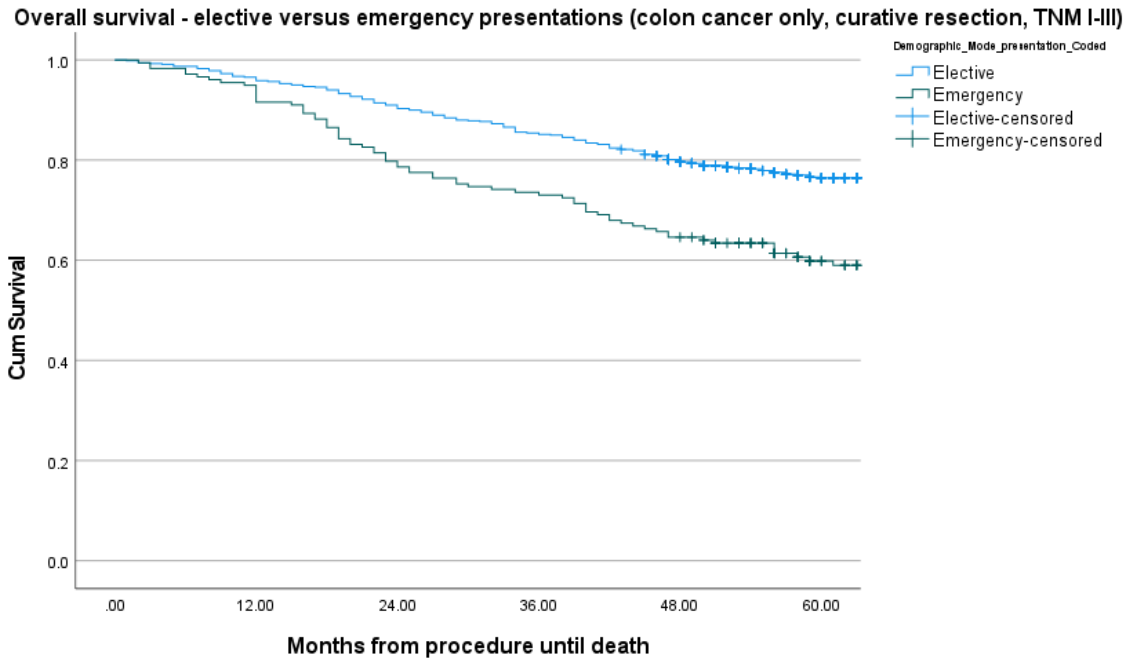


Figure 3-3 – Overall survival in elective versus emergency presentations of colon cancer (TNM I-III, curative resectional surgery, colon only)

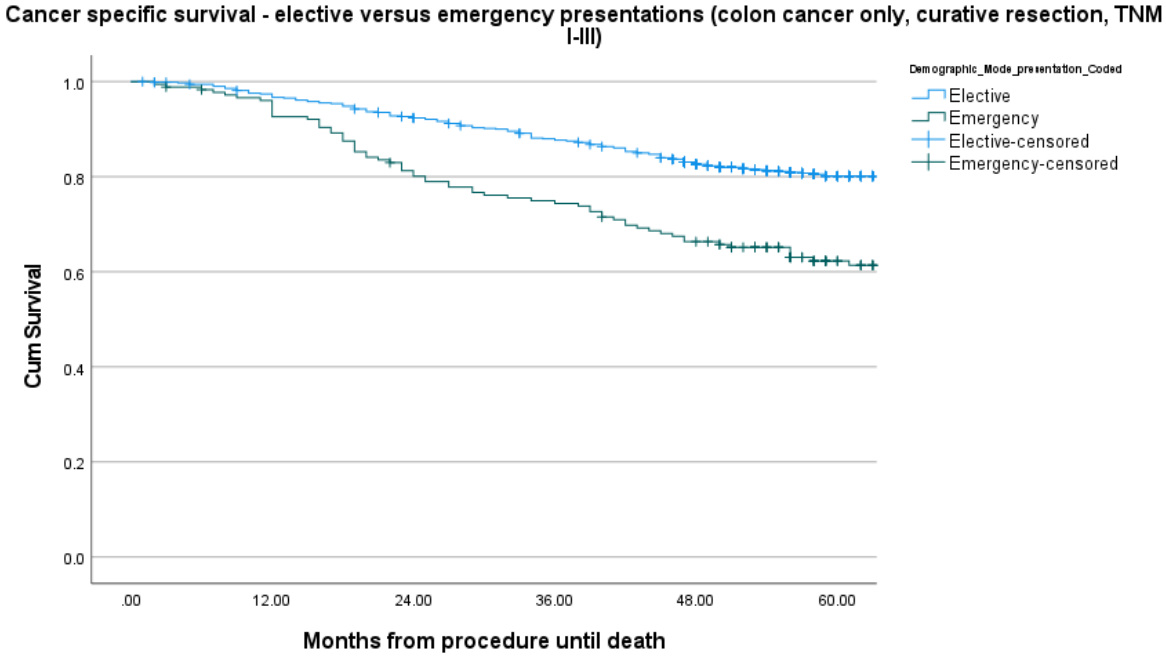


Figure 3-4 – Cancer-specific survival in elective versus emergency presentations of colon cancer (TNM I-III, curative resectional surgery, colon only)

4 Chapter 4 - An Investigation Into the Association Between Tumour Factors, Host Factors, Mode of Presentation and Short-Term/Long-Term Survival in Colon Cancer

4.1 Introduction

In Chapter 1, a number of clinicopathological factors prognostically significant within colorectal cancer were described. Although colon and rectal cancer have traditionally been considered a single disease, they are now increasingly recognised to be different entities with differing management strategies. In colon cancer, TNM stage represents the most significant prognostic factor and is used to determine treatment aims (curative versus palliative), to guide the use of adjuvant chemotherapy and to predict prognosis. However, aside from tumour stage, it is recognised that a number of other factors pertaining to either the tumour or the host also influence clinical outcomes.

Emergency presentations of colon cancer, accounting for 10-30% of presentations[220,243,270,271], are widely reported to be associated with worse outcomes than elective presentations even after adjustment for tumour stage[211,212]. As described in Chapter 2 multiple differing tumour and host characteristics have been reported between elective and emergency presentations of colon and/or rectal cancer. It seems likely that a combination of tumour and host factors underpin the observed disparity in short-term and long-term. Nonetheless, emergency presentation is still considered to be an

independent predictor of poor prognosis and indeed, within TNM Stage II colon cancer, emergency presentation itself is considered a high-risk factor for which adjuvant chemotherapy should be considered[147,149,184].

As reported within Chapter 2, a number of studies analysed the association between mode of presentation and co-morbidity. Co-morbidity was predominantly compared using either the American Society of Anaesthesiologists (ASA) classification or overall Charlson Score. Additionally, a small number of studies compared individual comorbidities. In the literature review presented within Chapter 2, the association between increased ASA classification and emergency presentation was clear however the literature comparing Charlson co-morbidity index and mode of presentation was inconclusive.

ASA classification, often used as a surrogate for co-morbidity, is not merely an assessment of other medical co-morbidities. Instead, this subjective assessment may include medical co-morbidities, frailty, body composition, acute illness and functional status. ASA classification is routinely documented in patients undergoing surgery and is classified: 1 (fit and healthy patient), 2 (well controlled mild systemic disease), 3 (a severe chronic disease that is not life threatening), 4 (a severe systemic disease that is a threat to life) and 5 (a moribound patient who is not expected to survive without surgery).

Charlson Co-morbidity index is a measure of other medical co-morbidities. This scoring system was first described by Charlson and Colleagues[272] in 1987 and was subsequently revised by the Royal College of Surgeons[273] to facilitate registry based research. A number of co-morbidities are included within this score as included in Table 4-9 with 1 point awarded for each comorbidity. The overall

Charlson score is usually categorised as 0/1/2/3+. Any of the included co-morbidities would typically result in an ASA score of >1.

The present study aims, within a cohort of patients undergoing curative surgery for colon cancer, to determine the basic tumour and host factors that are independently associated with emergency presentation including co-morbidity. Of these characteristics, it subsequently aims to determine those that are additionally associated with adverse short-term and long-term outcomes and finally aims to establish whether emergency presentation remains independently associated with worse short-term and long-term survival after adjustment for these other factors.

4.2 Methods

Patients were identified from the West of Scotland Managed Clinical Network dataset as described in Chapter 3. Patients undergoing curative surgery for either an elective or an emergency diagnosis of TNM Stage I-III colon cancer between January 2011 and December 2014 were included. Those patients with Stage IV disease, rectal (including rectosigmoid) tumours, patients with macroscopically involved margins (R2 resections) and those patients undergoing local/palliative procedures were excluded.

Tumours were staged using the TNM classification system. Socio-economic status has been classified using the Scottish Index of Multiple Deprivation (SIMD)[208]. Preoperative bloods were regarded as the most recent set of preoperative blood results, in the case of elective patients within one month prior to surgery and in the case of emergency patients from admission to hospital. Co-morbidity was classified using both the ASA classification (as prospectively recorded at time of surgery) and the Royal College of Surgeons Charlson Score[273]. Co-morbidities for inclusion within the Charlson Index were obtained from electronic records from the time of cancer diagnosis including preoperative documentation and GP referral letters containing coded co-morbidities. Survival was calculated as described in Chapter 3.

4.2.1 Statistical Analysis

The association between clinicopathological characteristics (including co-morbidities) and mode of presentation was examined using the Chi-squared test.

The association between ASA classification and Charlson Score and the association between clinicopathological characteristics and diabetic status were examined using the Chi-squared test. Variables with a p-value of <0.1 on univariate analysis were entered into a backwards conditional multivariate model using binary logistic regression to calculate odds ratios (ORs) and 95% confidence intervals. Variables with p<0.1 on multivariate analysis were entered into subsequent analyses for short-term/long-term outcomes.

Overall and cancer specific survival were calculated after exclusion of postoperative mortality (within 30 days of index procedure). The relationship between clinicopathological characteristics and long-term survival was examined using Cox's proportional hazards model to calculate Hazard Ratios (HRs) and 95% confidence intervals (95% CIs). Variables with a p-value of <0.1 on univariate analysis were entered into a backwards conditional multivariate model in which variables with a significance of p≥0.1 were removed from the model in a stepwise fashion. 3-year overall and cancer specific survival were examined using the life table function of SPSS and results were displayed as percentage 3-year survival and percentage standard error. On survival analysis, statistical significance was calculated using the log-rank test. Overall and cancer-specific survival has been shown graphically on Kaplan-Meier curves with 30-day mortality included.

Two-tailed p-values of <0.05 were considered statistically significant throughout. Statistical analysis was carried out using IBM SPSS Statistics for Windows Version 28 (IBM Corporation, Armonk, New York, USA).

4.3 Results

2707 patients were identified who had been diagnosed with TNM Stage I-III colon cancer in the West of Scotland from January 2011 to December 2014 and subsequently underwent curative resectional surgery. As shown in Tables 4-1 and 4-2, the majority of patients were aged >65 (70%), presented electively (84%) and presented with node negative disease (64%).

As shown in Table 4-3, a significant association was seen between emergency presentation and increased risk of postoperative mortality (8% vs 2%, p<0.001). After exclusion of 30-day mortality there were 818 deaths during follow-up, 463 of which were cancer related. Emergency presentations were associated with significantly worse overall and cancer specific survival (85% vs 68%, p<0.001 and 91% vs 74%, p<0.001 respectively). When adjusted for TNM Stage, emergency presentation remained associated with worse overall survival (TNM I - 98% vs 93%, TNM II - 87% vs 77%, TNM III - 76% vs 58% (all p<0.001)). Similar results were seen for cancer specific survival in TNM II and TNM III disease (TNM II – 94% vs 84%, TNM III - 81% vs 62% (both p<0.001)). No significant difference was seen in TNM I colon cancer for cancer specific survival.

4.3.1 Association Between Tumour and Host Factors and Mode of Presentation.

The relationship between tumour factors and mode of presentation is shown in Table 4-1. On univariate analysis, TNM Stage (p<0.001), T Stage (p<0.001), N Stage (p<0.001), tumour differentiation (p=0.007), extramural venous invasion

(p<0.001) and perineural invasion (p<0.001) were associated with emergency presentation. No significant association was seen between tumour site and mode of presentation (p=0.263).

The relationship between host factors and mode of presentation is shown in Table 4-2. On univariate analysis, age either <65 or 75+ (p<0.001), female sex (p=0.002), increased socio-economic deprivation (p=0.002), increased ASA classification (p<0.001), current smokers (p<0.001), BMI <25 (p<0.001), and preoperative anaemia (p=0.025) were associated with emergency presentation. No significant association was seen between ethnicity (p=0.482) or RCS Charlson Score (p=0.427) and mode of presentation.

When tumour and host factors independently associated with emergency presentation were entered into a combined multivariate model (Table 4-4): younger age (OR 0.64, p<0.001), ASA classification (OR 1.51, p<0.001), BMI (OR 0.75, p<0.001) and T Stage (OR 3.54, p<0.001) remained independently associated with emergency presentation. A borderline association was seen between smoking, EMVI and emergency presentation (OR 1.22, p=0.056 and OR 1.36, p=0.063 respectively).

4.3.2 Association Between Tumour Factors, Host Factors, Mode of Presentation and Postoperative Mortality

The association between tumour factors, host factors, mode of presentation and 30-day mortality is shown in Table 4-5. On univariate analysis, age (p<0.001), ASA classification (p<0.001), T Stage (p<0.001), EMVI (p=0.047) and mode of presentation (p<0.001) were associated with postoperative mortality. No

association was seen between smoking or BMI and postoperative mortality (p=0.211/0.723 respectively). When those factors significant on univariate analysis were entered into the multivariate model: age (OR 2.09, p<0.001), ASA classification (OR 2.01, p<0.001), T Stage (OR 1.57, p=0.016) and mode of presentation (OR 2.32, p=0.002) remained associated with postoperative mortality.

4.3.3 Association Between Tumour Factors, Host Factors, Mode of Presentation and Long-Term Survival

The association between tumour factors, host factors, mode of presentation and long-term outcomes are shown in Table 4-6. On univariate analysis, age (p<0.001), ASA classification (p<0.001), smoking status (p=0.018), BMI (p=0.003), T Stage (p<0.001), EMVI (p<0.001) and mode of presentation (p<0.001) were associated with cancer specific survival. When those factors significant on univariate analysis were entered into the multivariate model: ASA classification (HR 1.28, p=0.005), T Stage (HR 2.73, p<0.001), EMVI (HR 1.76, p<0.001) and mode of presentation (HR 1.34, p=0.047) remained significant for cancer specific survival. The association between mode of presentation and cancer-specific survival stratified by TNM Stage is shown graphically in Figure 4-1.

On univariate analysis, age, ASA classification, smoking, BMI, T stage, EMVI and mode of presentation (all p<0.001) were associated with overall survival. When those factors significant on univariate analysis were entered into the multivariate model: age (HR 1.32, p<0.001), ASA classification (HR 1.55, p<0.001), smoking (HR 1.15, p=0.038), BMI (HR 0.88, p=0.010), T stage (HR 1.77,

p<0.001), EMVI (HR 1.33, p=0.006) and mode of presentation (HR 1.29, p=0.041) remained significant for overall survival. The association between mode of presentation and overall survival stratified by TNM Stage is shown graphically in Figure 4-2.

4.3.4 Association between ASA Classification and Charlson Score

The association between ASA classification and Charlson Score is shown in Table 4-7. There was a significant association between increased ASA classification and increased Charlson Score.

4.3.5 Association Between ASA Classification, Charlson Score and 3-Year Overall Survival

The association between ASA classification, Charlson Score and 3-year overall survival is shown in Table 4-8. After exclusion of 30-day mortality, 3-year overall survival across the entire cohort (n=2476) was 83%.

When survival was stratified by ASA, 3-year overall survival ranged from 90% (ASA 1) to 60% (ASA 4) (p<0.001). ASA remained significantly associated with 3-year overall survival in patients with Charlson Score 0 – 91%/88%/77%/75% (p<0.001), Charlson Score 1 – 89%/85%/77%/76% (p<0.001), Charlson Score 2 - x/78%/77%/40% (p=0.011) and Charlson Score 3+ - x/88%/76%/25% (p<0.001) for ASA 1/2/3/4 respectively.

When survival was stratified by Charlson Score, 3-year overall survival ranged from 86% (Charlson Score – 0) to 69% (Charlson Score 3+). Charlson Score

remained significantly associated with 3-year overall survival in ASA 2 (88%/85%/78%/88%, p<0.001) and ASA 4 (75%/76%/40%/25%, p=0.005) patients for Charlson 0/1/2/3+ respectively.

4.3.6 Association Between Mode of Presentation and Co-morbidities

The association between mode of presentation and individual comorbidities included within the RCS Charlson Score is shown in Table 4-9. There was a significant association between diabetic status and elective presentation – 16% vs 10%, p=0.003. There was a trend between a previous history of malignancy and elective presentations however this did not reach statistical significance (10% vs 7%, p=0.076). There was no association between mode of presentation and other comorbidities included in the RCS Charlson Score.

4.3.7 Association Between Mode of Presentation and Diabetic Characteristics

The association between mode of presentation and diabetic characteristics is shown in Table 4-10. There was no association between mode of presentation and diabetes type (p=0.455), preoperative HbA1c (p=0.655), route of diabetic control (p=0.202) or preoperative metformin/sulfonylurea/insulin use (p=0.311/p=0.260/p=0.279 respectively).

4.3.8 Association Between Clinicopathological Factors and Diabetes

The association between clinicopathological factors and diabetes is shown in Table 4-11. On univariate analysis, older age (p<0.001), male sex (p<0.001), higher ASA classification (p<0.001), previous smokers (p=0.085), BMI 30+ (p<0.001) and preoperative anaemia (p<0.001) were associated with diabetes.

4.3.9 Association Between Clinicopathological Characteristics and Mode of Presentation of Colon Cancer

The association between clinicopathological characteristics including co-morbidities (excluding anaemia and BMI) is shown in Table 4-12a. On multivariate analysis, female sex (OR 1.42, p=0.005), lower SIMD (OR 0.91, p=0.026), smoking status (OR 1.22, p=0.021), T Stage (OR 3.19, p<0.001) and EMVI (OR 1.30, p=0046) were associated with emergency presentation. Diabetic patients were less likely to present emergently (OR 0.57, p=0.006).

The association between clinicopathological characteristics including co-morbidities and BMI (anaemia excluded) is shown in Table 4-12b. Younger age (OR 0.72, p<0.001), smoking status (OR 1.28, p=0.015), lower BMI (OR 0.82, p=0.012), more advanced T Stage (OR 3.37, p<0.001) and trend of EMVI (OR 1.34, p=0.075) were associated with emergency presentation. Diabetic patients were less likely to present emergently however this did not reach statistical significance (OR 0.63, p=0.076).

The association between clinicopathological characteristics including co-morbidities and anaemia (BMI excluded) is shown in Table 4-12c. Female sex (OR

1.42, p=0.005), SIMD (OR 0.91, p=0.032), smoking status (OR 1.22, p=0.023), more advanced T Stage (OR 3.31, p<0.001) and EMVI (OR 1.30, p=0.051) were associated with Emergency Presentation. Diabetic patients were less likely to present emergently (OR 0.59, p=0.010).

4.3.10 Association Between Diabetes, Mode of Presentation and Short-Term/Long-Term Survival in Colon Cancer

As shown in Table 4-13, emergency presentation was associated with increased 30-day mortality in the combined diabetic/non-diabetic cohort (5.5% vs 1.8%, p<0.001) and the non-diabetic cohort (5.8% vs 1.6%, p<0.001). There was no association between mode of presentation and 30-day mortality in the diabetic cohort (p=0.912). A trend, albeit not reaching statistical significance was observed between diabetic status and 30-day mortality in the elective cohort (2.9% vs 1.6%, p=0.087).

Across TNM I-III colon cancer, for overall survival, emergency presentation was associated with adverse 3-year overall survival in the combined diabetic/non-diabetic cohort (70% vs 85%, p<0.001), non-diabetic cohort (71% vs 86%, p<0.001) and diabetic cohort (62% vs 79%, p=0.006). Diabetes was associated with worse 3-year overall survival in the combined elective/emergency cohort (78% vs 84%, p=0.009) and elective cohort (79% vs 86%, p=0.001) but not emergency cohort (62% vs 71%, p=0.428). For cancer specific survival, emergency presentation was associated with worse 3-year cancer specific survival in the combined diabetic/non-diabetic cohort (75% vs 91%, p<0.001), non-diabetic cohort (76% vs 91%, p<0.001) and diabetic cohort (66% vs 87%, p<0.001). There was no association between diabetic status and 3-year CSS in the combined

elective/emergency cohort (89% vs 85%, p=0.292), elective cohort (91% vs 87%, p=0.094) or emergency cohort (76% vs 66%, p=0.578).

In TNM Stage I colon cancer, for overall survival, emergency presentation was associated with adverse 3-year survival in the combined diabetic/non-diabetic cohort (79% vs 94%, p<0.001) and non-diabetic cohort (79% vs 95%, p<0.001). Diabetes was associated with worse 3-year survival in the combined elective/emergency cohort (87% vs 95%, p=0.049) and elective cohort (87% vs 95%, p=0.024). For cancer specific survival, there was no association between mode of presentation and 3-year survival in either the combined non-diabetic/diabetic cohort (92% vs 98%, p=0.194) or non-diabetic cohort (92% vs 99%, p=0.111). Diabetes was associated with worse 3-year cancer specific survival in the combined elective/emergency cohort (94% vs 99%, p=0.036) and elective cohort (94% vs 99%, p=0.026).

In TNM Stage II colon cancer, for overall survival, emergency presentation was associated with adverse 3-year survival in the combined diabetic/non diabetic cohort (80% vs 87%, p<0.001) and non-diabetic cohort (81% vs 88%, p<0.001). There was a trend in the diabetic cohort however this did not reach statistical significance (71% vs 84%, p=0.054). There was a trend between diabetic status and worse survival in the combined elective/emergency cohort however this did not reach statistical significance (82% vs 86%, p=0.096). There was no significant association between diabetic status and 3-year survival in the elective cohort (84% vs 88%, p=0.134) or emergency cohort (71% vs 81%, p=0.209). For cancer specific survival, emergency presentation was associated with adverse 3-year survival in the combined diabetic/non-diabetic cohort (85% vs 94%, p<0.001), non-diabetic cohort (86% vs 94%, p<0.001) and diabetic cohort (75% vs 95%,

p<0.001). There was no significant association between diabetic status and 3-year survival in the combined elective/emergency cohort (92% vs 93%, p=0.385), elective only cohort (95% vs 94%, p=0.220) or emergency only cohort (75% vs 86%, p=0.366).

In TNM Stage III colon cancer, for overall survival, emergency presentation was associated with adverse 3-year survival in the combined diabetic/non-diabetic cohort (60% vs 77%, p<0.001) and non-diabetic cohort (60% vs 77%, p<0.001). There was no significant association between mode of presentation and 3-year survival in the diabetic cohort (50% vs 70%, p=0.110). There was no significant association between diabetic status and 3-year survival in the combined elective/emergency (68% vs 74%, p=0.335), elective cohort (70% vs 77%, p=0.100) or emergency cohort (50% vs 60%, p=0.922). For cancer specific survival, emergency presentation was associated with adverse 3-year survival in the combined diabetic/non-diabetic cohort (59% vs 76%, p<0.001) and non-diabetic cohort (64% vs 83%, p<0.001). There was no significant association between mode of presentation and 3-year survival in the diabetic cohort (54% vs 75%, p=0.132). There was no significant association between diabetic status and 3-year survival in the combined elective/emergency cohort (73% vs 79%, p=0.358), elective cohort (75% vs 83%, p=0.102) or emergency cohort (54% vs 64%, p=0.896).

4.4 Discussion

The results of the present study show that within a regional cohort of patients undergoing curative surgery for TNM I-III colon cancer, emergency presentation was associated with worse 3-year overall and cancer specific survival despite adjustment for TNM Stage. A number of factors, in particular younger age, higher ASA classification, lower BMI, higher T stage, smoking status and EMVI were independently associated with emergency presentations. Although these factors in part explain the disparity in outcomes observed, emergency presentation remained independently significant for both short-term and long-term survival therefore other factors must be investigated to better understand the disparity in outcomes. It was clear that although emergency presentation was associated with increased co-morbid status when stratified by ASA classification however there was no significant difference in co-morbid status when stratified by overall Charlson Index. When individual components of the Charlson index were analysed, only diabetes was associated with mode of presentation and interestingly appeared to be protective against emergency presentation.

The emergency presentation rate of 16% is consistent with previous literature[243,270,271]. Large bowel obstruction is currently the 4th most common indication for emergency laparotomy in the United Kingdom accounting for 14% of emergency laparotomies performed[137] and colorectal malignancy is likely to be the main underlying pathology. The adverse outcomes observed within those patients presenting as an emergency, even after adjustment for TNM stage is again in keeping with previous literature[211,212]. Consistent with the findings of the meta-analysis presented in Chapter 2, higher ASA classification, more advanced tumour stage and EMVI are independently associated with mode of

presentation. Furthermore, the present results show that these factors are additionally associated with oncological outcomes. These are recognised to be high risk factors and within the context of TNM Stage II colon cancer both more advanced T Stage (T4 disease) and the presence of extramural venous invasion are indicators for consideration of adjuvant chemotherapy[147,149,184].

The present results show that older age is associated with adverse short-term and long-term outcomes (overall survival) in patients undergoing curative surgery for colon cancer. Given the association between age and increased risk of death in the general population, an association between overall survival and older age was expected. It is noteworthy however that emergency presentation was associated with younger age at presentation. The relationship between age and mode of presentation was not clear from the literature review performed within Chapter 2 and due to data heterogeneity the identified studies were not suitable for inclusion within the meta-analysis. Further investigation into this association is required. The patient cohort included within the present study is from a Scottish population with an established bowel screening programme[274]. Individuals below the age of 50 were not eligible for screening, individuals aged 50-75 were routinely invited for screening on a biennial basis and individuals aged over 75 were not routinely invited but were eligible to request screening. The present findings may be the consequence of screening eligibility/participation or alternatively may be the results of delays by either the patient or healthcare provider to report/investigate lower gastrointestinal symptoms due to the higher likelihood of these resulting from less significant, benign pathology in younger patients[51]. Alternatively, recent research has shown that the incidence of colorectal cancer in younger patients (typically those aged under 50) is increasing[275-277] and furthermore is associated with adverse

outcomes. This may suggest more aggressive disease characteristics within the younger population and may predispose them to presenting emergently.

Within the present study, ASA classification was used as a surrogate for co-morbidity and indeed, in keeping with the findings of Chapter 2, higher ASA classification was independently associated with emergency presentation and furthermore with adverse outcomes. ASA classification, albeit widely utilised, is somewhat subjective and unlike some scoring systems (for example Charlson Score[272]) is not simply a measure of medical co-morbidities. Instead, this somewhat subjective assessment may encompass age, frailty, body composition, medical co-morbidities and the state of unwellness from acute pathology for example bowel obstruction or perforation.

As described within Chapter 2, previous literature comparing mode of presentation of patients with colorectal cancer and co-morbidity is highly variable. The present finding that diabetes appears to be protective against emergency presentation is of interest and there may be several reason for this. Diabetes has been associated with an increased risk of developing colorectal cancer however this relationship is complex and confounded by shared risk factors including older age, male sex and obesity. Both diabetes and obesity are recognised to be pro-inflammatory and this is likely to impact on both the incidence and outcomes of colorectal cancer. However, although diabetes has been reported to be associated with adverse overall and disease specific survival in patients with colorectal cancer[103], based on the present results this does not appear to be related to mode of presentation. Patients with diabetes undergo regular blood tests as part of routine diabetic follow-up/monitoring. Therefore, patients with diabetes may be more likely to be diagnosed with an incidental

iron deficiency anaemia resulting in elective investigation and subsequently diagnosis of colorectal cancer. Although similar findings may have been expected in patients with other co-morbidities is seems likely that patients with diabetes undergo more intensive follow up than some other co-morbidities. This is an interesting area for further investigation and, if this hypothesis is true, consideration should be given to carrying out regular (perhaps annual) blood tests as an additional population screening measure.

The patient population included within the present study are from a population with an established bowel cancer screening programme (biennial, patients aged 50-74 routinely invited, individuals aged 75+ also eligible for participation). Although not assessed within the present study, previous literature has reported individuals with diabetes to be less likely to participate in screening[278]. Therefore, converse to the present findings, one may have expected that diabetes may be associated with increased likelihood of emergency presentation.

Within the present study, low BMI has been shown to be associated with mode of presentation and adverse overall survival. The association between emergency presentation and low BMI is likely to be multifactorial and related to factors including poor nutrition and the loss of skeletal muscle due to the systemic inflammatory response[254]. The association between BMI and survival is complex. Termed the obesity paradox, patients at either end of the BMI spectrum are recognised to have increased morbidity and mortality[279]. BMI, despite being readily calculable, does not stratify body composition – either muscle of fat. Within the last decade there has been increased awareness of the important of body composition. Body composition analysis provides more detailed analysis of

body mass including visceral obesity, skeletal muscle mass and skeletal muscle density. These have been reported to be associated with both short-term outcomes[280], long-term outcomes[281] and the systemic inflammatory response[254]. To date, the association between body composition and the mode of presentation of colon cancer has yet to be studied and may prove more useful than BMI. Within the present study, 99% of diabetic patients had Type 2 Diabetes. Given the well established link between obesity and Type 2 diabetes[282] it is unsurprising that diabetes was less common in patients with a low or normal BMI. As low BMI was associated with emergency presentation, it seems likely that BMI represents a major confounding factor in the relationship between diabetes and mode of presentation. Indeed, when adjusted for other clinicopathological factors including BMI, the association between diabetes and mode of presentation was less clear although a trend did remain suggesting that other factors are involved.

A number of studies have reported an association between metformin use, a reduction in colorectal adenoma/carcinoma formation and improved oncological outcomes in patients with colorectal cancer[283]. This observation may suggest that metformin could slow the rate of cancer growth and therefore increases the likelihood of caner being diagnosed electively, either symptomatically or through screening. However, the present results show that on subgroup analysis of diabetic patients, there was no significant association between mode of presentation and metformin use or other diabetic characteristics including HbA1C levels, sulfonylurea use or insulin use.

The present study has several limitations. The retrospective nature of this study carries with it the lack of availability of some data, in particular BMI, perineural

invasion (not routinely reported at the time of this study) and ethnicity. On univariate analysis, perineural invasion was associated with emergency presentation however was not included in further analyses due to the quantity of missing data. Nonetheless it has been reported to be associated with adverse outcomes[284] and further research into the association between perineural invasion, mode of presentation and outcomes is warranted. Despite missing data for BMI, this was included within the present study and the missing data was not felt to have an adverse effect on results. Multiple studies, particularly those from the USA, have reported an association between ethnicity, mode of presentation and outcomes[127,131]. Ethnicity would have been of interest to study within the UK free at point of care NHS. However, due to the quantity of missing data and small proportion of patients of ethnic minority status within the present cohort, this study was not able to assess this. Due to the free at point of care National Health Service, the present results, particularly related to the association between co-morbidity and mode of presentation may not be generalisable to nations with alternative health care systems including the United States of America. Prescribing data was taken from prescribed medication at time of referral and thus does not take into account the duration of medication use or patient compliance. Individuals without a diagnosis of diabetes do not have a preoperative HbA1c carried out. Particularly in an increasingly overweight/obese population, it is likely that diabetes is underdiagnosed within the general population. Further investigation of this would be of interest in the form of a prospective study investigating the association between preoperative HbA1c, mode of presentation and short-term/long-term outcomes following curative surgery for colon cancer. The present results show that a number of patients had an ASA Classification of 1 however had a Charlson Score of ≥1. ASA classification was taken from the

anaesthetic chart (prospectively recorded). ASA classification was not retrospectively calculated or altered. It seems likely that the included patients with a Charlson Score of ≥1 should have had an ASA >1. Nonetheless, the proportion of patients seemingly miscoded was small and these patients were likely to be minimally affected by their co-morbid status therefore the impact of this discrepancy on the findings of this study are likely to be minimal.

In conclusion, within a regional cohort of patients undergoing curative surgery for TNM I-III colon cancer, emergency presentation remains common and associated with adverse outcomes even after adjustment for TNM Stage. A number of factors independently associated with emergency presentation, in particular age, ASA classification, BMI, tumour stage and EMVI are independently associated with tumour stage and outcomes and partially explain this disparity in outcomes. However, increased medical comorbidity, when stratified by the overall Charlson Score was not associated with mode of presentation. When the components of the Charlson Score are individually compared with mode of presentation diabetes appears to be protective against emergency presentation. The precise reason for this protective effect remains unclear and further, details comparison of the route to diagnosis (and presenting symptoms/signs) in diabetic compared to non-diabetic patients is required. Nonetheless, within the present study, emergency presentation remained independently significant for both short-term and long-term outcomes therefore the study of other clinicopathological factors is required. Furthermore, the investigation of other factors that may be subjectively included in ASA Classification but do not feature in the Charlson Score including frailty, the systemic inflammatory response and body composition should be carried out.

4.5 Tables

Table 4-1 - Association between tumour factors and mode of presentation – univariate analysis

	Total	Elective	Emergency	P
TNM Stage	2707	2265 (84%)	442 (16%)	<0.001
I	556 (21%)	539 (24%)	17 (4%)	
II	1162 (43%)	936 (41%)	226 (51%)	
III	989 (37%)	790 (35%)	199 (45%)	
T Stage	2703	2261 (84%)	442 (16%)	<0.001
1	289 (11%)	283 (13%)	6 (1%)	
2	359 (13%)	346 (15%)	13 (3%)	
3	1328 (49%)	1159 (51%)	169 (38%)	
4	727 (27%)	473 (21%)	254 (58%)	
N Stage	2707	2265 (84%)	442 (16%)	<0.001
0	1718 (64%)	1475 (65%)	243 (55%)	
1	634 (23%)	522 (23%)	112 (25%)	
2	355 (13%)	268 (12%)	87 (20%)	
Tumour site	2684	2246 (84%)	438 (16%)	0.263
Right	1442 (54%)	1196 (53%)	246 (56%)	
Left	1242 (46%)	1050 (47%)	192 (44%)	
Differentiation	2697	2255 (84%)	442 (16%)	0.007
Mod-well	2220 (82%)	1876 (83%)	344 (78%)	
Poorly	477 (18%)	379 (17%)	98 (22%)	
EMVI	2659	2219 (84%)	440 (17%)	<0.001
Negative	1540 (58%)	1376 (62%)	164 (37%)	
Positive	1119 (42%)	843 (38%)	276 (63%)	
Perineural invasion	354	268 (76%)	86 (24%)	<0.001
Negative	187 (53%)	160 (60%)	27 (31%)	
Positive	167 (47%)	108 (40%)	59 (69%)	

Table 4-2 Association between host factors and mode of presentation – univariate analysis

	Total	Elective	Emergency	P
Age	2707	2265 (84%)	442 (16%)	<0.001
<65	823 (30%)	671 (30%)	152 (34%)	
65-74	951 (35%)	841 (37%)	110 (25%)	
75+	933 (35%)	753 (33%)	180 (41%)	
Sex	2707	2265 (84%)	442 (16%)	0.002
Male	1403 (52%)	1204 (53%)	199 (45%)	
Female	1304 (48%)	1061 (47%)	243 (55%)	
Ethnicity	1517	1297 (86%)	220 (15%)	0.482
White British	1497 (99%)	1281 (99%)	216 (98%)	
Other	20 (1%)	16 (1%)	4 (2%)	
SIMD	2707	2265 (84%)	442 (16%)	0.002
1 (most deprived)	755 (28%)	599 (26%)	156 (35%)	
2	580 (21%)	501 (22%)	79 (18%)	
3	490 (18%)	406 (18%)	84 (19%)	
4	426 (16%)	365 (16%)	61 (14%)	
5 (least deprived)	456 (17%)	394 (17%)	62 (14%)	
ASA	2583	2181 (84%)	402 (16%)	<0.001
1	258 (10%)	224 (10%)	34 (9%)	
2	1411 (55%)	1248 (57%)	163 (41%)	
3	810 (31%)	646 (30%)	164 (41%)	
4	102 (4%)	63 (3%)	39 (10%)	
5	2 (<1%)	0	2 (1%)	
RCS Charlson Score	2536	2153 (85%)	383 (15%)	0.427
0	1490 (59%)	1251 (58%)	239 (62%)	
1	706 (28%)	606 (28%)	100 (26%)	
2	274 (11%)	239 (11%)	35 (9%)	
3+	66 (3%)	57 (3%)	9 (2%)	
Smoking	2537	2153 (85%)	384 (15%)	<0.001
Non smoker	1201 (47%)	1027 (48%)	174 (45%)	
Ex-smoker	994 (39%)	875 (41%)	119 (31%)	
Smoker	342 (14%)	251 (12%)	91 (24%)	
BMI	1882	1635 (87%)	247 (13%)	<0.001
<18.5	41 (2%)	29 (2%)	12 (5%)	
18.5-24.9	620 (33%)	515 (32%)	105 (43%)	
25-29.9	659 (35%)	576 (35%)	83 (34%)	
30-34.9	363 (19%)	337 (21%)	26 (11%)	
35+	199 (11%)	178 (11%)	21 (9%)	
Anaemia	2631	2193 (83%)	438 (17%)	0.025
No	1521 (58%)	1289 (59%)	232 (53%)	
Yes	1110 (42%)	904 (41%)	206 (47%)	

Table 4-3 Association between mode of presentation and short-term/long-term survival

Outcomes	Total	Elective	Emergency	P
Postoperative mortality	2707	2265 (84%)	442 (16%)	<0.001
No death	2631 (97%)	2222 (98%)	409 (93%)	
Death	76 (3%)	43 (2%)	33 (8%)	
Outcome during follow-up (exc 30-day mortality)	2631	2222 (85%)	409 (16%)	<0.001
Alive	1813 (69%)	1615 (73%)	198 (48%)	
Cancer death	463 (18%)	318 (14%)	145 (36%)	
Non-cancer death	355 (14%)	289 (13%)	66 (16%)	
% 3-year survival				
All stages	n=2631	n=2222	n=409	
OS	82% (SE 1%)	85% (SE 1%)	68% (SE 2%)	<0.001
CSS	88% (SE 1%)	91% (SE 1%)	74% (SE 2%)	<0.001
TNM I	n=553	n=537	n=16	
OS	93% (SE 1%)	94% (SE 1%)	81% (SE 10%)	<0.001
CSS	98% (SE 1%)	98% (SE 1%)	93% (SE 7%)	0.259
TNM II	n=1124	n=917	n=207	
OS	85% (SE 1%)	87% (SE 1%)	77% (SE 3%)	<0.001
CSS	92% (SE 1%)	94% (SE 1%)	84% (SE 3%)	<0.001
TNM III	n=954	n=768	n=186	
OS	72% (SE 1%)	76% (SE 2%)	58% (SE 4%)	<0.001
CSS	77% (SE 1%)	81% (SE 1%)	62% (SE 4%)	<0.001

Table 4-4 Association between tumour/host factors and mode of presentation – multivariate analysis

Variable	Tumour or host	
	OR (95% CI)	**P**
Age	0.64 (0.52-0.78)	<0.001
Sex	-	0.129
SIMD	-	0.316
ASA	1.51 (1.20-1.92)	<0.001
Smoking	1.22 (1.00-1.49)	0.056
BMI	0.75 (0.65-0.88)	<0.001
Preop anaemia	-	0.384
T Stage	3.54 (2.71-4.62)	<0.001
N Stage	-	0.832
Differentiation	-	0.332
EMVI	1.36 (0.98-1.89)	0.063

Table 4-5 Association between tumour factors, host factor and mode of presentation and postoperative mortality

Variable	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	P	OR (95% CI)	P
Age	2.92 (2.02-4.20)	<0.001	2.09 (1.44-3.05)	<0.001
ASA	2.93 (2.12-4.06)	<0.001	2.01 (1.42-2.85)	<0.001
Smoking	1.26 (0.88-1.80)	0.211	-	-
BMI	0.93 (0.62-1.39)	0.723	-	-
T Stage	1.92 (1.40-2.63)	<0.001	1.57 (1.09-2.26)	0.016
EMVI	1.59 (1.01-2.53)	0.047	-	0.725
Mode of presentation	4.17 (2.62-6.64)	<0.001	2.32 (1.35-3.98)	0.002

Table 4-6 Association between tumour factors, host factors, mode of presentation and overall/cancer specific survival

Variable	Cancer specific survival				Overall survival			
	UVA		MVA		UVA		MVA	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age	1.27 (1.14-1.43)	<0.001	-	0.368	1.65 (1.50-1.80)	<0.001	1.32 (1.17-1.49)	<0.001
ASA	1.55 (1.35-1.77)	<0.001	1.28 (1.08-1.52)	0.005	1.85 (1.68-2.05)	<0.001	1.55 (1.34-1.78)	<0.001
Smoking	1.18 (1.03-1.35)	0.018	-	0.417	1.22 (1.10-1.35)	<0.001	1.15 (1.01-1.31)	0.038
BMI	0.84 (0.75-0.94)	0.003	-	0.184	0.82 (0.75-0.90)	<0.001	0.88 (0.80-0.97)	0.010
T Stage	3.43 (2.95-3.99)	<0.001	2.73 (2.20-3.38)	<0.001	2.04 (1.86-2.25)	<0.001	1.77 (1.53-2.04)	<0.001
EMVI	3.43 (2.82-4.17)	<0.001	1.76 (1.34-2.30)	<0.001	2.21 (1.93-2.54)	<0.001	1.33 (1.09-1.62)	0.006
Mode of pres.	2.95 (2.42-3.59)	<0.001	1.34 (1.00-1.78)	0.047	2.30 (1.96-2.69)	<0.001	1.29 (1.01-1.64)	0.041

Table 4-7 - Association between ASA Classification and Charlson Score

		Charlson Score					
		Total	0	1	2	3+	P
ASA	Total	2536	1490 (59%)	706 (28%)	274 (11%)	66 (3%)	<0.001
	1	253 (10%)	213 (14%)	35 (5%)	5 (2%)	0 (0%)	
	2	1392 (55%)	925 (62%)	346 (49%)	105 (38%)	16 (24%)	
	3	795 (31%)	322 (22%)	296 (42%)	141 (52%)	36 (55%)	
	4	94 (4%)	30 (2%)	27 (4%)	23 (8%)	14 (21%)	
	5	2 (<1%)	0 (0%)	2 (<1%)	0 (0%)	0 (0%)	

Table 4-8 - Association between ASA Classification, Charlson Score and 3-year overall survival

	Charlson Score										
ASA		n	3yr OS (SE)	n	3yr OS (SE)	n	3yr OS (SE)	n	3yr OS (SE)	n	3yr OS (SE)
		Total		0		1		2		3+		p
	Total	2476	83% (1%)	1471	86% (1%)	684	81% (1%)	260	75% (3%)	61	69% (6%)	<0.001
	1	253	90% (2%)	213	91% (2%)	35	89% (5%)	5	-	0	-	0.206
	2	1371	86% (1%)	917	88% (1%)	340	85% (2%)	98	78% (4%)	16	88% (8%)	<0.001
	3	766	77% (2%)	313	77% (2%)	283	77% (3%)	137	77% (4%)	33	76% (7%)	0.141
	4	85	60% (5%)	28	75% (8%)	25	76% (9%)	20	40% (11%)	12	25% (13%)	0.005
	5	1	-	0	-	1	-	0	-	0	-	-
	p	<0.001		<0.001		<0.001		0.011		<0.001		

Table 4-9 - Association between individual components of the Charlson Score and mode of presentation in patients undergoing curative surgery for colon cancer – univariate analysis

Co-morbidity	Total	Elective	Emergency	P
Previous MI	2536	2153 (85%)	383 (15%)	0.260
No	2385 (94%)	2020 (94%)	365 (95%)	
Yes	151 (6%)	133 (6%)	18 (5%)	
PVD	2536	2153 (85%)	383 (15%)	0.360
No	2465 (97%)	2090 (97%)	375 (98%)	
Yes	71 (3%)	63 (3%)	8 (2%)	
CKD	2536	2153 (85%)	383 (15%)	0.315
No	2262 (89%)	1926 (90%)	336 (88%)	
Yes	274 (11%)	227 (11%)	47 (12%)	
Diabetes	2536	2153 (85%)	383 (15%)	0.003
No	2159 (85%)	1814 (84%)	345 (90%)	
Yes	377 (15%)	339 (16%)	38 (10%)	
Liver disease	2536	2153 (85%)	383 (15%)	0.205
No	2516 (99%)	2134 (9%)	382 (>99%)	
Yes	20 (1%)	19 (1%)	1 (<1%)	
Rheumtaological	2536	2153 (85%)	383 (15%)	0.427
No	2498 (99%)	2119 (98%)	379 (99%)	
Yes	38 (2%)	34 (2%)	4 (1%)	
Respiratory disease	2536	2153 (85%)	383 (15%)	0.473
No	2175 (86%)	1842 (85%)	333 (87%)	
Yes	361 (14%)	311 (14%)	50 (13%)	
CCF	2536	2153 (85%)	383 (15%)	0.281
No	2469 (97%)	2093 (97%)	376 (98%)	
Yes	67 (3%)	60 (3%)	7 (2%)	
CVA	2536	2153 (85%)	383 (15%)	0.815
No	2323 (92%)	1971 (92%)	352 (92%)	
Yes	213 (8%)	182 (9%)	31 (8%)	
Dementia	2536	2153 (85%)	383 (15%)	0.431
No	2512 (99%)	2134 (99%)	378 (99%)	
Yes	24 (1%)	19 (1%)	5 (1%)	
Hemi/paraplegia	2536	2153 (85%)	383 (15%)	0.952
No	2529 (>99%)	2147 (>99%)	382 (>99%)	
Yes	7 (<1%)	6 (<1%)	1 (<1%)	
HIV	2536	2153 (95%)	383 (15%)	-
No	2536 (100%)	2153 (100%)	383 (100%)	
Yes	0	0	0	
Malignancy	2536	2153 (85%)	383 (15%)	0.076
No	2295 (91%)	1939 (90%)	356 (93%)	
Yes	241 (10%)	214 (10%)	27 (7%)	
Metastatic disease	2536	2153 (85%)	383 (15%)	0.673
No	2535 (>99%)	2152 (>99%)	383 (100%)	
Yes	1 (<1%)	1 (<1%)	0	

Table 4-10 - Association between mode of presentation and diabetic characteristics within the cohort of patients with diabetes undergoing curative surgery for TNM I-III colon cancer

Characteristic	Total	Elective	Emergency	P
Diabetes Type	373	336 (90%)	37 (10%)	0.455
Type 1	5 (1%)	5 (2%)	0	
Type 2	368 (99%)	331 (99%)	37 (100%)	
Preop HbA1c	320	296 (93%)	24 (8%)	0.655
<6.5	264 (83%)	245 (83%)	19 (79%)	
6.5+	56 (18%)	51 (17%)	5 (21%)	
Diabetic control	366	331 (90%)	35 (10%)	0.202
Diet	131 (36%)	114 (34%)	17 (49%)	
Tablet	194 (53%)	178 (54%)	16 (46%)	
Insulin	41 (11%)	39 (12%)	2 (6%)	
Preop metformin use	366	331 (90%)	35 (10%)	0.311
No	169 (46%)	150 (45%)	19 (54%)	
Yes	197 (54%)	181 (55%)	16 (46%)	
Preop sulfonylurea use	366	331 (90%)	35 (10%)	0.260
No	263 (72%)	235 (71%)	28 (80%)	
Yes	103 (28%)	96 (29%)	7 (20%)	
Preop insulin use	366	331 (90%)	35 (10%)	0.279
No	325 (89%)	292 (8%)	33 (94%)	
Yes	41 (11%)	39 (12%)	2 (6%)	

Table 4-11 - Association between clinicopathological factors and diabetes

Clinicopathological factor	Total	No Diabetes	Diabetes	P
Age	2536	2159 (85%)	377 (15%)	<0.001
<65	771 (30%)	690 (32%)	81 (22%)	
65-74	894 (35%)	739 (34%)	155 (41%)	
75+	871 (34%)	730 (32%)	141 (37%)	
Sex	2536	2159 (85%)	377 (15%)	<0.001
Male	1320 (52%)	1093 (51%)	227 (60%)	
Female	1216 (48%)	1066 (49%)	150 (40%)	
SIMD	2536	2159 (85%)	377 (15%)	0.094
1 (most deprived)	720 (28%)	601 (28%)	119 (32%)	
2	543 (21%)	455 (21%)	88 (23%)	
3	454 (18%)	383 (18%)	71 (19%)	
4	390 (15%)	346 (16%)	44 (12%)	
5 (least deprived)	429 (17%)	374 (17%)	55 (15%)	
ASA Classification	2536	2159 (85%)	377 (15%)	<0.001
1	253 (10%)	238 (11%)	15 (4%)	
2	1392 (55%)	1212 (56%)	180 (48%)	
3	795 (31%)	628 (29%)	167 (44%)	
4	94 (4%)	79 (4%)	15 (4%)	
5	2 (<1%)	2 (<1%)	0	
Smoking	2415	2055 (85%)	360 (15%)	0.085
Non smoker	1144 (47%)	982 (48%)	162 (45%)	
Ex-smoker	950 (39%)	791 (39%)	159 (44%)	
Smoker	321 (13%)	282 (14%)	39 (11%)	
BMI	1814	1555 (86%)	259 (14%)	<0.001
<18.5	38 (2%)	36 (2%)	2 (1%)	
18.5-24.9	601 (33%)	556 (36%)	45 (17%)	
25-29.9	631 (35%)	543 (35%)	88 (34%)	
30-34.9	349 (19%)	278 (18%)	71 (27%)	
35+	195 (11%)	142 (9%)	53 (21%)	
Anaemia	2470	2105 (85%)	365 (15%)	<0.001
No	1426 (58%)	1251 (59%)	175 (48%)	
Yes	1044 (42%)	854 (41%)	190 (52%)	
T Stage	2532	2156 (85%)	376 (15%)	0.605
1	285 (11%)	247 (12%)	38 (10%)	
2	340 (13%)	285 (13%)	55 (15%)	
3	1241 (49%)	1050 (49%)	191 (51%)	
4	666 (26%)	574 (27%)	92 (25%)	
N Stage	2536	2159 (85%)	377 (15%)	0.342
0	1623 (64%)	1394 (65%)	229 (61%)	
1	588 (23%)	491 (23%)	97 (26%)	
2	325 (13%)	274 (13%)	51 (14%)	
Differentiation	2526	2152 (85%)	374 (15%)	0.779
Mod-well	2074 (82%)	1765 (82%)	309 (83%)	
Poorly	452 (18%)	387 (18%)	65 (17%)	
EMVI	2489	2120 (85%)	369 (15%)	0.120
Negative	1453 (58%)	1224 (58%)	229 (62%)	
Positive	1036 (42%)	896 (42%)	140 (38%)	

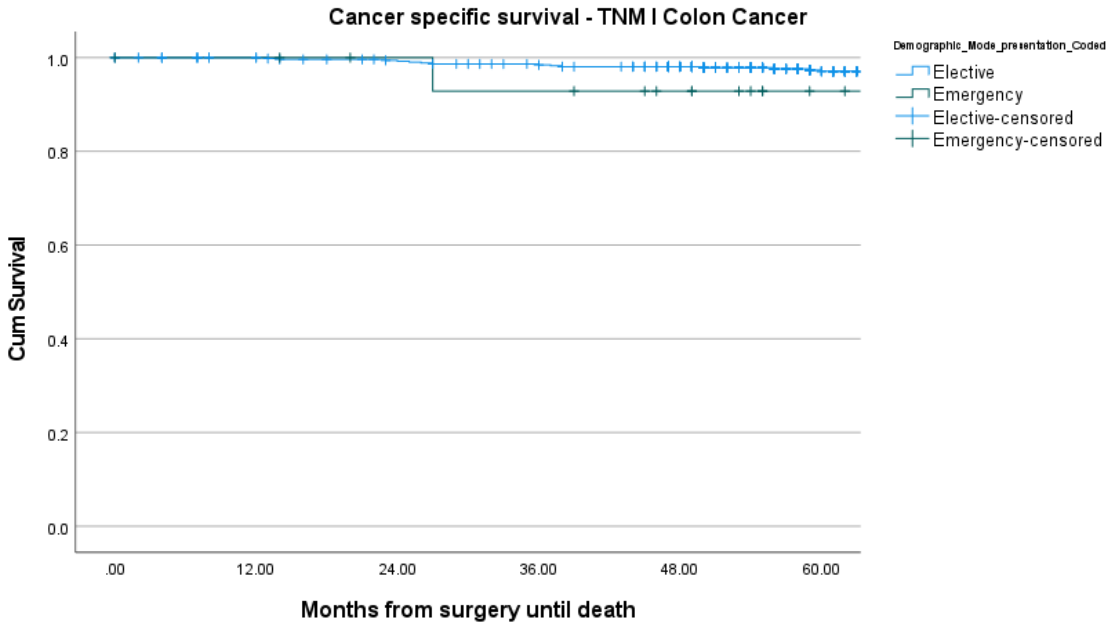
Table 4-12 - Association between clinicopathological characteristics including co-morbidities and mode of presentation in colon cancer (not anaemia or BMI) – multivariate analysis

Variable	OR (95% CI)	p
4-12a Not controlled for anaemia or BMI		
Age	-	0.805
Sex	1.42 (1.11-1.82)	0.005
SIMD	0.91 (0.83-0.99)	0.026
Smoking	1.22 (1.03-1.44)	0.021
Diabetes	0.57 (0.39-0.85)	0.006
Other malignancy	-	0.209
T Stage	3.19 (2.61-3.92)	<0.001
N Stage	-	0.172
Differentiation	-	0.522
EMVI	1.30 (1.01-1.69)	0.046
4-12b Controlled for BMI, not anaemia		
Age	0.72 (0.60-0.87)	<0.001
Sex	-	0.161
SIMD	-	0.194
Smoking	1.28 (1.05-1.56)	0.015
Diabetes	0.63 (0.37-1.05)	0.076
Other malignancy	-	0.112
BMI	0.82 (0.70-0.96)	0.012
T Stage	3.37 (2.60-4.36)	<0.001
N Stage	-	0.656
Differentiation	-	0.408
EMVI	1.34 (0.97-1.86)	0.075
4-12c Controlled for anaemia, not BMI		
Age	-	0.775
Sex	1.42 (1.11-1.82)	0.005
SIMD	0.91 (0.83-0.99)	0.032
Smoking	1.22 (1.03-1.44)	0.023
Diabetes	0.59 (0.40-0.88)	0.010
Other malignancy	-	0.205
Anaemia	-	0.414
T Stage	3.31 (2.69-4.07)	<0.001
N Stage	-	0.241
Differentiation	-	0.373
EMVI	1.30 (1.00-1.68)	0.051

Table 4-13 - Association between diabetes and short-term/long-term survival in patients undergoing curative surgery for colon cancer

Outcome	Total		Elective		Emergency		P
30-day mortality	2536	2.4%	2153	1.8%	383	5.5%	<0.001
Non diabetic	2159	2.3%	1814	1.6%	345	5.8%	<0.001
Diabetic	377	2.9%	339	2.9%	38	2.6%	0.912
p	0.445		0.087		0.416		
3-year survival – TNM I-III							
OS	2476	83% (1%)	2114	85% (1%)	362	70% (2%)	<0.001
Non diabetic	2110	84% (1%)	1785	86% (1%)	325	71% (3%)	<0.001
Diabetic	366	78% (2%)	329	79% (2%)	37	62% (8%)	0.006
P	0.009		0.001		0.428		
CSS	2476	(89% (1%)	2114	91% (1%)	362	75% (2%)	<0.001
Non Diabetic	2110	89% (1%)	1785	91% (1%)	325	76% (2%)	<0.001
Diabetic	366	85% (2%)	329	87% (2%)	37	66% (8%)	<0.001
p	0.292		0.094		0.578		
3-year survival – TNM I							
OS	536	94% (1%)	522	94% (1%)	14	79% (11%)	<0.001
Non diabetic	461	95% (1%)	447	95% (1%)	14	79% (11%)	<0.001
Diabetic	75	87% (4%)	75	87% (4%)	0	0	-
p	0.049		0.024		-		
CSS	536	98% (1%)	522	98% (1%)	14	92% (2%)	0.194
Non-diabetic	461	99% (0%)	447	99% (0%)	14	92% (8%)	0.111
Diabetic	75	94% (3%)	75	94% (3%)	0	-	-
p	0.036		0.026		-		
3-year survival – TNM II							
OS	1057	86% (1%)	871	87% (1%)	186	80% (3%)	<0.001
Non diabetic	910	86% (1%)	745	88% (1%)	165	81% (3%)	<0.001
Diabetic	147	82% (3%)	126	84% (3%)	21	71% (10%)	0.054
p	0.096		0.134		0.209		
CSS	1057	92% (1%)	871	94% (1%)	186	85% (3%)	<0.001
Non-diabetic	910	93% (1%)	745	94% (1%)	165	86% (3%)	<0.001
Diabetic	147	92% (2%)	126	95% (2%)	21	75% (10%)	<0.001
p	0.385		0.220		0.366		
3-year survival – TNM III							
OS	883	73% (1%)	721	76% (2%)	162	59% (4%)	<0.001
Non diabetic	739	74% (2%)	593	77% (2%)	146	60% (4%)	<0.001
Diabetic	144	68% (4%)	128	70% (4%)	16	50% (13%)	0.110
p	0.335		0.100		0.922		
CSS	883	78% (1%)	721	81% (1%)	162	63% (4%)	<0.001
Non-diabetic	739	79% (2%)	593	83% (2%)	146	64% (4%)	<0.001
Diabetic	144	73% (4%)	128	75% (4%)	16	54% (13%)	0.132
p	0.358		0.102		0.896		

4.6 Figures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Cum Survival
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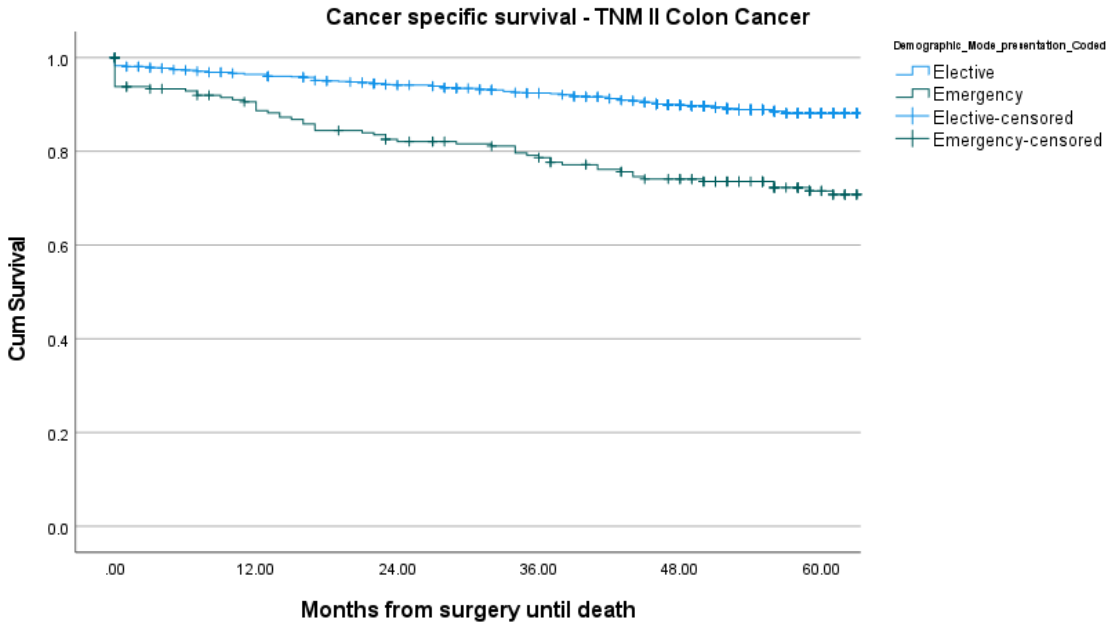
0.8
0.6
0.4
0.2
0.0
.00
12.00
24.00
36.00
48.00
60.00
Months from surgery until death
Demographic_Mode_presentation_Coded
Elective
Emergency
Elective-censored
Emergency-censored


Cancer specific survival - TNM II Colon Cancer
Cum Survival
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0.8
0.6
0.4
0.2
0.0
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12.00
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60.00
Months from surgery until death
Demographic_Mode_presentation_Coded
Elective
Emergency
Elective-censored
Emergency-censored

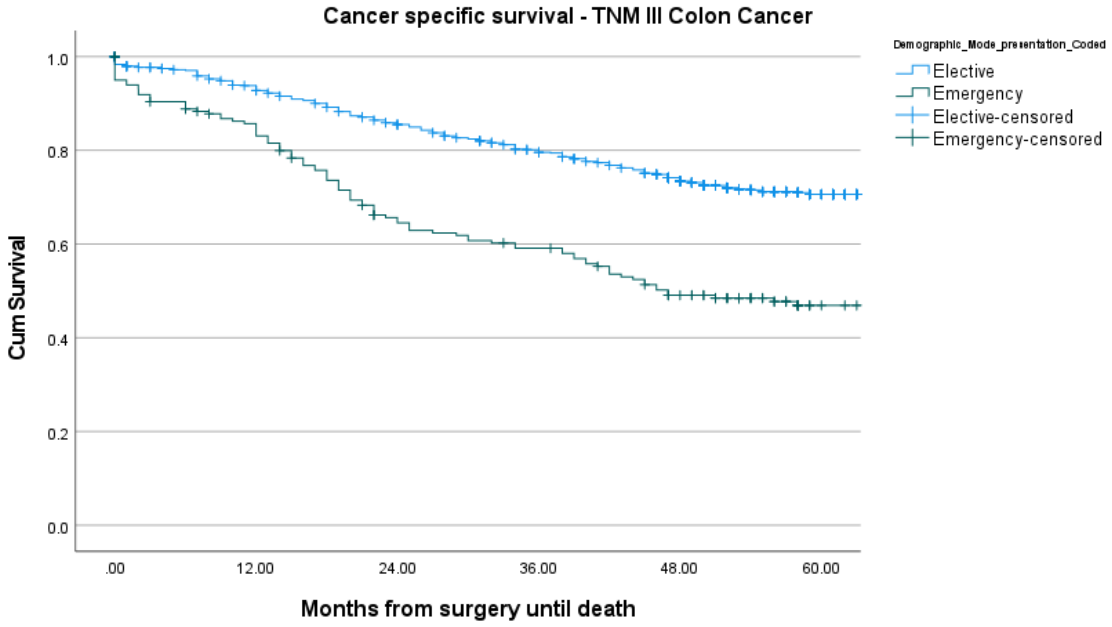
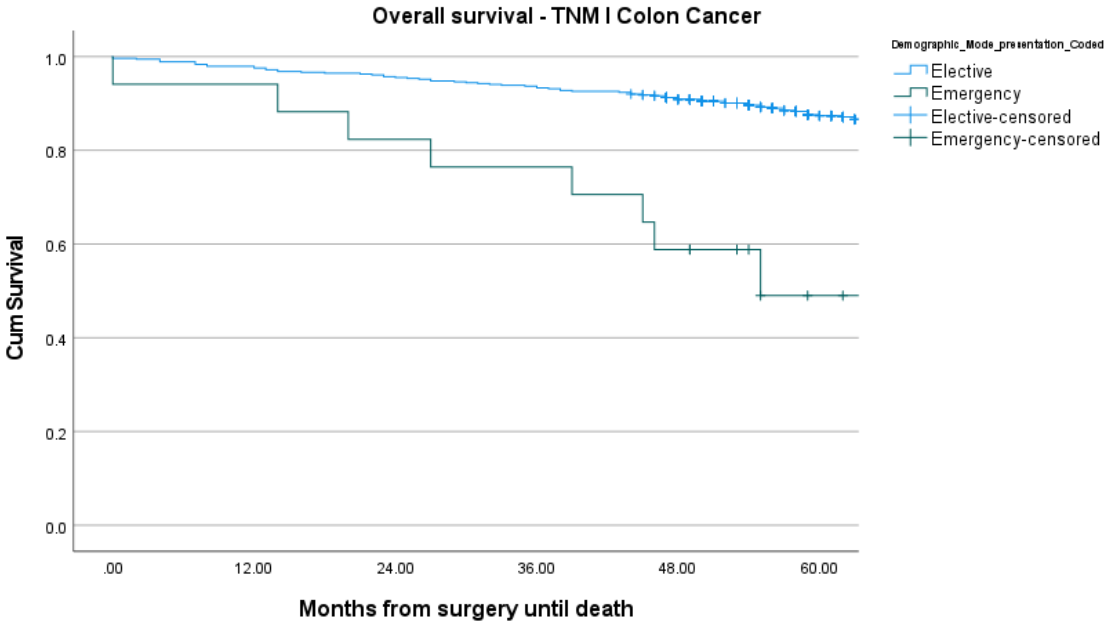


Figure 4-1 – Cancer-specific survival in elective versus emergency presentations of colon cancer in TNM I (top), TNM II (middle) and TNM III (bottom) disease (elective surgery with curative intent for TNM I-III colon cancer)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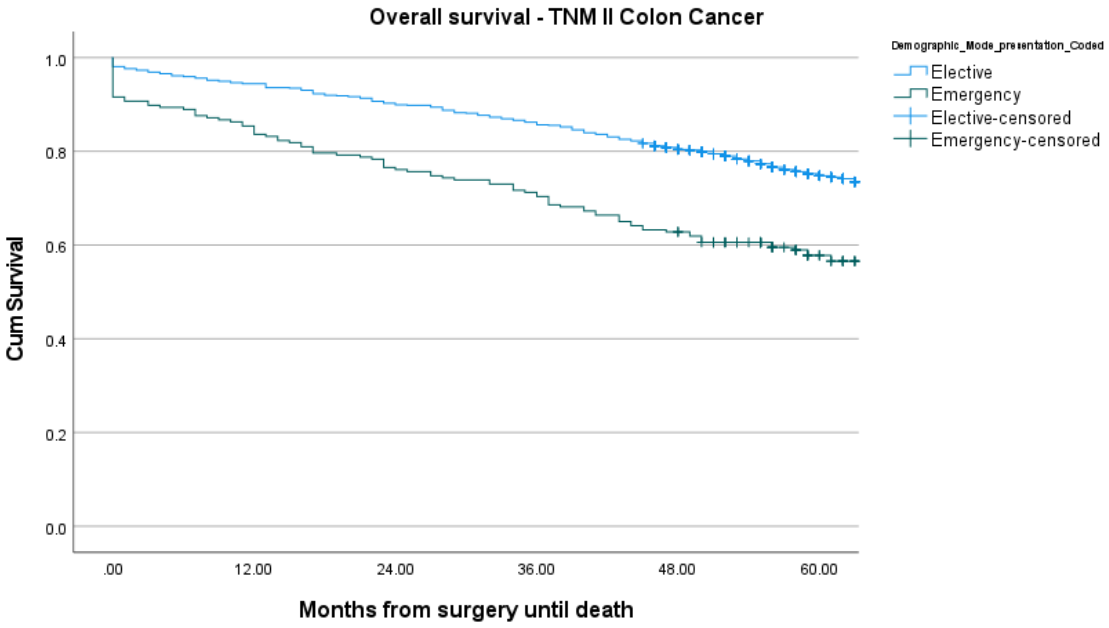
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
.00
12.00
24.00
36.00
48.00
60.00
Months from surgery until death
Demographic_Mode_presentation_Coded
Elective
Emergency
Elective-censored
Emergency-censored


Overall survival - TNM II Colon Cancer
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
.00
12.00
24.00
36.00
48.00
60.00
Months from surgery until death
Demographic_Mode_presentation_Coded
Elective
Emergency
Elective-censored
Emergency-censored

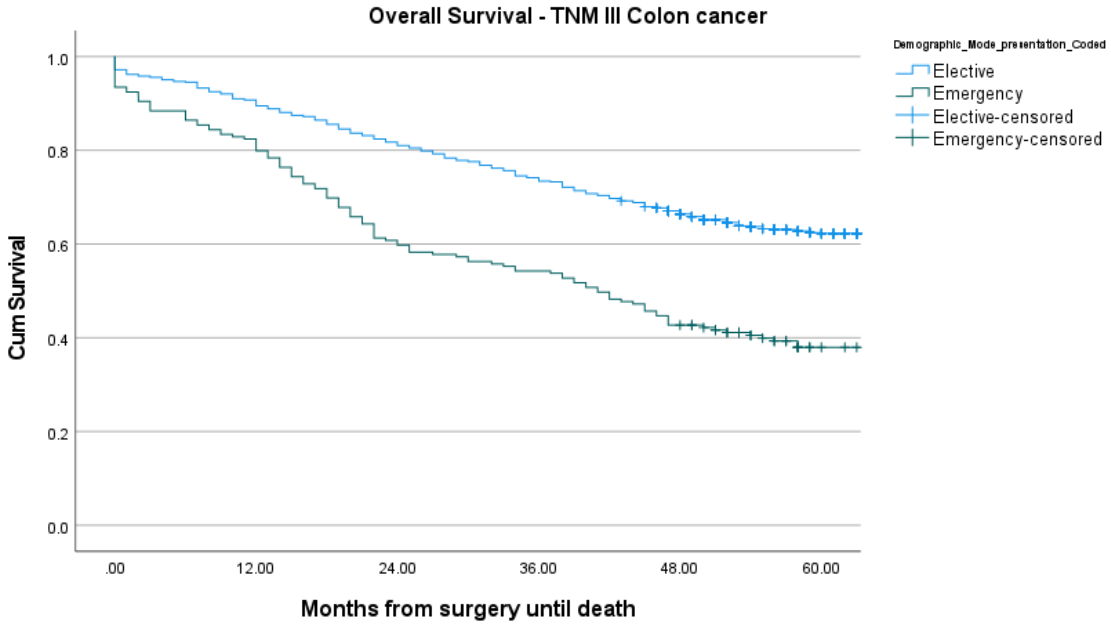


Figure 4-2 – Overall survival in elective versus emergency presentations of colon cancer in TNM I (top), TNM II (middle) and TNM III (bottom) disease (elective surgery with curative intent for TNM I-III colon cancer)

5 Chapter 5 - An Investigation Into the Association Between Mode of Presentation, the Systemic Inflammatory Response and Short-Term/Long-Term Survival in Colon Cancer

5.1 Introduction

As described within Chapter 1, an elevated systemic inflammatory response is prevalent in patients with colorectal cancer and associated with adverse short-term and long-term outcomes. This systemic inflammatory response can be quantified through cumulative scores or composite ratios, either using acute phase proteins or the differential white cell count. To date, the most common scoring methods are the modified Glasgow Prognostic Score (mGPS)[41] and the Neutrophil-Lymphocyte ratio (NLR)[40].

The prognostic value of scoring systems of the systemic inflammatory response has been summarised in several recent studies including two systematic reviews and meta-analyses[42,285]. A further observational study that directly compared the use of different composite ratios and cumulative scores found these to be of prognostic value independent of TNM Stage in patients undergoing curative surgery for colon cancer[286]. More recently, a Japanese study by Inamoto and co-authors[287] reported the possibility of more accurately stratifying overall, cancer-specific and disease-free survival by combining two different measures of the systemic inflammatory response (Glasgow Prognostic Score and Neutrophil-

Lymphocyte ratio). However, this study was in a relatively small cohort (n=448) and included both colonic and rectal cancers.

As described within the literature review presented in Chapter 2, two studies were identified that analysed the association between mode of presentation and the preoperative systemic inflammatory response. Park and co-authors[250] reported an association between emergency presentation and increased systemic inflammatory response regardless of whether this was stratified by either mGPS or NLR within a dual nationality (British and Japanese) cohort of 1140 patients undergoing curative surgery for TNM Stage I-III colorectal cancer. Catena and co-authors[233] reported an association between emergency presentation and increased median preoperative CRP within an Italian cohort of 106 patients undergoing resectional surgery for TNM I-IV colon/high rectal cancers. Given this observation, it seems likely that the systemic inflammatory response is a significant contributing factor to the adverse outcomes seen in emergency presentations of colon cancer.

The present study aims to analyse the potential to better stratify the systemic inflammatory response using both the modified Glasgow Prognostic Score[288] and Neutrophil-Lymphocyte Ratio[40] within a regional cohort of patients undergoing curative resectional surgery for TNM I-III colon cancer and subsequently aims to analyse the association between the systemic inflammatory response, mode of presentation and short-term/long-term survival.

5.2 Methods

Patients diagnosed with and undergoing resectional surgery with curative intent for colon cancer, between January 2011 and December 2014 within the West of Scotland, were identified as previously described in Chapters 3 and 4 and tumour and host factors were defined as described in Chapter 4. Patients who did not have the laboratory data to calculate a minimum of both mGPS and NLR were excluded. This is shown diagrammatically in Figure 5-1.

Preoperative blood results were regarded as the most recent set of preoperative blood results, in the case of elective patients within one month prior to surgery and in the case of emergency patients from admission to hospital.

The preoperative systemic inflammatory response was calculated using the modified Glasgow Prognostic Score and neutrophil-lymphocyte ratio as described in Chapter 1. NLR was classified as 0 (NLR <3), 1 (NLR 3-5) or 2 (NLR>5). The mGPS was classified as 0 (CRP ≤10), 1 (CRP>10 and albumin ≥35) or 2 (CRP >10 and albumin <35). Patients were considered to have received adjuvant chemotherapy if adjuvant chemotherapy was commenced regardless of chemotherapeutic agent/dose/number of cycles received.

The association between tumour and host factors and mode of presentation and subsequent survival analysis (short-term and long-term) has been carried out using the variables found within Chapter 4 to be significant on univariate analysis for mode of presentation. Survival was calculated as described in Chapter 3.

5.2.1 Statistical Analysis

The unadjusted association between clinicopathological characteristics and mode of presentation was examined using the Chi-squared test. For multivariate analysis, binary logistic regression was used in which factors with a significance of $p<0.010$ were removed from the model in a stepwise fashion.

The relationship between clinicopathological characteristics, including measurements of the systemic inflammatory response, and overall or cancer specific survival was examined using Cox's proportion hazards model to calculate hazard ratios (HRs) and 95% confidence intervals (95% CIs). Variables with a p-value of <0.1 on univariate analysis were entered into a multivariate model using the backwards conditional method in which variables with a significance of p-value of 0.1 were removed from the model in a stepwise fashion. The association between co-variates with more than two levels and overall survival were visually inspected using Kaplan-Meier curves confirming linearity with overall survival therefore analysis using categorical co-variates was not carried out.

Three-year overall and cancer-specific survival were carried out using the life table function of SPSS and results were displayed as percentage 3-year survival and percentage standard error. Where there were fewer than 10 patients in a group, survival analysis was not carried out due to potential inaccuracies resulting from small sample size. On survival analysis, statistical significance was calculated using the log-rank test. Outcomes have been displayed graphically using Kaplan-Meier curves.

Statistical analysis was carried out using IBM SPSS Statistics for Windows Version 28 (IBM Corporation, Armonk, New York, USA). For survival stratified by SIG, a p-

value of <0.01 was considered significant due to the number of statistical comparisons.

5.3 Results

5.3.1 Patient Characteristics

As shown in Figure 5-1, 6549 patients were identified who had been diagnosed with colorectal cancer in the West of Scotland from January 2011 to December 2014, 2706 of whom had undergone a curative resection for TNM Stage I-III colon cancer. After exclusion of those patients who did not have the required preoperative blood test results available to calculate both the modified Glasgow Prognostic Score (mGPS) and neutrophil-lymphocyte ratio (NLR), 1707 patients remained who were included in this study.

As shown in Table 5-1, the majority of patients were aged >65 (70%), presented electively (76%) and underwent an R0 resection (97%) for node negative (TNM I-II) disease (62%). 58%/19%/23% of patients had a preoperative mGPS of 0/1/2 respectively and 45%/31%/24% of patients had a preoperative NLR of <3/3-5/5+ respectively. The median follow-up between date of surgery and date of death/censoring was 58 months (range 0-95 months). When only survivors were included, the median follow-up was 70 months (range 43-95 months). After exclusion of postoperative deaths there were 590 deaths during follow-up of which 58% were cancer related.

5.3.2 Association Between Clinicopathological Characteristics (Including mGPS and NLR) and Overall Survival

The association between clinicopathological characteristics and overall survival is shown in Table 5-2. On univariate analysis: age ($p<0.001$), tumour site ($p=0.006$), SIMD classification ($p=0.006$), mode of presentation ($p<0.001$), ASA classification ($p<0.001$), TNM Stage ($p<0.001$), margin involvement ($p<0.001$), adjuvant chemotherapy ($p<0.001$), smoking status ($p<0.001$), mGPS ($p<0.001$) and NLR ($p<0.001$) were associated with overall survival. When those factors significant on univariate analysis were entered into the multivariate model: age (HR 1.30, $p<0.001$), mode of presentation (HR 1.30, $p=0.015$), ASA classification (HR 1.46, $p<0.001$), TNM Stage (HR 1.86, $p<0.001$), margin involvement (HR 2.49, $p<0.001$), adjuvant chemotherapy (HR 0.52, $p<0.001$), smoking (HR 1.20, $p=0.005$), mGPS (HR 1.15, $p=0.015$) and NLR (HR 1.21, $p=0.001$) remained associated with overall survival. It was of particular interest that both mGPS and NLR retained independent significance with similar hazard ratios.

5.3.3 Three-Year Overall Survival Stratified by mGPS and NLR

The individual and complementary use of mGPS and NLR in stratifying 3-year overall survival in both the whole cohort of patients and when subclassified into individual TNM Stages is shown in Table 5-3.

Within the whole patient cohort (Table 5-3a), when overall survival was stratified using mGPS 3-year survival ranged from 83% (mGPS 0) to 58% (mGPS 2). When NLR was used it ranged from 84% (NLR<3) to 62% (NLR >5). When a

combination of mGPS/NLR was used, overall survival ranged from 87% (mGPS 0, NLR <3) to 54% (mGPS 2, NLR >5). When NLR <3 was stratified by mGPS (0/1/2) (n=571/111/92) 3-year survival was 87%/84%/68% (p<0.001), for NLR 3-5 (n=299/115/110) 3-year survival was 82%/77%/58% (p<0.001) and for NLR >5 (n=120/104/185) 3-year survival was 72%/64%/54% (p<0.001).

Within the TNM Stage I cohort (Table 5-3b), when overall survival was stratified using mGPS 3-year survival was 90%/94%/77% for mGPS 0/1/2 respectively. When stratified by NLR 3-year survival was 88%/95%/87% for NLR <3/3-5/>5 respectively. 3-year overall survival stratified by both mGPS and NLR is shown in Table 5-3b however due to small numbers (n<10) within groups this analysis was limited.

Within the TNM Stage II cohort (Table 5-3c), when overall survival was stratified using mGPS, 3-year survival ranged from 87% (mGPS 0) to 65% (mGPS 2). When NLR was used it ranged from 88% (NLR<3) to 69% (NLR>5). When a combination of mGPS/NLR was used, overall survival ranged from 91% (mGPS 0, NLR <3) to 60% (mGPS 2, NLR>5). When NLR<3 was stratified by mGPS (0/1/2) (n=209/45/54) 3-year survival was 91%/91%/72% (p=0.031), for NLR 3-5 (n=139/48/62) was 83%/81%/65% (p=0.019) and for NLR>5 (n=60/46/96) was 77%/78%/60% (p=0.004).

Within the TNM Stage III cohort (Table 5-3d), when overall survival was stratified using mGPS 3-year survival ranged from 75% (mGPS 0) to 49% (mGPS 2). When NLR was used it ranged from 77% (NLR<3) to 49% (NLR>5). When a combination of mGPS/NLR was used, overall survival ranged from 80% (mGPS 0, NLR<3) to 44% (mGPS 2, NLR>5). When NLR<3 was stratified by mGPS (0/1/2) (n=198/54/34) 3-year survival was 80%/76%/62% (p=0.013), for NLR 3-5 (n=102/50/43) was

70%/68%/49% (p=0.012) and for NLR >5 (n=38/54/85) was 58%/50%/44% (p=0.276).

5.3.4 Formation of Systemic Inflammatory Grade

Within the present study NLR has been stratified into <3, 3-5 and >5 and assigned a respective score of 0/1/2 and mGPS 0/1/2. When mGPS (0-2) and NLR (0-2) were added cumulatively to form a combined Systemic Inflammatory Grade (SIG) this classified patients into 5 grades from 0-4 (Table 5-4). Both mGPS and NLR had similar hazard ratios (mGPS – HR 1.15, 95% CI 1.03-1.29 and NLR – HR 1.21, 95% CI 1.06-1.36) and therefore had a similar contribution to the prognostic value of SIG. When both overall and cancer-specific survival were stratified by a combination of either SIG and mGPS or SIG and NLR, only SIG retained independent significance.

5.3.5 Three-Year Overall/Cancer-Specific Survival Stratified by SIG

Three-year overall and cancer specific survival for the combined cohort of patients (TNM I-III) and for each TNM Stage stratified by SIG is shown in Table 5-5 and is shown graphically in Figure 5-2 (overall survival) and Figure 5-3 (cancer specific survival).

Within the whole cohort for SIG 0/1/2/3/4, 3-year overall survival was 88%/84%/76%/65%/60% and cancer-specific survival was 94%/90%/82%/74%/71%.

Within TNM Stage I disease <10 TNM Stage I patients had either SIG 3 or 4 therefore survival analysis was not carried out for these groups. For SIG 0/1/2, 3-year overall survival was 89%/97%/88% and cancer-specific survival was 98%/99%/97%. Within TNM Stage II colon cancer, for SIG 0/1/2/3/4, 3-year overall survival was 93%/87%/81%/75%/68% and cancer-specific survival was 97%/96%/87%/87%/81%. Within TNM Stage III colon cancer for SIG 0/1/2/3/4, 3-year overall survival was 82%/73%/65%/53%/48% and cancer-specific survival was 87%/80%/69%/58%/58%.

5.3.6 Association Between Clinicopathological Factors and Mode of Presentation

The association between tumour factors, host factors and mode of presentation (univariate analysis) is shown in Table 5-1. Age<65 and 75+ ($p<0.001$), female sex ($p=0.001$), increased socio-economic deprivation ($p=0.014$), higher ASA classification ($p<0.001$), smokers ($p<0.001$), BMI <25 ($p<0.001$), more advanced T Stage/N Stage ($p<0.001/=0.001$), the presence of extramural venous invasion ($p<0.001$) and the systemic inflammatory response (regardless of whether stratified by mGPS, NLR or SIG (all $p<0.001$)) were associated with mode of presentation. When those tumour and host factors significant on univariate analysis and SIG were entered into the multivariate model (Table 5-6): age (OR 0.63, $p<0.001$), ASA classification (OR 1.27, $p=0.080$), BMI (OR 0.81, $p=0.018$), T Stage (OR 2.25, $p<0.001$), EMVI (OR 1.65, $p=0.008$) and SIG (OR 1.83, $p<0.001$) remained associated with emergency presentation.

5.3.7 Association Between Clinicopathological Factors Including Systemic Inflammatory Grade and Mode of Presentation and Postoperative Mortality

The association between tumour factors and host factors (that were independently associated with emergency presentation) and postoperative (30-day) mortality is shown in Table 5-7. On univariate analysis, age ($p<0.001$), ASA classification ($p<0.001$), T Stage ($p=0.001$), Systemic Inflammatory Grade ($p<0.001$) and mode of presentation ($p<0.001$) were associated with postoperative mortality. When those factors significant on univariate analysis were entered into the multivariate model: age (OR 1.83, $p=0.004$), ASA classification (OR 2.14, $p<0.001$), SIG (OR 1.33, $p=0.009$) and mode of presentation (OR 1.86, $p=0.043$) remained associated with postoperative mortality.

5.3.8 Association Between Clinicopathological Factors Including Systemic Inflammatory Grade and Mode of Presentation and Long-Term Survival

The association between tumour factors and host factors (that were independently associated with emergency presentation of colon cancer) and overall and cancer-specific survival after exclusion of 30-day mortality is shown in Table 5-8.

For cancer-specific survival: older age, higher ASA classification, low BMI, more advanced T Stage, the presence of extramural venous invasion, higher Systemic Inflammatory Grade and emergency presentation were associated with adverse outcomes on univariate analysis (all $p<0.001$). When those factors significant on univariate analysis were entered into the multivariate model: higher ASA classification (HR 1.29, $p=0.018$), low BMI (HR 0.84, $p=0.018$), more advanced T Stage (HR 2.23, $p<0.001$), the presence of extramural venous invasion (HR 1.97, $p<0.001$) and raised Systemic Inflammatory Grade (HR 1.17, $p<0.001$) remained associated with cancer-specific survival. Of note, emergency presentation was not independently associated with cancer specific survival ($p=0.498$).

For overall survival: older age, higher ASA classification, low BMI, more advanced T Stage, the presence of extramural venous invasion, higher Systemic Inflammatory Grade and emergency presentation were associated with adverse outcomes on univariate analysis (all $p<0.001$). When those factors significant on univariate analysis were entered into the multivariate model: older age (HR 1.25, $p=0.003$), higher ASA classification (HR 1.51, $p<0.001$), low BMI (HR 0.84, $p=0.003$), more advanced T Stage (HR 1.53, $p<0.001$), the presence of extramural venous invasion (HR 1.38, $p=0.009$) and raised Systemic inflammatory Grade (HR 1.13, $p=0.006$) remained associated with overall survival. Of note, emergency presentation was not independently associated with overall survival ($p=0.531$).

5.4 Discussion

The results of the present study show that survival following curative surgery for colon cancer can be stratified using SIG. Both mGPS and NLR were independently associated with overall survival after adjustment for other common clinicopathological factors and on this basis these scores were combined to form SIG. This SIG simply and effectively stratified overall and cancer-specific survival in the TNM Stage I-III cohort and in the TNM Stage II and Stage III cohorts and was superior to mGPS or NLR alone in predicting overall and cancer-specific survival. SIG remained independently associated with emergency presentation after adjustment for the tumour and host factors identified in Chapter 4. Furthermore, after adjustment for those clinicopathological characteristics that differed between elective and emergency presentations of colon cancer, emergency presentation was no longer associated with adverse oncological outcomes although it did remain independently associated with 30-day mortality.

The prognostic value of either mGPS or NLR has been extensively reported within the literature in operable and non-operable cancer[42,289]. To date, the combined prognostic value of mGPS and NLR has been reported in two studies. The first of these by Inamoto and co-authors[287] reported that in 450 patients undergoing surgery for colorectal cancer, both GPS and NLR were independent prognostic factors. The second by McSorley and co-authors[290] reported that in a cohort of 300 patients undergoing surgery for oesophagogastric tumours, mGPS and NLR had complimentary value. The present study, within a cohort of 1700 patients undergoing curative surgery for colon cancer, externally validates the independent prognostic value of mGPS and NLR and furthermore combines these

into an overall Systemic Inflammatory Grade. It was of interest that both mGPS and NLR were similar in terms of hazard ratios for association with overall survival and therefore had a similar contribution to the prognostic value of SIG. On multivariate analysis for a combination of either SIG and mGPS or SIG and NLR, only SIG remained independently significant. The biological rational for combining mGPS and NLR is clear since they represent the response of two different organ systems to the development of a significant inflammatory response. Therefore, SIG is a simple, objective measure of the SIR that has prognostic value in colon cancer.

Emergency presentation has been widely reported to be an independent adverse prognostic indicator in patients undergoing curative surgery for colorectal cancer. However as described in Chapter 2 the pre-existing literature comparing the preoperative systemic inflammatory response in elective compared to emergency presentations of colorectal cancer is limited to two previous studies[291]. The present study confirms that emergency presentations of colon cancer are strongly associated with an elevated preoperative systemic inflammatory response (as measured by SIG) after adjustment for other common clinicopathological factors and, furthermore, it is this elevated SIG rather than emergency presentations per se that is independently associated with adverse long-term oncological outcomes (both overall and cancer-specific survival). The present results confirm that at time of presentation, patients presenting emergently have a greater systemic inflammatory response than those that present electively. However, based on these inflammatory markers, it is impossible to tell whether this elevated systemic inflammatory response occurred acutely at the time of the event that led to emergency presentation (for example perforation or complete obstruction) or whether a chronically

inflamed state predisposed the individual to more rapid tumour progression and subsequent emergency presentation.

The exact link between tumour and host response remains to be determined and further research is required in this area. Certain factors have been reported to be associated with a raised systemic inflammatory response including T stage, tumour necrosis[292] and tumour glucose metabolism[293]. However, the association between the systemic inflammatory response and other factors (including tumour mutational status and circulating tumour cells/micro metastatic disease) have not been widely investigated. Further research into these areas may help to establish a causative relationship between the tumour and the host inflammatory response and increase the potential for therapeutic intervention. Furthermore, an association between the systemic inflammatory response and CT-derived body composition, in particular the loss of lean muscle mass, has been reported in the literature[254] although the association between this and mode of presentation of colon cancer has yet to be investigated. This loss of lean muscle mass relates more to a chronically inflamed state as opposed to an acute inflammatory event at time of emergency presentation and would be of interest in future studies.

For postoperative survival, both emergency presentation and SIG were associated with adverse outcomes. Prior research has shown an association between the preoperative and postoperative systemic inflammatory response and short-term outcomes including both morbidity and mortality[47,294], albeit predominantly within patients undergoing elective surgery. The postoperative systemic inflammatory response and postoperative morbidity was outwith the scope of the present study although this warrants further investigation within

the context of elective versus emergency presentations. The postoperative systemic inflammatory response has been stratified using the postoperative Glasgow Prognostic Score (poGPS)[47]. Given the present findings, the utility of a combined approach including both postoperative Glasgow Prognostic Score and postoperative Neutrophil-Lymphocyte ratio to better stratify the postoperative systemic inflammatory response would be worthy of future investigation.

The importance of the tumour-host immune/inflammatory response is increasingly recognised[295]. Although complex, the processes involved provide several potential therapeutic targets to improve cancer outcomes, however this creates a need to optimise stratification of the systemic inflammatory response. We have shown that this SIG has utility in stratifying survival in both TNM Stage II and TNM Stage III disease. The potential to modulate this response is relevant both to elective and emergency presentations of colon cancer but given the strong association between emergency presentations of colon cancer and an elevated systemic inflammatory response it is of particular interest within this high-risk emergency cohort. Furthermore, a previous multicentre observational study of 2295 patients reported that in patients undergoing resectional surgery with curative intent for TNM III colorectal cancer, better outcomes were observed with oxaliplatin based adjuvant chemotherapy regimens as opposed to 5-flurouracil within patients with an elevated preoperative systemic inflammatory response[39]. Further research into the association between systemic inflammatory grade and outcomes in patients undergoing adjuvant chemotherapy is warranted.

Within TNM Stage II colon cancer, patients are considered high-risk or low-risk depending on a number of clinicopathological factors. Those patients considered

high-risk are considered for adjuvant chemotherapy[149]. The evidence regarding chemotherapy within these TNM Stage II patients is more limited, nevertheless some trials including the QUASAR trial[185] have reported improved survival outcomes with adjuvant chemotherapy in Stage II colon cancer, albeit the effect is small. Emergency presentation is currently regarded as one of these high-risk features however the preoperative Systemic Inflammatory Response is not currently recognised to be a high-risk factor. On the basis of the present results, the simple and objective SIG is a better predictor of outcome than mode of presentation and the routine use of SIG within the clinical setting should be considered a potential opportunity to improve outcomes through more targeted use of adjuvant therapy. Future research investigating the ability of SIG to identify high risk stage II disease would be of interest. Given the inclusion of T4 colon cancer in high-risk TNM Stage II disease and the known association between T Stage and the systemic inflammatory response, a significant proportion of patients with TNM Stage II colon cancer and an elevated SIG may already be considered high-risk. Survival analysis of patients traditionally considered low-risk however have an elevated SIG should be carried out as it may be appropriate to consider the need to include elevated SIG as a marker of high-risk TNM Stage II disease. The application of this finding to TNM Stage II disease is of particular importance due to the introduction of population level bowel cancer screening programmes that have been reported to have resulted in an increasing proportion of patients presenting with TNM Stage I-II disease (57 to 65%, $p<0.001$)[134]. With more widespread introduction of screening programmes and further optimisation of existing screening programmes this proportion is likely to increase further.

The present study has several limitations. Not all patients undergoing curative surgery for TNM Stage I-III colon cancer had both mGPS and NLR available and were excluded from this study. This was predominantly due to the lack of availability of a pre-operative CRP and the availability of this did vary between healthboards. This may introduce bias into the present analysis. For example, it may be speculated that patients with more risk factors such as infection or chronic inflammatory diseases were more likely to have mGPS and NLR laboratory values. However, more than 60% of the eligible colon cancer patients had both preoperative mGPS and NLR available to calculate SIG (n=1707) and therefore confirms their independent prognostic value and the clinical utility of SIG. Moreover, the present study cohort is the largest to date that has evaluated the combined prognostic value of mGPS and NLR. Within the literature, the optimal normal threshold for NLR remains uncertain. For the purposes of this study, the neutrophil-lymphocyte ratio was subdivided into <3/3-5/>5 as 3 and 5 as these were the most common cut off values identified in a recent meta-analysis[42]. Finally, it seems likely that as seen in TNM II/III disease, SIG also has utility in TNM Stage I disease. However, due to the lesser systemic inflammatory response observed within the TNM Stage I cohort and overall excellent prognosis within TNM Stage I disease, the present study was underpowered to reliably assess this.

Further work is required to study the effect on survival of the preoperative systemic inflammatory response measured by SIG within TNM Stage II disease, when adjusted for current high-risk features including emergency presentation. The analysis of SIG within randomised trials in patients with colon cancer, particularly regarding adjuvant chemotherapy in TNM Stage II disease would be of interest. While a previous meta-analysis[285] examined the role of systemic

inflammation-based scores in randomised clinical trials of colon cancer, it included only those patients with metastatic disease. Within pancreatic cancer, an international consensus statement recommends a minimum reporting dataset for those patients undergoing systemic treatment for advanced disease[296]. This includes the components required for SIG and its equivalent in colon cancer would be useful. The interactions between SIG and outcomes in TNM Stage IV disease remains of interest. Although not included in the present study, TNM Stage IV disease represents a significantly different disease process than TNM I-III colon cancer with different treatment strategies and outcomes and would be of interest in future work. The present study identified an association between emergency presentation and the use of adjuvant chemotherapy. The relationship between adjuvant chemotherapy and mode of presentation/outcomes was not further explored in the present study because, in relation to mode of presentation, this study focussed on tumour and host factors. The association between emergency presentation and adjuvant chemotherapy is likely to reflect predominantly the more advanced stage of disease seen in emergency presentations however further investigation into mode of presentation and adjuvant chemotherapy would be of interest including use of adjuvant treatment, duration between surgery and commencement of therapy and compliance with therapeutic regimen.

In conclusion, the present study shows that the preoperative systemic inflammatory response in colon cancer can be best stratified using a Systemic Inflammatory Grade that combines both the modified Glasgow Prognostic Score and Neutrophil-Lymphocyte Ratio. This is important, not only in providing patients with clinically relevant prognostic information, but may be an avenue to target novel therapy with the aim of attenuating the systemic inflammatory

response and therefore improving outcomes. Furthermore, the present results confirm that when adjusted for other clinicopathological factors including TNM Stage and Systemic Inflammatory Grade, emergency presentation does not remain independently associated with long-term oncological outcomes however does remain independently associated with 30-day mortality.

5.5 Tables

Table 5-1 Association between clinicopathological factors and mode of presentation

Clinicopathological factor	Total	Elective	Emergency	P
Age	1707	1299 (76%)	408 (24%)	<0.001
<65	517 (30%)	382 (29%)	135 (33%)	
65-74	567 (33%)	469 (36%)	98 (24%)	
75+	623 (37%)	448 (35%)	175 (43%)	
Sex	1707	1299 (76%)	408 (24%)	0.001
Male	876 (51%)	695 (54%)	181 (44%)	
Female	831 (49%)	6004 (47%)	227 (56%)	
Site	1691	1287 (76%)	404 (24%)	0.168
Right	908 (54%)	679 (53%)	229 (57%)	
Left	783 (46%)	608 (47%)	175 (43%)	
SIMD	1707	1299 (76%)	408 (24%)	0.014
1 (most deprived)	498 (29%)	354 (27%)	144 (35%)	
2	366 (21%)	296 (23%)	70 (17%)	
3	309 (18%)	233 (18%)	76 (19%)	
4	258 (15%)	200 (15%)	58 (14%)	
5 (least deprived)	276 (16%)	216 (17%)	60 (15%)	
ASA classification	1623	1253 (77%)	370 (23%)	<0.001
1	132 (8%)	102 (8%)	30 (8%)	
2	848 (52%)	705 (56%)	143 (39%)	
3	561 (35%)	405 (32%)	156 (42%)	
4	80 (5%)	41 (3%)	39 (11%)	
5	2 (<1%)	0	2 (1%)	
Smoking	1595	1239 (78%)	356 (23%)	<0.001
Non smoker	755 (47%)	591 (48%)	164 (46%)	
Ex-smoker	607 (38%)	497 (40%)	110 (31%)	
Smoker	233 (15%)	151 (12%)	82 (23%)	
BMI	1111	888 (80%)	223 (20%)	<0.001
<18.5	30 (3%)	18 (2%)	12 (5%)	
18.5-24.9	386 (35%)	289 (33%)	97 (44%)	
25-29.9	379 (34%)	305 (34%)	74 (33%)	
30-34.9	202 (18%)	179 (20%)	23 (10%)	
35+	114 (10%)	97 (11%)	17 (8%)	
Anaemia	1705	1297 (76%)	408 (24%)	0.504
No	923 (54%)	708 (55%)	215 (53%)	
Yes	782 46%)	589 (45%)	193 (47%)	
T Stage	1705	1297 (76%)	408 (58%)	<0.001
1	147 (9%)	143 (11%)	4 (1%)	
2	194 (11%)	183 (14%)	11 (3%)	
3	811 (48%)	656 (51%)	155 (38%)	
4	553 (32%)	315 (24%)	238 (58%)	
N Stage	1707	1299 (76%)	408 (24%)	0.001
0	1049 (62%)	827 (64%)	222 (54%)	
1	409 (24%)	301 (23%)	108 (27%)	
2	249 (15%)	171 (13%)	78 (19%)	
Differentiation	1702	1294 (76%)	408 (24%)	0.127
Mod-well	1363 (80%)	1047 (81%)	316 (78%)	
Poorly	339 (20%)	247 (19%)	92 (23%)	
EMVI	1688	1282 (76%)	406 (24%)	<0.001
Negative	939 (56%)	784 (61%)	155 (38%)	
Positive	749 (44%)	498 (39%)	251 (62%)	
Adjuvant chemotherapy	1701	1298 (76%)	403 (24%)	0.003
No	1146 (67%)	899 (69%)	247 (61%)	
Yes	555 (33%)	399 (31%)	156 (39%)	
Margin involvement	1695	1291 (76%)	404 (24%)	0.003

No	1641 (97%)	1259 (98%)	382 (95%)	
Yes	54 (3%)	32 (3%)	22 (5%)	
mGPS	1707	1299 (76%)	408 (24%)	<0.001
0	990 (58%)	880 (68%)	110 (27%)	
1	330 (19%)	210 (16%)	120 (29%)	
2	387 (23%)	209 (16%)	178 (44%)	
NLR	1707	1299 (76%)	408 (24%)	<0.001
<3	774 (45%)	676 (52%)	98 (24%)	
3-5	524 (31%)	419 (32%)	105 (26%)	
>5	409 (24%)	204 (16%)	205 (50%)	
SIG	1707	1299 (76%)	408 (24%)	<0.001
0	571 (34%)	532 (41%)	39 (10%)	
1	410 (24%)	346 (27%)	64 (16%)	
2	327 (19%)	237 (18%)	90 (22%)	
3	214 (13%)	101 (8%)	113 (28%)	
4	185 (11%)	83 (6%)	102 (25%)	
30-day mortality	1707	1299 (76%)	408 (24%)	<0.001
No	1645 (96%)	1269 (98%)	376 (92%)	
Yes	62(4%)	30 (2%)	32 (8%)	
3-year survival	1645	1269	376	
Overall survival	79% (1%)	82% (1%)	68% (2%)	<0.001
Cancer specific survival	86% (1%)	90% (1%)	74% (2%)	<0.001

Table 5-2 The association between clinicopathological factors including the preoperative systemic inflammatory response (measured by both mGPS and NLR) and overall survival – univariate and multivariate analysis (30-day mortality included)

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age (<65/65-74/>74)	1.69 (1.53-1.87)	<0.001	1.30 (1.14-1.48)	<0.001
Sex (male/female)	0.93 (0.80-1.09)	0.344	-	-
Site (right/left)	0.93 (0.88-0.98)	0.006	-	0.819
SIMD Classification (1/2/3/4/5)	0.93 (0.88-0.98)	0.006	-	0.438
Mode of presentation (Elective/emergency)	2.10 (1.78-2.46)	<0.001	1.30 (1.05-1.60)	0.015
ASA classification (1/2/3/4/5)	1.93 (1.72-2.15)	<0.001	1.46 (1.28-1.67)	<0.001
TNM Stage (1/2/3)	1.73 (1.54-1.94)	<0.001	1.86 (1.59-2.17)	<0.001
Margin involvement (negative/positive)	3.23 (2.42-4.58)	<0.001	2.49 (1.74-3.55)	<0.001
Adjuvant chemotherapy (no/yes)	0.62 (0.52-0.74)	<0.001	0.52 (0.40-0.66)	<0.001
Smoking (non-smoker/ex-smoker/smoker)	1.23 (1.10-1.38)	<0.001	1.20 (1.06-1.35)	0.005
mGPS (0/1/2)	1.59 (1.45-1.73)	<0.001	1.15 (1.03-1.29)	0.015
NLR (<3/3-5/>5)	1.55 (1.41-1.70)	<0.001	1.21 (1.08-1.36)	0.001

Table 5-3 Three-year overall survival displayed as percentage survival and percentage standard error stratified by mGPS and NLR in all TNM Stages (6-3a), TNM Stage II (6-3b) and TNM Stage III (Table 5-3c) colon cancer (30-day mortality included)

5-3a All TNM Stages									
	NLR < 3		NLR 3-5		NLR >5		Total		p
	n	%3yr OS (%SE)	n	%3yr OS (%SE)	n	%3yr OS (%SE)	n	%3yr OS (%SE)	
mGPS 0	571	87% (1%)	299	82% (2%)	120	72% (4%)	990	83% (1%)	<0.001
mGPS 1	111	84% (3%)	115	77% (4%)	104	64% (5%)	330	75% (2%)	0.009
mGPS 2	92	68% (5%)	110	58% (5%)	185	54% (4%)	387	58% (3%)	0.006
Total	774	84% (1%)	524	76% (2%)	409	62% (2%)	1707	76% (1%)	<0.001
p	<0.001		<0.001		<0.001		<0.001		
5-3b TNM Stage I Disease									
	NLR < 3		NLR 3-5		NLR >5		Total		p
	n	%3yr OS (%SE)	n	%3yr OS (%SE)	n	%3yr OS (%SE)	n	%3yr OS (%SE)	
mGPS 0	164	88% (SE 2%)	58	98% (SE 2%)	22	82% (SE 8%)	244	90% (SE 2%)	<0.001
mGPS 1	12	92% (SE 8%)	17	94% (SE 6%)	4	-	33	94% (SE 4%)	0.707
mGPS 2	4	-	5	-	4	-	13	77% (SE 12%)	0.848
Total	180	88% (SE 2%)	80	95% (SE 2%)	30	87% (SE 6%)	290	90% (SE 2%)	0.002
p	0.887		0.002		0.722		0.393		
5-3c TNM Stage II Disease									
	NLR < 3		NLR 3-5		NLR >5		Total		p
	n	%3yr OS (%SE)	n	%3yr OS (%SE)	n	%3yr OS (%SE)	n	%3yr OS (%SE)	
mGPS 0	209	91% (2%)	139	83% (3%)	60	77% (5%)	408	87% (2%)	0.017
mGPS 1	45	91% (4%)	48	81% (6%)	46	78% (6%)	139	83% (3%)	0.282
mGPS 2	54	72% (6%)	62	65% (6%)	96	60% (5%)	212	65% (3%)	0.021
Total	308	88% (2%)	249	78% (3%)	202	69% (3%)	759	80% (1%)	<0.001
p	0.031		0.019		0.004		<0.001		
5-3d TNM Stage III Disease									
	NLR < 3		NLR 3-5		NLR >5		Total		p
	n	%3yr OS (%SE)	n	%3yr OS (%SE)	n	%3yr OS (%SE)	n	%3yr OS (%SE)	
mGPS 0	198	80% (3%)	102	70% (5%)	38	58% (8%)	338	75% (2%)	0.005
mGPS 1	54	76% (6%)	50	68% (7%)	54	50% (7%)	158	65% (4%)	0.030
mGPS 2	34	62% (8%)	43	49% (8%)	85	44% (5%)	162	49% (4%)	0.348
Total	286	77% (2%)	195	65% (3%)	177	49% (4%)	658	66% (2%)	<0.001
p	0.013		0.012		0.276		<0.001		

Table 5-4 Combination of modified Glasgow Prognostic Score and Neutrophil-Lymphocyte Ratio to form Systemic Inflammatory Grade (SIG)

	NLR 0 (NLR <3)	NLR 1 (NLR 3-5)	NLR 2 (NLR>5)
mGPS 0	SIG 0	SIG 1	SIG 2
mGPS 1	SIG 1	SIG 2	SIG 3
mGPS 2	SIG 2	SIG 3	SIG 4

Table 5-5 Three year overall/cancer specific-survival displayed as percentage survival and percentage standard error for each TNM Stage stratified by SIG (30-day mortality excluded)

Overall survival	TNM I-III		TNM I		TNM II		TNM III	
	n	%3-yr OS (%SE)	n	%3-yr OS (%SE)	n	%3-yr OS (%SE)	n	%3-yr OS (%SE)
Overall	1645	79% (1%)	288	91% (2%)	725	84% (1%)	632	69% (2%)
SIG 0	562	88% (1%)	163	89% (2%)	205	93% (2%)	194	82% (3%)
SIG 1	403	84% (2%)	70	97% (2%)	180	87% (2%)	153	73% (4%)
SIG 2	313	76% (2%)	42	88% (5%)	153	81% (3%)	118	65% (4%)
SIG 3	201	65% (3%)	9	-	102	75% (4%)	90	53% (5%)
SIG 4	166	60% (4%)	4	-	85	68% (5%)	77	48% (6%)
p	<0.001		0.059		<0.001		<0.001	
Cancer specific survival	TNM I-III		TNM I		TNM II		TNM III	
	n	%3-yr OS (%SE)	n	%3-yr OS (%SE)	n	%3-yr OS (%SE)	n	%3-yr OS (%SE)
Overall	1645	86% (SE 1%)	288	98% (1%)	725	91% (1%)	632	74% (2%)
SIG 0	562	94% (1%)	163	98% (1%)	205	97% (1%)	194	87% (2%)
SIG 1	403	90% (2%)	70	99% (1%)	180	96% (2%)	153	80% (3%)
SIG 2	313	82% (2%)	42	97% (3%)	153	87% (3%)	118	69% (4%)
SIG 3	201	74% (3%)	9	-	102	87% (3%)	90	58% (5%)
SIG 4	166	71% (4%)	4	-	85	81% (4%)	77	58% (6%)
p	<0.001		0.644		<0.001		<0.001	

Table 5-6 Association between tumour factors, host factors and mode of presentation (multivariate analysis)

Variable	OR (95% CI)	p
Age	0.63 (0.50-0.79)	<0.001
Sex	-	0.189
SIMD	-	0.535
ASA classification	1.27 (0.97-1.66)	0.080
Smoking	-	0.342
BMI	0.81 (0.68-0.96)	0.018
T Stage	2.25 (1.67-3.03)	<0.001
N Stage	-	0.375
EMVI	1.65 (1.14-2.40)	0.008
SIG	1.83 (1.60-2.11)	<0.001

Table 5-7 Association between clinicopathological factors independently associated with emergency presentation and postoperative (30-day) mortality

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Age	2.59 (1.75-3.83)	<0.001	1.83 (1.21-2.75)	0.004
ASA classification	3.13 (2.17-4.51)	<0.001	2.14 (1.44-3.17)	<0.001
BMI	0.95 (0.57-1.57)	0.842	-	-
T Stage	1.83 (1.27-2.62)	0.001	-	0.379
EMVI	1.31 (0.78-2.18)	0.303	-	-
SIG	1.69 (1.40-2.03)	<0.001	1.33 (1.07-1.64)	0.009
Mode of presentation	3.60 (2.16-6.00)	<0.001	1.86 (1.02-3.40)	0.043

Table 5-8 Association between clinicopathological factors including Systemic Inflammatory Grade, mode of presentation and overall/cancer specific survival (30-day mortality excluded)

Variable	Cancer Specific Survival				Overall Survival			
	UVA		MVA		UVA		MVA	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Age	1.28 (1.12-1.46)	<0.001	-	0.877	1.64 (1.47-1.82)	<0.001	1.25 (1.08-1.44)	0.003
ASA	1.53 (1.31-1.79)	<0.001	1.29 (1.04-1.58)	0.018	1.84 (1.63-2.07)	<0.001	1.51 (1.27-1.80)	<0.001
BMI	0.78 (0.68-0.90)	<0.001	0.84 (0.72-0.97)	0.018	0.79 (0.71-0.89)	<0.001	0.84 (0.75-0.94)	0.003
T Stage	3.18 (2.66-3.81)	<0.001	2.23 (1.72-2.89)	<0.001	1.89 (1.69-2.12)	<0.001	1.53 (1.28-1.82)	<0.001
EMVI	3.16 (2.52-3.97)	<0.001	1.97 (1.43-2.71)	<0.001	2.05 (1.74-2.42)	<0.001	1.38 (1.08-1.75)	0.009
SIG	1.43 (1.33-1.55)	<0.001	1.17 (1.04-1.30)	0.006	1.37 (1.29-1.45)	<0.001	1.13 (1.04-1.23)	0.006
Mode of present.	2.62 (2.11-3.26)	<0.001	-	0.498	1.98 (1.67-2.35)	<0.001	-	0.531

5.6 Figures

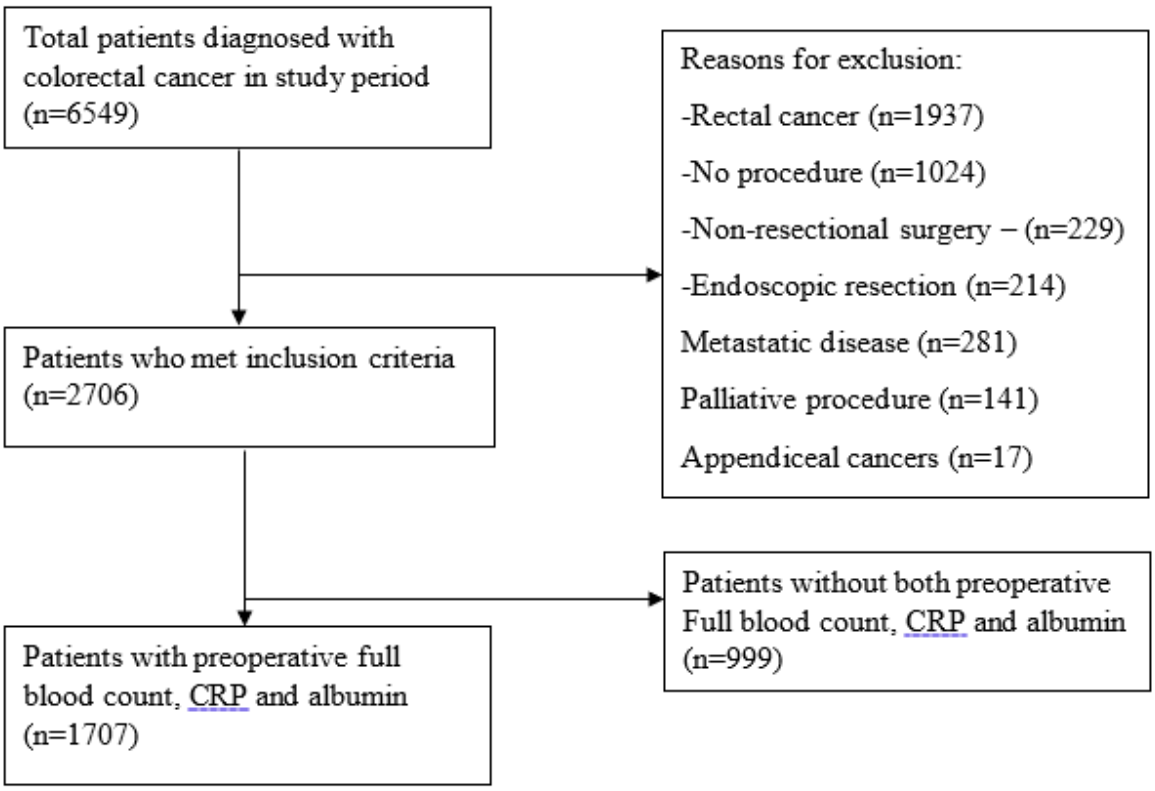
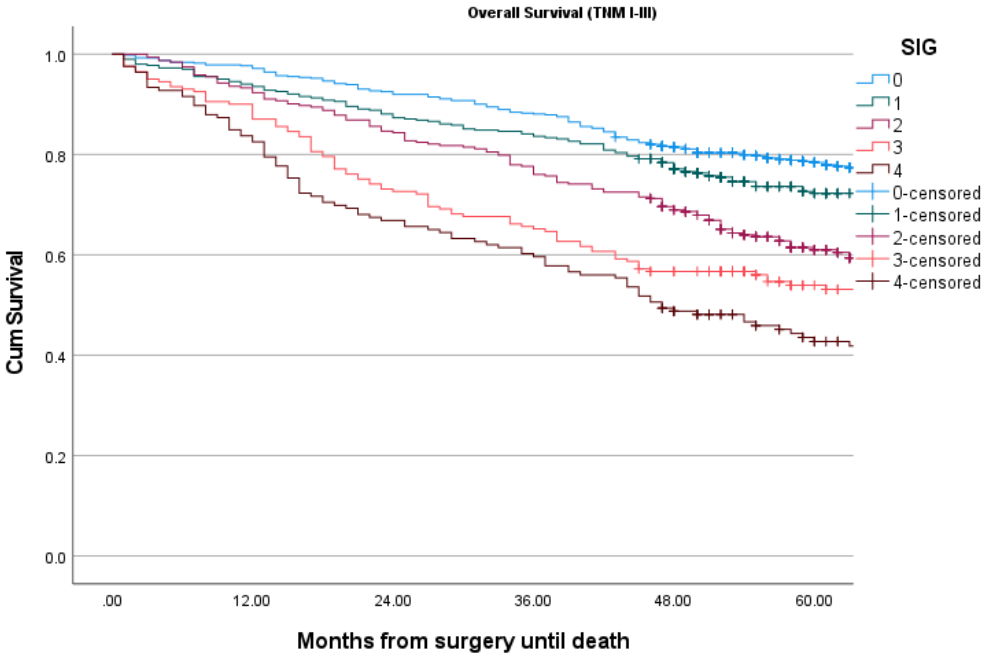
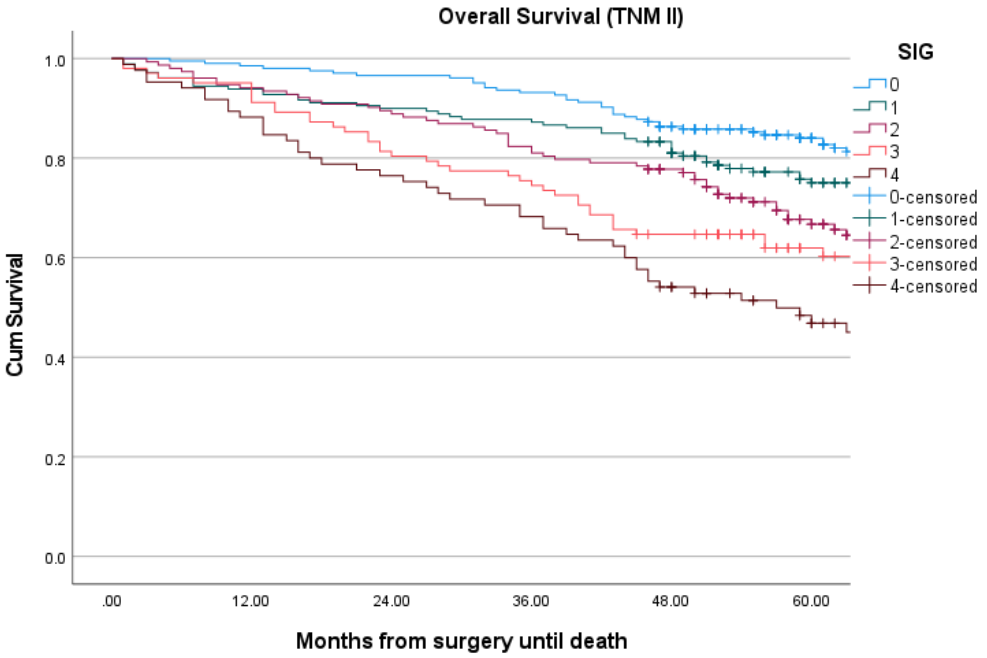


Figure 1 – Flow Chart of Case Selection

Figure 5-1 Flow chart of case selection including inclusion/exclusion criteria


Overall Survival (TNM I-III)
SIG
0
1
2
3
4
0-censored
1-censored
2-censored
3-censored
4-censored
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
.00
12.00
24.00
36.00
48.00
60.00
Months from surgery until death


Overall Survival (TNM II)
SIG
0
1
2
3
4
0-censored
1-censored
2-censored
3-censored
4-censored
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
.00
12.00
24.00
36.00
48.00
60.00
Months from surgery until death

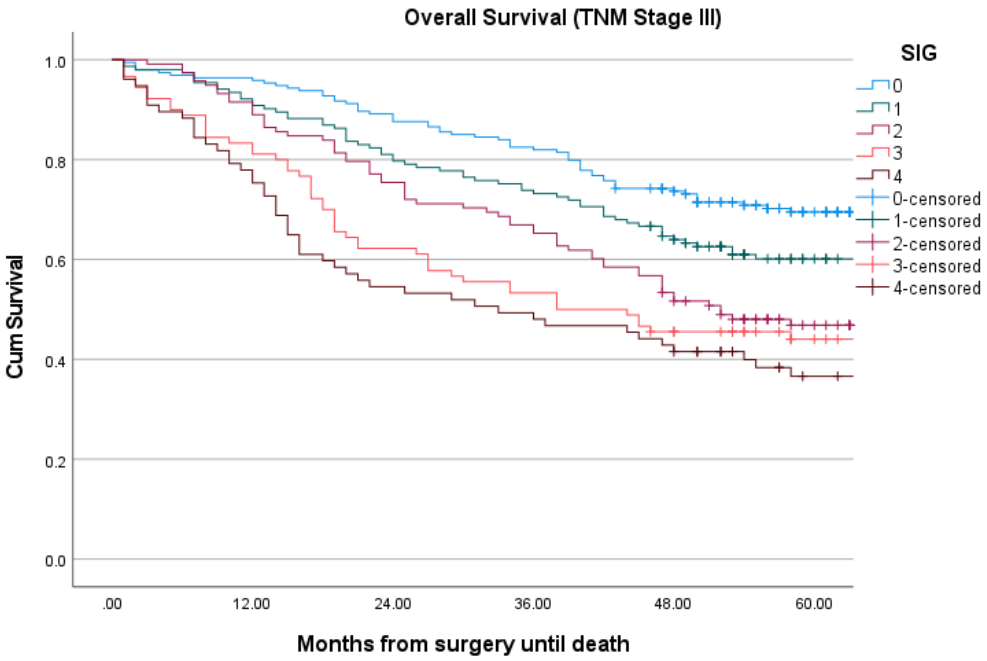
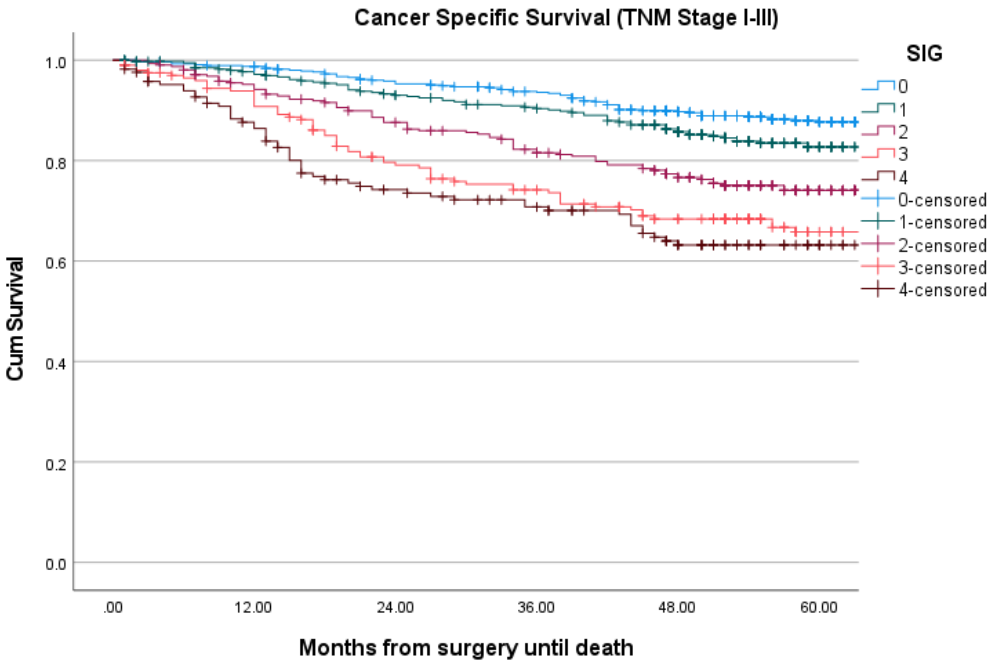
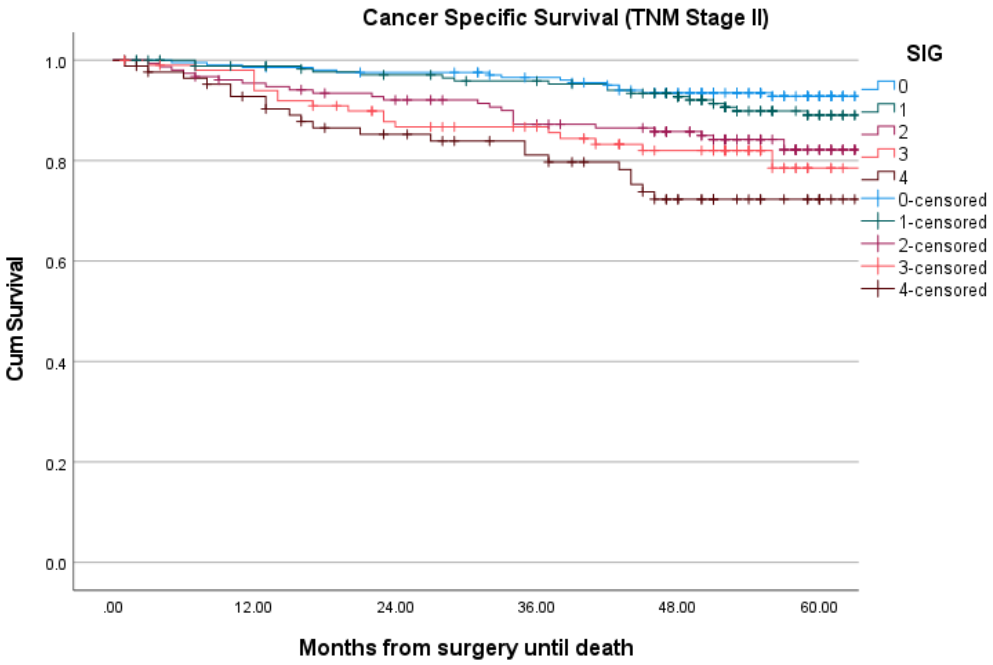


Figure 5-2 Overall survival stratified by SIG in: TNM Stage I-III colon cancer, TNM Stage II colon cancer and TNM Stage III colon cancer


Cancer Specific Survival (TNM Stage I-III)
SIG
0
1
2
3
4
0-censored
1-censored
2-censored
3-censored
4-censored
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
.00
12.00
24.00
36.00
48.00
60.00
Months from surgery until death


Cancer Specific Survival (TNM Stage II)
SIG
0
1
2
3
4
0-censored
1-censored
2-censored
3-censored
4-censored
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
.00
12.00
24.00
36.00
48.00
60.00
Months from surgery until death

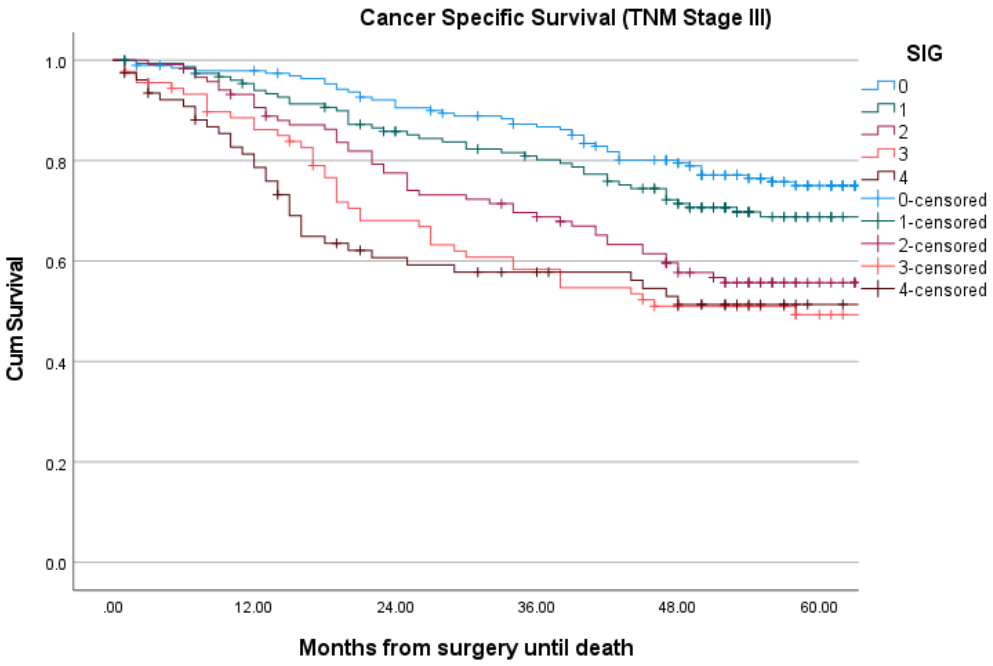


Figure 5-3 Cancer specific survival stratified by SIG in TNM Stage I-III colon cancer, TNM Stage II colon cancer and TNM Stage III colon cancer

6 Chapter 6 - An Investigation into the Association Between CT-Derived Body Composition, Mode of Presentation and Short-Term/Long-Term Survival in Colon Cancer

6.1 Introduction

Cachexia is closely associated with a number of systemic illnesses including cancer and organ failure. The syndrome of cachexia, previously described as “an ongoing loss of skeletal muscle with or without loss of fat mass not entirely reversible with nutritional support” is, in a similar way to the hallmarks of cancer, now recognised to be inextricably linked to inflammatory responses, in particular the systemic inflammatory response[254]. This has resulted in cachexia being redefined as “weight loss, reduced BMI and reduced muscle mass and function in combination with an underlying disease that displays biochemical indices of ongoing elevated inflammatory activity” or more simply put as “disease related malnutrition with inflammation”[297]. In the context of cancer, the prevalence of cachexia varies with tumour type, site and stage however is it recognised to be particularly common in gastrointestinal and lung cancer[298] and strongly associated with poor outcomes.

As described in Chapter 1 and Chapter 5, there is a clear link between an increased preoperative systemic inflammatory response and adverse outcomes following curative surgery for colon cancer. Traditional markers of cachexia and malnutrition: absolute BMI, weight loss and a characteristic “cachectic

appearance", although readily available, are now becoming less clear in the increasingly obese Western population. BMI, while being readily calculated carries the major limitation of being unable to differentiate between fat and muscle mass. This has resulted in the development of alternative anthropometric measurements[299], in particular image-based body composition. The loss of skeletal muscle mass has been most widely studied. This is often termed sarcopenia although the true definition of sarcopenia includes not just the loss of muscle mass, but also muscle function.

Within oncology, CT derived body composition is the most widely utilised anthropometric measurement due to the routine availability of CT imaging primarily obtained for cancer staging. Typically, a single CT slice is analysed for fat and muscle characteristics at the level of the third lumbar vertebrae including muscle area/density. Image analysis software (for example ImageJ[300]) can differentiate between fat and muscle using previously validated Hounsfield Unit (HU) thresholds (fat -190HU to -30HU, muscle -29HU to +150HU). These measurements can be subsequently stratified into normal/abnormal using a number of variables including sex, height and BMI to obtain four main measurements of body composition: subcutaneous fat index (SFI), visceral fat area (VFA), skeletal muscle index (SMI) and skeletal muscle density (SMD).

As reported in a recent review[254], body composition and the systemic inflammatory response are inextricably linked, independent of tumour stage however the causal nature of this relationship is not clear. As reported within the literature review in Chapter 2 and observational study in Chapter 5, emergency presentations are associated with an elevated systemic inflammatory response compared to elective presentations and this, in part, explains the

adverse outcomes seen in emergency presentations of TNM Stage I-III colon cancer. No studies comparing body composition (CT-derived or otherwise) in elective versus emergency presentations of colon cancer were identified within the literature review presented in Chapter 2. It is clear from Chapter 5 that emergency presentation is independently associated with an elevated systemic inflammatory response as measured by Systemic Inflammatory Grade (SIG). However, this SIG does not give an impression of whether this raised systemic inflammatory response is acute (within hours to days of emergency presentation) or more chronic (weeks to months) and therefore potentially predisposing to emergency presentation. Given that the effect on body composition of a raised systemic inflammatory response seems unlikely to occur within hours to days the association between CT derived body composition and mode of presentation is of interest as this would suggest that the elevated systemic inflammatory response seen within patients presenting emergently is more long-standing and may therefore predispose to emergency presentation.

The aim of the present study is to compare the association between CT-derived body composition, mode of presentation and the systemic inflammatory response in a regional cohort of patients undergoing curative surgery for TNM Stage I-III colon cancer and to investigate the effect of this on short-term/long-term survival.

6.2 Methods

Patients undergoing curative surgery for TNM I-III colon cancer within the West of Scotland from 2011-2014 were identified as previously described. Those without an available BMI and/or the laboratory data required to calculate Systemic Inflammatory Grade (preoperative Neutrophil/Lymphocyte count and preoperative C-reactive protein/albumin) as described in Chapter 5 were excluded.

Clinicopathological factors were stratified as described in Chapter 4. The preoperative systemic inflammatory response has been stratified using Systemic Inflammatory Grade[301] as described in Chapter 5. Survival was calculated as previously described in Chapters 3 and 4.

6.2.1 Anthropometric Measurements

A single image was obtained at the level of the third lumbar vertebra from the routine staging CT scan carried out at time of cancer diagnosis. Scans with significant movement artefact or a missing region of interest were excluded. CT scan images were obtained from the NHS PACS (Picture Archiving Communications Systems) after approval from the Public Benefit and Privacy Panel (NHS Scotland). Images were analysed using a freeware program – NIH ImageJ Version 1.52 (National Institutes of Health, USA).

Standard Hounsfield Unit (HU) ranges were used to define adipose tissue (-190 to -30) and skeletal muscle (-29 to +150). Measurements were made of

subcutaneous fat area, visceral fat area, skeletal muscle area (all cm^2) and skeletal muscle density (mean HU). For subcutaneous fat area, all fat regions within the CT slice were included. For visceral fat area a region of interest was marked just within the abdominal wall and psoas muscles. For skeletal muscle area and density, muscle areas including rectus abdominus, oblique muscle groups, psoas, erector spinae muscles and quadratus lumborum were selected. Image analysis is shown graphically in Figures 6-1/6-2 for fat/muscle measurements respectively. This allowed measurements of fat/muscle areas (cm^2) and muscle density (HU)

Subcutaneous fat area and skeletal muscle area were subsequently normalised for $height^2$ to create subcutaneous fat and skeletal muscle indices (SFI and SMI respectively, cm^2/m^2). Stratification of anthropometric measurements as normal/abnormal was carried out for SFI, VFA, SMI and SMD as previously described by Ebadi[302], Doyle[303], Martin[304] and Xiao[305] respectively (Table 6-1).

CT image retrieval at the third lumbar vertebrae was performed by a single individual (Allan Golder). The majority of CT images were analysed by Allan Golder with assistance from others as described within the Author's Declaration section of this thesis.

6.2.2 Statistical Analysis

The relationship between TNM Stage, Systemic Inflammatory Grade and CT-derived body composition has been carried out using the Chi squared test. Results are displayed as the total number of patients within each TNM Stage/SIG

category and percentage of the total number with the relevant abnormal CT-derived body composition marker.

The association between clinicopathological factors including CT derived body composition and mode of presentation has been carried out on univariate analysis using the Chi squared test and on multivariate analysis using binary logistic regression to calculated Odds Ratios (ORs) and 95% confidence intervals (95% CIs). Variables with a p-value of <0.1 on univariate analysis were entered into the multivariate model.

Three-year overall survival was calculated using the life table function of SPSS and results were displayed as percentage 3-year survival and percentage standard error. Where there were fewer than 10 patients in a group survival analysis was not carried out due to potential inaccuracies resulting from small sample size. On survival analysis, statistical significance was calculated using the log rank test.

6.3 Results

6.3.1 Patient Characteristics

Patient characteristics are shown in Table 6-2. 1057 patients were eligible for inclusion, the majority of whom presented electively (80%) with TNM II/III disease (41%/44%). 80%/75% had a high subcutaneous fat index/visceral fat area respectively. 55%/70% of patients had a low skeletal muscle index/skeletal muscle density respectively. Of the 1057 patients who underwent curative surgery there were 14 postoperative deaths (1%). Following exclusion of postoperative deaths, 3-year overall survival within the whole cohort was 84%.

6.3.2 Association Between TNM Stage, Systemic Inflammatory Grade and Anthropometric Measurements

6.3.2.1 BMI Defined Obesity

As shown in Table 6-3a, within the overall cohort there was a trend, albeit not of statistical significance between TNM Stage and proportion of patients with a BMI greater than 25 – 70%/60%/62% (p=0.099) of patients with TNM Stage I/II/III disease respectively. When patients were subgrouped by SIG, no significant association was seen between TNM Stage and BMI defined obesity within any subgroup.

In the overall cohort there was a significant inverse association between SIG and the proportion of patients with BMI greater than 25 – 71%/65%/59%/59%/33%

(p<0.001) of patients with SIG 0/1/2/3/4 respectively. When patients were subgrouped by TNM Stage a significant association was seen within the TNM Stage II cohort – 68%/60%/58%/65%/33% (p=0.001) and TNM Stage III cohort – 72%/67%/61%/54%/31% (p<0.001) of patients with SIG 0/1/2/3/4 respectively.

6.3.2.2 CT Derived Body Composition – Subcutaneous Fat Index

As shown in Table 6-3b, within the overall cohort there was a significant association between TNM Stage and the proportion of patients with a high SFI – 87%/76%/81% (p=0.006) of patients with TNM I/II/III disease respectively. When patients were subgrouped by SIG no significant association was seen between TNM Stage and SFI within any subgroup.

In the overall cohort there was a significant inverse association between SIG and the proportion of patients with a high SFI – 84%/81%/79%/79%/65% (p=0.004) of patients with SIG 0/1/2/3/4 respectively. When patients were subgrouped by TNM Stage a significant inverse association was seen in the TNM Stage II cohort – 81%/76%/73%/81%/58% (p=0.040) with SIG 0/1/2/3/4 respectively.

6.3.2.3 CT Derived Body Composition – Visceral Fat Area

As shown in Table 6-3c, within the whole cohort there was no significant association (p=0.367) between TNM Stage and VFA. When patients were subgrouped by SIG no significant association was seen between TNM Stage and VFA within any subgroup.

In the overall cohort there was a significant inverse association between SIG and the proportion of patients with a high VFA – 79%/78%/70%/73%/61% (p=0.001) of patients with SIG 0/1/2/3/4 respectively. When patients were subgrouped by TNM Stage a borderline significant inverse association was seen in the TNM Stage II cohort – 81%/76%/69%/68%/61% (p=0.054) of patients with SIG 0/1/2/3/4 respectively.

6.3.2.4 CT Derived Body Composition – Skeletal Muscle Index

As shown in Table 6-3d, within the overall cohort there was a significant association between TNM Stage and proportion of patients with a low SMI – 43%/60%/55% (p<0.001) of patients with TNM Stage I/II/III disease respectively. When patients were subgrouped by SIG a significant association was seen in the SIG 3 cohort – 70%/59% (p=0.007) of patients with TNM II/III disease respectively (n<10 for TNM Stage I disease).

In the overall cohort there was a significant association between SIG and the proportion of patients with a low SMI – 47%/52%/61%/62%/79% (p<0.001) of patients with SIG 0/1/2/3/4 respectively. When patients were subgrouped by TNM Stage a significant association was seen in the TNM Stage II subgroup – 48%/60%/64%/70%/77% (p=0.002) and TNM Stage III subgroup – 51%/48%/58%/59%/80% (p=0.004) of patients with SIG 0/1/2/3/4 respectively.

6.3.2.5 CT Derived Body Composition – Skeletal Muscle Density

As shown in Table 6-3e, within the overall cohort there was no significant association between TNM Stage and SMD (p=0.203). When patients were subgrouped by SIG no significant association was seen between TNM Stage and SMD within any subgroup.

In the overall cohort there was a significant association between SIG and the proportion of patients with a low SMD – 61%/69%/72%/78%/92% (p<0.001) of patients with SIG 0/1/2/3/4 respectively. When patients were subgrouped by TNM Stage a significant association was seen in the TNM Stage II subgroup – 64%/70%/74%/72%/95% (p=0.003) and TNM Stage III subgroup – 61%/68%/68%/83%/89% (p<0.001) of patients with SIG 0/1/2/3/4 respectively.

6.3.3 Association Between Clinicopathological Factors Including CT Derived Body Composition and Mode of Presentation

As shown in Table 6-4, on univariate analysis: younger age (p=0.004), female sex (p=0.069), current smokers (p<0.001), higher ASA classification (p=0.038), more advanced TNM Stage (p<0.001), more advanced T Stage (p<0.001), more advanced N Stage (p=0.021), extramural venous invasion (p<0.001), increased SIG (p<0.001), BMI ≤25 (p<0.001), normal SFI (p<0.001), normal VFA (p<0.001), low SMI (p<0.001) and low SMD (p=0.002) were associated with emergency presentation.

When those factors associated with emergency presentation on univariate analysis were entered into the multivariate model (Table 6-5): age (OR 0.62, p<0.001), sex (OR 1.50, p=0.036), more advanced T Stage (OR 2.20, p<0.001), EMVI (OR 1.68, p=0.008), higher SIG (OR 1.82, p<0.001), low SFI (OR 0.58, p=0.013) and low SMI (OR 1.85, p=0.002) remained associated with emergency presentation.

6.3.4 Association Between CT Derived Body Composition, SIG and 3-Year Overall Survival in TNM Stage II Colon Cancer

The association between body composition, Systemic Inflammatory Grade and 3-year overall survival in TNM Stage II colon cancer is shown in Table 6-6. 3-year OS within the whole cohort was 89%. When stratified by SIG, overall survival ranged from 95% (SIG 0) to 73% (SIG 4).

6.3.4.1 Subcutaneous Fat Index

Within the overall cohort of patients, SFI did not have a significant effect on survival (3yr OS 88% vs 89%, p=0.248) however there was a significant association between SFI and 3yr OS in the SIG 3 (60% vs 90%, p=0.001) and SIG 4 (94% vs 60%, p=0.040) subgroups. SIG was associated with worse survival independent of SFI in both the normal SFI and high SFI subgroups – 3yr OS 93%/92%/88%/60%/94% (p=0.003) and 95%/90%/89%/90%/60% (p<0.001) for SIG 0/1/2/3/4 respectively.

6.3.4.2 Visceral Fat Area

Within the overall cohort of patients, VFA did not have a significant effect on survival (3yr OS 90% vs 89%, p=0.473). When patients were subgrouped by SIG, no significant effect of VFA on 3yr OS was seen in any SIG subgroup. SIG was associated with worse survival independent of VFA in both the normal VFA and high VFA subgroups – 3yr OS 96%/100%/86%/83%/81% (p=0.011) and 95%/87%/90%/84%/68% (p<0.001) for SIG 0/1/2/3/4 respectively.

6.3.4.3 Skeletal Muscle Index

Within the overall cohort of patients, low SMI was associated with adverse survival (3yr OS 92% vs 87%, p=0.001). When patients were subgrouped by SIG, an independent effect of SMI on survival was only seen in the SIG 2 subgroup (3yr OS 94% vs 86%, p=0.008). SIG was only associated with adverse survival in the low SMI group (3yr OS 94%/92%/86%/82%/68%, p=0.002 for SIG 0/1/2/3/4).

6.3.4.4 Skeletal Muscle Density

Within the overall cohort of patients low SMD was associated with adverse survival (3yr OS 97% vs 86%, p<0.001). When patients were subgrouped by SIG, an independent effect of SMD on survival was seen in the SIG 1 (3yr OS 97% vs 88%, p=0.023) and SIG 3 (94% vs 80%, p=0.044) subgroups. SIG was only associated with adverse survival in the low SMD subgroup (3yr OS 93%/88%/87%/80%/72%, p<0.001 for SIG 0/1/2/3/4)

6.3.5 Association Between CT Derived Body Composition, SIG and 3-year Overall Survival in TNM Stage III Colon Cancer

The relationship between body composition, Systemic Inflammatory Grade and 3-year overall survival in TNM Stage III colon cancer is shown in Table 6-7. 3-year OS in the whole cohort was 75%. When stratified by SIG, overall survival ranged from 83% (SIG 0) to 56% (SIG 4).

6.3.5.1 Subcutaneous Fat Index

Within the overall cohort of patients, low SFI was associated with poorer survival (3yr OS 65% vs 78%, p=0.029). When patients were subgrouped by SIG, an independent effect of SFI on survival was seen in the SIG 4 subgroup (38% vs 63%, p=0.022). SIG was associated with survival in the low (normal) SFI subgroup and in the high SFI subgroup - 3yr OS 76%/79%/50%/67%/38% (p=0.006) and 84%/79%/78%/64%/63% (p=0.023) for SIG 0/1/2/3/4 respectively.

6.3.5.2 Visceral Fat Area

Within the overall cohort of patients, low VFA was associated with poorer survival (3yr OS 50% vs 60%, p=0.024). When patients were subgrouped by SIG, an independent effect of VFA on survival was only seen in the SIG 2 subgroup (3yr OS 52% vs 81%, p=0.026). SIG was associated with survival in the high VFA

subgroup and a trend, albeit not reaching statistical significance was seen in the low VFA subgroup – 3yr OS 84%/82%/81%/64%/60% (p=0.014) and 81%/71%/52%/67%/50% (p=0.055) for SIG 0/1/2/3/4 respectively.

6.3.5.3 Skeletal Muscle Index

Within the overall cohort of patients, a trend, albeit not reaching statistical significance was seen between low SMI and poorer survival (3yr OS 77% vs 73%, p=0.091). When patients were subgrouped by SIG, an independent effect of SMI on survival was seen only in the SIG 1 subgroup (3yr OS 85% vs 73%, p=0.027). SIG was associated with worse survival independent of SMI in both the normal SMI and low SMI subgroups – 3yr OS 85%/85%/69%/54%/- (p=0.004) and 81%/73%/77%/72%/54% (p=0.013) for SIG 0/1/2/3/4 respectively.

6.3.5.4 Skeletal Muscle Density

Within the overall cohort of patients, low SMD was associated with worse survival (3yr OS 84% vs 71%, p=0.001). When patients were subgrouped by SIG, a trend, albeit not reaching statistical significance was seen in the SIG 1 subgroup (3yr OS 92% vs 73%, p=0.075) and SIG 2 subgroup (81% vs 70%, p=0.091). SIG was associated with worse survival independent of SMD in the low SMD subgroup – 3yr OS 80%/73%/70%/67%/55% (p=0.010) for SIG 0/1/2/3/4 respectively.

6.4 Discussion

The results of the present study show that CT-derived body composition changes are highly prevalent in patients undergoing resectional surgery with curative intent for TNM Stage I-III colon cancer and are associated with both the systemic inflammatory response and TNM Stage. Body composition, in particular a low subcutaneous fat index and low skeletal muscle index are independently associated with emergency presentation after adjustment for other common clinicopathological characteristics including SIG. Finally, both SIG and markers of CT-derived body composition while being associated retain independent prognostic value for 3-year overall survival after adjustment for tumour stage in patients undergoing curative surgery for colon cancer.

The high proportion of abnormal CT-derived anthropometric measurements in patients with colon cancer is in keeping with previous literature[281,306]. A recent review[254] reported a clear association between the systemic inflammatory response and markers of body composition and the present results validate this finding. McSorley and colleagues[307] previously reported no association between CT derived body composition measurements and TNM Stage after adjustment for the SIR (as measured by GPS). Within the present study, findings varied for different anthropometric measurements and subgroups of Systemic Inflammatory Grade. McSorley and colleagues grouped patients by TNM Stage into node negative (TNM I-II) and node positive (TNM III) disease. The present study shows that within non-metastatic patients, TNM I and TNM II disease represented each end of the body composition spectrum with TNM Stage III disease representing intermediate values. This suggests that tumour as opposed to nodal stage is more closely related to body composition, in particular lean muscle

area/density. Nonetheless, CT-derived body composition was more closely associated with the systemic inflammatory response than disease stage.

Within the literature review presented in Chapter 2, no studies were identified that compared CT-derived body composition between elective and emergency patients undergoing curative surgery for TNM I-III colon cancer. The present results show, that after adjustment for other common clinicopathological factors including Systemic Inflammatory Grade and tumour stage, CT-derived body composition, in particular Skeletal Muscle Index and Superficial Fat Index remained independently associated with emergency presentations. Given the association between body composition and the systemic inflammatory response, this may suggest that the elevated systemic inflammatory response seen in patients presenting emergently is long-standing and not merely an acute event at time of presentation. This elevated inflammatory state may predispose to emergency presentation. It is widely recognised that emergency presentations of colon cancer are associated with worse long-term outcomes than elective presentations[126,127,130] even after adjustment for other factors including TNM Stage. The present findings may in part explain the discrepancy in outcomes between elective and emergency presentations. The association between T Stage and lean muscle mass remains of interest. It is not clear whether it is T Stage per se that is related to lean muscle mass or whether tumour size (regardless of depth of invasion) is related to lean muscle mass. It is possible that the tumour may excrete inflammatory cytokines and this may drive the loss of lean muscle. It seems likely that a correlation would be seen between tumour cytokine expression and tumour size. Conversely, an elevated systemic inflammatory response may drive both tumour growth and the loss of lean muscle. Further work within this area would be of interest.

Limitations of the present study include the retrospective nature of this study and the need to exclude patients with missing data, in particular BMI or preoperative laboratory results. TNM Stage I colon cancer carries an excellent prognosis and only 6 TNM Stage I patients had SIG > 2. The present study was therefore underpowered to assess this group. It is clear that abnormal markers of CT-derived body composition are highly prevalent within colon cancer. The CT-derived body composition of this cohort prior to developing colon cancer is unknown – little is known about CT derived body composition within the healthy population and longitudinal studies of this nature comparing body composition in the healthy population would be of interest. This study had aimed to investigate the effect of body composition on short-term outcomes (30-day mortality). However, only 14 patients died within 30 days of surgery therefore the present study was not adequately powered to assess this.

Low lean muscle mass and the systemic inflammatory response are associated with adverse outcomes in colon cancer. Both of these are potential targets to manipulate with the aim of improving these outcomes. One such strategy is prehabilitation using structured exercise programmes in the intervening period between diagnosis and surgery[308]. However, major obstacles exist in terms of the short window of opportunity from diagnosis to surgery and the high levels of patient engagement required. Furthermore, while this may be feasible within the elective setting it is not possible within the emergency setting. Based on available evidence, benefits also remain uncertain. While some studies have demonstrated an improvement in preoperative functional capacity with exercise training[309,310] the effect of prehabilitation on the systemic inflammatory response and short-term/long-term outcomes is unclear. Alternatively, pharmacological manipulation of the systemic inflammatory response may

improve lean muscle mass and outcomes. These strategies are likely to be relevant both to the elective and emergency cohorts.

In conclusion, abnormal body composition is prevalent within TNM I-III colon cancer and associated with both the systemic inflammatory response and, albeit to a lesser extent, tumour stage. Abnormal CT derived body composition, in particular low skeletal muscle index and low subcutaneous fat index is associated with emergency presentation after adjustment for other common factors including TNM Stage and Systemic Inflammatory Grade. The present results would suggest that within patients presenting as an emergency, there may be a longstanding inflammatory process for weeks-months (or longer) prior to presentation. This may predispose these patients to presenting as an emergency and furthermore is likely to contribute to the worse prognosis seen in emergency presentations.

6.5 Tables

Table 6-1 Classification of abnormal CT-derived body composition

High subcutaneous fat index		
Males	Ebadi[302]	>50cm2m2
Females		>42cm2m2
High visceral fat area		
Males	Doyle[303]	VFA >160
Females		VFA >80
Low skeletal muscle index		
Males, BMI ≤25	Martin[304]	SMI <45
Males, BMI >25		SMI <53
Females, BMI ≤25		SMI <39
Females, BMI >25		SMI <41
Low skeletal muscle density		
Males	Xiao[305]	<35.5 HU
Females		<32.5 HU

Table 6-2 Patient characteristics

Variable	Total
Age (years)	1057
<65	392 (37%)
65-74	363 (34%)
75+	302 (27%)
Sex	1057
Male	545 (52%)
Female	512 (48%)
SIMD	1057
1 (most deprived)	314(30%)
2	221 (21%)
3	172 (16%)
4	161 (15%)
5 (least deprived)	189 (18%)
Mode of presentation	1057
Elective	846 (80%)
Emergency	211 (20%)
Smoking	1035
Non smoker	503 (49%)
Ex-smoker	382 (37%)
Smoker	150 (15%)
ASA classification	1024
1	90 (9%)
2	576 (56%)
3	331 (32%)
4	27 (3%)
Tumour site	1048
Right	557 (53%)
Left	491 (47%)
TNM Stage	1057
I	162 (15%)
II	432 (41%)
III	463 (44%)
T Stage	1057
1	88 (8%)
2	113 (11%)
3	509 (48%)
4	347 (33%)
N Stage	1057
0	594 (56%)
1	295 (28%)
2	168 (16%)
Differentiation	1054
Mod/well	858 (81%)
Poor	196 (19%)
EMVI	1049
Negative	560 (53%)
Positive	489 (47%)
SIG	1057
0	394 (37%)
1	254 (24%)
2	195 (18%)
3	125 (12%)
4	88 (8%)
BMI	1057
≤25	395 (37%)
>25	662 (63%)
Superficial fat index	1057
Normal	213 (20%)

High	844 (80%)
Visceral fat area	1057
Normal	264 (25%)
High	793 (75%)
Skeletal muscle index	1057
Normal	473 (45%)
Low	584 (55%)
Skeletal muscle density	1057
Normal	321 (30%)
Low	736 (70%)
Postoperative death	1057
No	1043 (99%)
Yes	14 (1%)
Survival (excluding 30-day mortality)	1043
Overall survival	84% (1%)
Cancer specific survival	88% (1%)

Table 6-3 Association between markers of body composition and Systemic Inflammatory Grade after adjustment for TNM Stage

6.3a BMI >25										
		TNM Stage								P
		I		II		III		Total		
		n	%	n	%	n	%	n	%	0.773
SIG	0	98	71%	139	68%	157	72%	394	71%	
	1	38	74%	103	60%	113	67%	254	65%	0.279
	2	20	55%	90	58%	85	61%	195	59%	0.838
	3	5	60%	57	65%	63	54%	125	59%	0.476
	4	1	100%	43	33%	45	31%	89	33%	0.348
	Total	162	70%	432	60%	463	62%	1057	63%	0.099
	P	0.536		0.001		<0.001		<0.001		
6.3b High subcutaneous fat index										
		TNM Stage								P
		I		II		III		Total		
		n	%	n	%	n	%	n	%	
SIG	0	98	87%	139	81%	157	84%	394	84%	0.439
	1	38	90%	103	76%	113	82%	254	81%	0.157
	2	20	80%	90	73%	85	84%	195	79%	0.257
	3	5	100%	57	81%	63	76%	125	79%	0.419
	4	1	100%	43	58%	45	71%	89	65%	0.338
	Total	162	87%	432	76%	463	81%	1057	80%	0.006
	P	0.740		0.040		0.260		0.004		
6.3c High visceral fat area										
		TNM Stage								P
		I		II		III		Total		
		n	%	n	%	n	%	n	%	
SIG	0	98	81%	139	81%	157	77%	394	79%	0.701
	1	38	84%	103	76%	113	79%	254	78%	0.549
	2	20	60%	90	69%	85	74%	195	70%	0.429
	3	5	80%	57	68%	63	76%	125	73%	0.592
	4	1	100%	43	61%	45	60%	89	61%	0.720
	Total	162	79%	432	73%	463	75%	1057	75%	0.367
	P	0.249		0.054		0.152		0.001		
6.3d Low skeletal muscle index										
		TNM Stage								P
		I		II		III		Total		
		n	%	n	%	n	%	n	%	
SIG	0	98	41%	139	48%	157	51%	394	47%	0.287
	1	38	42%	103	60%	113	48%	254	52%	0.079
	2	20	60%	90	64%	85	58%	195	61%	0.651
	3	5	0%	57	70%	63	59%	125	62%	0.007
	4	1	100%	43	77%	45	80%	89	79%	0.813
	Total	162	43%	432	60%	463	55%	1057	55%	<0.001
	P	0.105		0.002		0.004		<0.001		
6.3e Low skeletal muscle density										
		TNM Stage								P
		I		II		III		Total		
		n	%	n	%	n	%	n	%	
SIG	0	98	58%	139	64%	157	61%	394	61%	0.644
	1	38	68%	103	70%	113	68%	254	69%	0.959
	2	20	80%	90	74%	85	68%	195	72%	0.472
	3	5	80%	57	72%	63	83%	125	78%	0.376
	4	1	100%	43	95%	45	89%	89	92%	0.508
	Total	162	64%	432	72%	463	70%	1057	70%	0.203
	P	0.275		0.003		<0.001		<0.001		

Table 6-4 Association between clinicopathological factors including CT-derived body composition and mode of presentation

Variable	Total	Elective	Emergency	p
Age	1057	846 (80%)	211 (20%)	0.004
<65	392 (37%)	293 (35%)	99 (47%)	
65-74	363 (34%)	304 (36%)	59 (28%)	
75+	302 (27%)	249 (29%)	53 (25%)	
Sex	1057	846 (80%)	211 (20%)	0.069
Male	545 (52%)	448 (53%)	97 (46%)	
Female	512 (48%)	398 (47%)	114 (54%)	
SIMD	1057	846 (80%)	211 (20%)	0.130
1	314(30%)	240 (28%)	74 (35%)	
2	221 (21%)	189 (22%)	32 (15%)	
3	172 (16%)	139 (16%)	33 (16%)	
4	161 (15%)	126 (15%)	35 (17%)	
5	189 (18%)	152 (18%)	37 (18%)	
Smoking	1035	831 (80%)	204 (20%)	<0.001
Non smoker	503 (49%)	411 (50%)	92 (45%)	
Ex-smoker	382 (37%)	321 (39%)	61 (30%)	
Smoker	150 (15%)	99 (12%)	51 (25%)	
ASA classification	1024	827 (81%)	197 (19%)	0.038
1	90 (9%)	73 (9%)	17 (9%)	
2	576 (56%)	480 (58%)	96 (49%)	
3	331 (32%)	256 (31%)	75 (38%)	
4	27 (3%)	18 (2%)	9 (5%)	
Tumour site	1048	840 (80%)	208 (20%)	0.704
Right	557 (53%)	444 (53%)	113 (54%)	
Left	491 (47%)	396 (47%)	95 (46%)	
TNM Stage	1057	846 (80%)	211 (20%)	<0.001
I	162 (15%)	158 (19%)	4 (2%)	
II	432 (41%)	334 (40%)	98 (46%)	
III	463 (44%)	354 (42%)	109 (52%)	
T Stage	1057	846 (80%)	211 (20%)	<0.001
1	88 (8%)	87 (10%)	1 (1%)	
2	113 (11%)	109 (13%)	4 (2%)	
3	509 (48%)	432 (51%)	77 (37%)	
4	347 (33%)	218 (26%)	129 (61%)	
N Stage	1057	846 (80%)	211 (20%)	0.021
0	594 (56%)	492 (58%)	102 (48%)	
1	295 (28%)	230 (27%)	65 (31%)	
2	168 (16%)	124 (15%)	44 (21%)	
Differentiation	1054	843 (80%)	211 (20%)	0.727
Mod/well	858 (81%)	688 (82%)	170 (81%)	
Poor	196 (19%)	155 (18%)	41 (19%)	
EMVI	1049	838 (80%)	211 (20%)	<0.001
Negative	560 (53%)	490 (36%)	70 (33%)	
Positive	489 (47%)	348 (42%)	141 (67%)	
SIG	1057	846 (80%)	211 (20%)	<0.001
0	394 (37%)	369 (44%)	25 (12%)	
1	254 (24%)	222 (26%)	32 (15%)	
2	195 (18%)	143 (17%)	52 (25%)	
3	125 (12%)	67 (8%)	58 (28%)	
4	88 (8%)	45 (5%)	44 (21%)	
BMI	1057	846 (80%)	211 (20%)	<0.001
≤25	395 (37%)	288 (34%)	107 (51%)	
>25	662 (63%)	558 (66%)	104 (49%)	
Superficial fat index	1057	846 (80%)	211 (20%)	<0.001
Normal	213 (20%)	151 (18%)	62 (29%)	
High	844 (80%)	695 (82%)	149 (71%)	
Visceral fat area	1057	846 (80%)	211 (20%)	<0.001

Normal	264 (25%)	186 (22%)	78 (37%)	
High	793 (75%)	660 (78%)	133 (63%)	
Skeletal muscle index	1057	846 (80%)	211 (20%)	<0.001
Normal	473 (45%)	410 (49%)	63 (30%)	
Low	584 (55%)	436 (52%)	148 (70%)	
Skeletal muscle density	1057	846 (80%)	211 (20%)	0..002
Normal	321 (30%)	275 (33%)	46 (22%)	
Low	736 (70%)	571 (68%)	165 (78%)	
Postoperative death	1057	846 (80%)	211 (20%)	0.417
No	1043 (99%)	836 (99%)	207 (98%)	
Yes	14 (1%)	10 (1%)	4 (2%)	
Survival (excluding 30-day mortality)	1043	836	207	
Overall survival	84% (1%)	86% (1%)	75% (3%)	<0.001
Cancer specific survival	88% (1%)	91% (1%)	78% (3%)	<0.001

Table 6-5 Association between mode of presentation and clinicopathological factors - MVA

Variable	OR (95% CI)	p
Age	0.62 (0.49-0.79)	<0.001
Sex	1.50 (1.03-2.19)	0.036
Smoking	-	0.497
ASA classification	-	0.320
T Stage	2.20 (1.62-3.00)	<0.001
N Stage	-	0.421
EMVI	1.68 (1.14-2.47)	0.008
SIG	1.82 (1.58-2.10)	<0.001
SFI	0.58 (0.37-0.89)	0.013
VO	-	0.184
SMI	1.85 (1.24-2.75)	0.002
SMD	-	0.207

Table 6-6 3-year overall survival stratified by SIG and body composition in TNM Stage II colon cancer

Subcutaneous fat index								
		Normal		High		Total		p
SIG	0	27	93% (SE 5%)	111	95% (SE 2%)	138	95% (SE 2%)	0.197
	1	25	92% (SE 5%)	78	90% (SE 3%)	103	90% (SE 3%)	0.866
	2	24	88% (SE 7%)	66	89% (SE 4%)	90	89% (SE 3%)	0.851
	3	10	60% (SE 15%)	46	90% (SE 5%)	56	84% (SE 5%)	0.001
	4	16	94% (SE 6%)	25	60% (SE 10%)	41	73% (SE 7%)	0.040
	Total	102	88% (SE 3%)	326	89% (SE 2%)	428	89% (SE 2%)	0.248
	p	0.003		<0.001		<0.001		
Visceral Fat Area								
		Normal		High		Total		p
SIG	0	26	96% (SE 4%)	112	95% (SE 2%)	138	95% (SE 2%)	0.735
	1	25	100%	78	87% (SE 4%)	103	90% (SE 3%)	0.680
	2	28	86% (SE 7%)	62	90% (SE 4%)	90	89% (SE 3%)	0.971
	3	18	83% (SE 9%)	38	84% (SE 6%)	56	84% (SE 5%)	0.082
	4	16	81% (SE 10%)	25	68% (SE 9%)	41	73% (SE 7%)	0.455
	Total	113	90% (SE 3%)	315	89% (SE 2%)	428	89% (SE 2%)	0.473
		0.011		<0.001		<0.001		
Skeletal Muscle Index								
		Normal		Low		Total		p
SIG	0	72	96% (SE 2%)	66	94% (SE 3%)	138	95% (SE 2%)	0.237
	1	41	88% (SE 5%)	62	92% (SE 3%)	103	90% (SE 3%)	0.866
	2	32	94% (SE 4%)	58	86% (SE 5%)	90	89% (SE 3%)	0.008
	3	17	88% (SE 8%)	39	82% (SE 6%)	56	84% (SE 5%)	0.649
	4	10	90% (SE 9%)	31	68% (SE 8%)	41	73% (SE 7%)	0.220
	Total	172	92% (SE 2%)	256	87% (SE 2%)	428	89% (SE 2%)	0.001
	p	0.135		0.002		<0.001		
Skeletal Muscle Density								
		Normal		Low		Total		p
SIG	0	50	98% (SE 2%)	88	93% (SE 3%)	138	95% (SE 2%)	0.425
	1	31	97% (SE 3%)	72	88% (SE 4%)	103	90% (SE 3%)	0.023
	2	23	96% (SE 4%)	67	87% (SE 4%)	90	89% (SE 3%)	0.088
	3	16	94% (SE 6%)	40	80% (SE 6%)	56	84% (SE 5%)	0.044
	4	2	-	39	72% (SE 7%)	41	73% (SE 7%)	0.226
	Total	122	97% (SE 2%)	306	86% (SE 2%)	428	89% (SE 2%)	<0.001
	p	0.855		<0.001		<0.001		

Table 6-7 3-year overall survival stratified by SIG and body composition in TNM Stage III colon cancer

Subcutaneous fat index								
		Normal		High		Total		p
SIG	0	25	76% (SE 9%)	129	84% (SE 3%)	154	83% (SE 3%)	0.328
	1	19	79% (SE 9%)	92	79% (SE 4%)	111	79% (SE 4%)	0.771
	2	14	50% (SE 13%)	69	78% (SE 5%)	83	73% (SE 5%)	0.167
	3	15	67% (SE 12%)	47	64% (SE 7%)	62	65% (SE 6%)	0.757
	4	13	38% (SE 13%)	30	63% (SE 9%)	43	56% (SE 8%)	0.022
	Total	86	65% (SE 5%)	367	78% (SE 2%)	453	75% (SE 2%)	0.029
	p	0.006		0.023		<0.001		
Visceral Fat Area								
		Normal		High		Total		p
SIG	0	36	81% (SE 7%)	118	84% (SE 3%)	154	83% (SE 3%)	0.559
	1	24	71% (SE 9%)	87	82% (SE 4%)	111	79% (SE 4%)	0.532
	2	21	52% (SE 11%)	62	81% (SE 5%)	83	73% (SE 5%)	0.026
	3	15	67% (SE 12%)	47	64% (SE 7%)	62	65% (SE 6%)	0.934
	4	18	50% (SE 12%)	25	60% (SE 10%)	43	56% (SE 8%)	0.390
	Total	114	67% (SE 4%)	339	78% (SE 2%)	453	75% (SE 2%)	0.024
	p	0.055		0.014		<0.001		
Skeletal Muscle Index								
		Normal		Low		Total		p
SIG	0	75	85% (SE 4%)	79	81% (SE 4%)	154	83% (SE 3%)	0.610
	1	59	85% (SE 5%)	52	73% (SE 6%)	111	79% (SE 4%)	0.027
	2	36	69% (SE 8%)	47	77% (SE 6%)	83	73% (SE 5%)	0.436
	3	26	54% (SE 10%)	36	72% (SE 7%)	62	65% (SE 6%)	0.377
	4	8	-	35	54% (SE 8%)	43	56% (SE 8%)	0.266
	Total	204	77% (SE 3%)	249	73% (SE 3%)	453	75% (SE 2%)	0.091
	p	0.004		0.013		<0.001		
Skeletal Muscle Density								
		Normal		Low		Total		p
SIG	0	61	89% (SE 4%)	93	80% (SE 4%)	154	83% (SE 3%)	0.323
	1	36	92% (SE 5%)	75	73% (SE 5%)	111	79% (SE 4%)	0.075
	2	26	81% (SE 8%)	57	70% (SE 6%)	83	73% (SE 5%)	0.091
	3	11	55% (SE 15%)	51	67% (SE 7%)	62	65% (SE 6%)	0.986
	4	5	-	38	55% (SE 8%)	43	56% (SE 8%)	0.532
	Total	139	84% (SE 3%)	314	71% (SE 3%)	453	75% (SE 2%)	0.001
	p	0.319		0.010		<0.001		

6.6 Figures

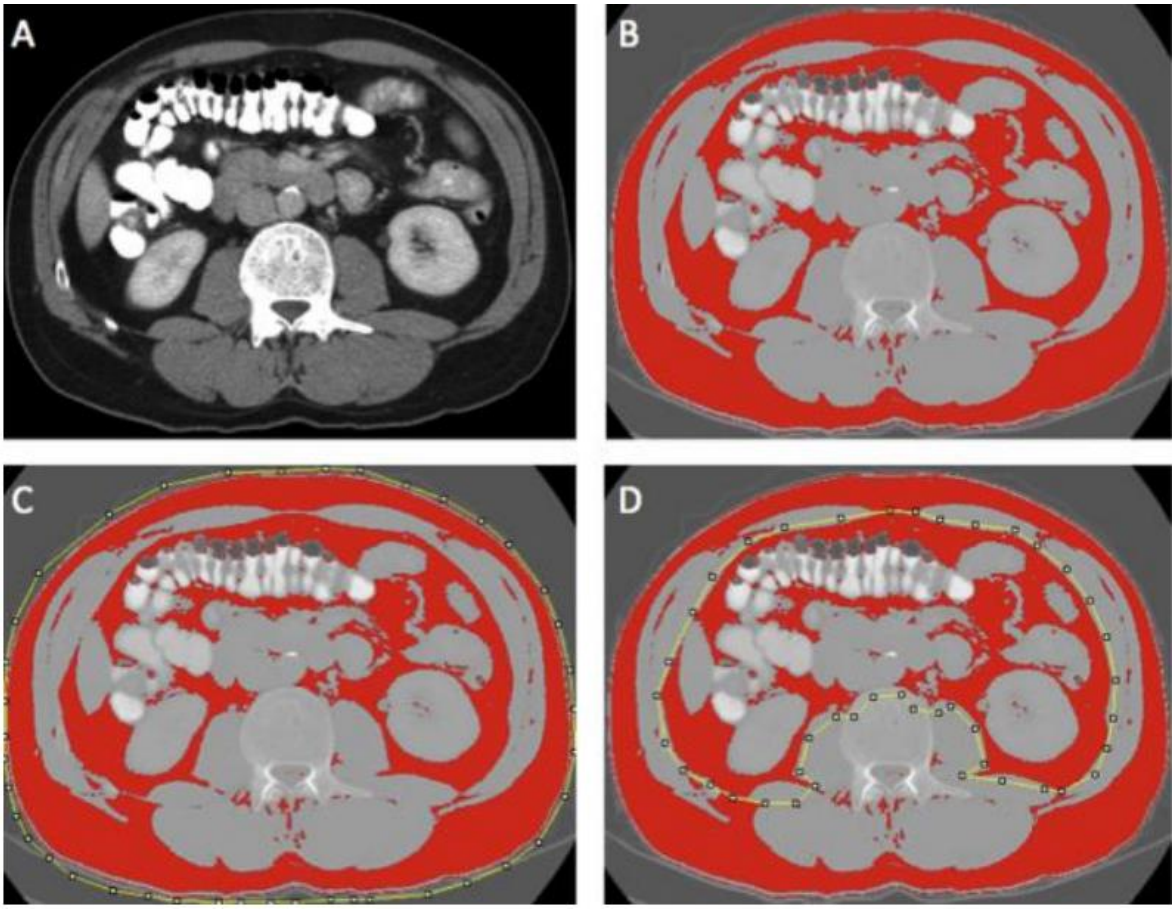


Figure 6-1 – The use of ImageJ for analysis of total/visceral fat area (A) Axial CT slice at L3 level in portal venous phase, (B) Threshold selection of adipose tissue, (C) Region of interest selection for total fat area, (D) Region of interest selection for visceral fat area

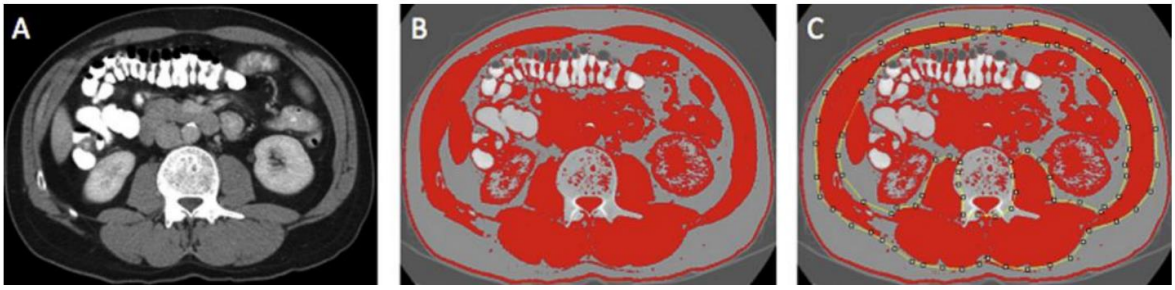


Figure 6-2 – The use of ImageJ for analysis of skeletal muscle area/density (A) Axial CT slice at L3 level in portal venous phase, (B) Threshold selection of skeletal muscle, (C) Region of interest selection for skeletal muscle mass/density

7 Chapter 7 - An Investigation Into the Association Between Bowel Screening, Mode of Presentation and Short-Term/Long-Term Survival in Colon Cancer

7.1 Introduction

As described within Chapter 1, bowel cancer screening programmes are now well established within the developed world[139,140] with the aim of: diagnosing and removing advanced polyps at a premalignant stage, identifying early-stage disease and reducing the proportion of emergency presentations. Available modalities of screening have been summarised in a recent review[311]. Currently, the most common first-line screening test is through the detection of blood in faecal samples either through guaiac based faecal occult blood testing (gFOBT) or, increasingly, faecal immunochemical testing (FIT). In a previous Cochrane review, screening programmes were reported to have a colorectal cancer mortality relative risk reduction of 15% overall and 25% following exclusion of non-responders[312]. The European guidelines for quality assurance in colorectal cancer screening and diagnosis recommend a minimum uptake to screening of 45% and desirable uptake of 65%[313] of the target population; however, to date participation has remained suboptimal at 50-60%. Some subsets of the population, particularly those of low socio-economic status, have been shown to have particularly poor engagement with screening[134,142,314,315].

Within Scotland, all adults aged between 50 and 74 years are routinely invited to participate in biennial bowel screening. Adults aged over 74, while not being routinely invited are eligible to continue to participate. This programme was rolled out nationally from 2007 and aims to have a minimum uptake of 60%[315]. Before 2017, gFOBT was the first-line screening test with positive results progressing to endoscopic investigation and borderline results progressing to FIT testing. Since 2017, FIT testing has been used as the first-line investigation. Previous literature suggests that the current participation rate is approximately 57% with a further 8% of patients with a positive screening sample failing to undergo further investigation[230]. Despite this, a significant reduction in both the proportion of patients diagnosed with late-stage disease and the proportion of emergency presentations following introduction of the bowel screening programme has been reported – 20% pre-screening versus 13% in the post screening cohort ($p<0.001$)[134]. However, a recent study that excluded individuals who did not participate in the bowel screening programme has suggested that the rate of emergency presentation could be reduced to as low as 5%[135] therefore there remains potential for significant improvement within the screening service.

Multiple studies have examined screening cohorts as a whole; however, the majority of these have failed to capture patients diagnosed with colorectal cancer outwith screening. In the present study, we aim to investigate the relationship between patients diagnosed with colorectal cancer in the West of Scotland and their involvement in the most recent round of screening within 2 years before diagnosis. Furthermore, we aim to identify which clinicopathological characteristics are associated with failure to progress through each stage of the screening programme and examine the relationship

between screening diagnosis and TNM Stage, mode of presentation and long-term outcomes in colorectal cancer. Finally, the present study analyses the associations between mode of presentation (elective-screening/elective-symptomatic/emergency) and clinicopathological factors discussed previously including the systemic inflammatory response and CT-derived body composition within a subcohort of patients undergoing resectional surgery with curative intent for TNM I-III colon cancer.

7.2 Methods

All patients diagnosed with colorectal cancer in the West of Scotland between January 2011 and December 2014 were identified as described in Chapter 3. Clinicopathological factors including comorbidity, the systemic inflammatory response and CT-derived body composition were defined as described in Chapters 4, 5 and 6. Overall and cancer-specific survival was defined as described in Chapter 3 however within the present study survival was calculated from date of diagnosis until date of death. All patients were followed up for a minimum of 4 years from diagnosis.

Through data linkage to the Scottish Bowel Screening Programme (SBoSP) dataset, the interaction of each patient with the most recent round of screening (within 2 years before diagnosis of colorectal cancer) was analysed. Engagement with the bowel screening programme was categorised as invited (yes/no), return of screening sample (yes/no), return of valid screening sample (yes/no), screening stool sample result (positive/negative), further investigation (yes/no) and diagnosis of cancer (yes/no). Further data were also available including the date of investigation and screening test used (gFOBT/FIT). Being before 2017, this patient population underwent first-line screening through the gFOBT test. Patients with positive tests progressed to endoscopic investigation. Patients with a borderline gFOBT underwent FIT with positive FIT subsequently progressing to endoscopic investigation. Screening was routinely offered to patients aged between 50 and 74 years. Patients aged 75 years and older were not routinely sent screening tests but were able to request them.

Ethical approval was granted for this project from the Public Benefit and Privacy Panel (NHS Scotland) for Health and Social Care (PBPP).

7.2.1 Statistical Analysis

The relationship between clinicopathological characteristics and interaction with each stage of the bowel screening programme was analysed using the Chi squared test. Three-year survival was calculated using the life table function of SPSS and results were displayed as percentage 3-year survival and percentage standard error. Statistical significance was calculated using the log-rank test.

Statistical analysis was carried out using IBM SPSS Statistics for Windows Version 27 (IBM Corporation, Armonk, New York, USA). A two-tailed p-value of <0.05 was considered significant throughout.

7.3 Results

Within the study period of January 2011-December 2014, 6549 patients were diagnosed with colorectal cancer in the West of Scotland, 4113 of whom were invited to participate in the bowel screening programme. Most patients presented electively (83%) with TNM Stage II (29%) or TNM Stage III (30%) disease. 77% of patients underwent either a curative or palliative procedure. During the follow-up period, there were 3519 deaths, 69% of which were cancer related.

7.3.1 Interaction With the Screening Programme

As shown in Figure 7-1, 6549 patients were diagnosed with colorectal cancer in the West of Scotland from January 2011 to December 2014. 19% of these patients (n=1217) were diagnosed through screening. Reasons for failure to diagnose through screening included: no invitation to screening (37%, n=2436), patient invited to screening but no valid sample returned (29%, n=1884), valid sample returned however negative result (12%, n=844), positive sample returned but no further investigation (2%, n=137) or further investigation but no malignancy found (0.5%, n=31).

7.3.2 Association Between Screening Diagnosis and Clinicopathological Factors

The association between screening diagnosis and clinicopathological factors including mode of presentation, treatment type and survival is shown in Table 7-1. Of host factors, screening diagnosis was associated with age <75 years, male sex, lower socio-economic deprivation, less comorbid status (as measured by both ASA classification and Charlson score) and non-smokers (all $p<0.001$). Of tumour factors, patients diagnosed through screening had less advanced, well-moderately differentiated tumours without extramural venous invasion (all $p<0.001$). Right-sided tumours were less likely to be diagnosed through screening ($p<0.001$). Those patients diagnosed through screening were more likely to undergo elective procedures with resectional surgery (both $p<0.001$). As shown in Figure 7-2, diagnosis through screening was associated with a significantly improved 3-year overall survival (86% vs 51%, $p<0.001$) and cancer specific survival (90% vs 58%, $p<0.001$).

7.3.3 Non-Invitation to Screening

Of the 6549 patients diagnosed with colorectal cancer during the study period, 37% (n=2436) had not been invited to participate in screening. As shown in Table 7-2, of those patients not invited, 14% (n=350) were below the age threshold for screening of whom 79% were aged between 40 and 49 years (n=277). 84% of patients (n=2035) were above the upper limit of routine invitation to screening. When patient age was categorised by decade, 27%, 64% and 9% were aged 75-79,

80-89 and 90+ years old respectively. The reason for non-invitation to screening for the remaining 2% (n=51) of patients was uncertain.

7.3.4 Non-Return of Screening Test

Of 4113 patients invited to participate in the bowel cancer screening programme, 46% (n=1884) of patients failed to return a valid stool sample. One patient returned a screening test; however, the sample container had expired, and the remaining 1883 patients failed to return a test. The association between clinicopathological factors and return versus non-return of the screening test is shown in Table 7-3. Patients aged between 65 and 74 years ($p<0.001$), female patients ($p<0.001$), patients of a higher socio-economic status ($p<0.001$), patients with a less comorbid status as measured by both ASA classification and Charlson score ($p<0.001/0.030$, respectively), non-smokers ($p<0.001$) and patients with an increased BMI ($p=0.007$) were more likely to return a screening test. No significant association was seen between ethnicity and non-return of a screening test ($p=0.574$).

7.3.5 Return of a Negative Screening Test

Of the 2229 patients who returned a valid stool sample, 38% (n=844) returned a negative sample. The association between clinicopathological factors and screening test result is shown in Table 7-4. Female sex ($p<0.001$), BMI $<30kg/m^2$ ($p=0.002$), increased comorbidity as measured by Charlson Score ($p=0.002$), preoperative anaemia ($p<0.001$), poorly differentiated tumours ($p<0.001$),

extramural venous invasion (p=0.001), right-sided cancers (p<0.001) and patients screened using gFOBT (p<0.001) were associated with negative screening results.

7.3.6 Return of a Positive Sample But No Further Investigation

Of the 1385 patients who had a positive screening test, 90% underwent further investigation. Of the 10% of patients (n=137) who did not undergo further investigation, the reason for this could not be established in 51 patients. For the remaining 86 patients, this was either a patient decision (44%, n=18), patient did not attend (21%, n=18), patient already under endoscopic surveillance (19%, n=6), clinician decision (15%, n=13) or the patient died while waiting for further investigation (1%, n=1).

7.3.7 Further Investigation But Cancer Not Diagnosed

Thirty-one patients (2%) had a negative colonoscopy after a positive screening test. Colonoscopies were complete in twenty patients, incomplete in three patients and no results were available for the remaining eight patients.

7.3.8 Subgroup Analysis of Patients Undergoing Resectional Surgery With Curative Intent for TNM I-III Colon Cancer

A subgroup analysis has been performed within patients undergoing curative resectional surgery for TNM I-III colon cancer. This subgroup analysis (Table 7-5)

compares the association between screening versus non-screening diagnosis and Systemic Inflammatory Grade and CT derived body composition.

For all patients undergoing resectional surgery with curative intent for TNM I-III colon cancer, screening diagnosis was associated with a lower Systemic Inflammatory Grade ($p<0.001$), high subcutaneous fat index ($p<0.001$), high visceral fat area ($p<0.001$), normal/high skeletal muscle index ($p<0.001$) and normal/high skeletal muscle density ($p<0.001$).

For all patients of routine screening age (50-74) undergoing resectional surgery with curative intent for TNM Stage I-III colon cancer, screening diagnosis was associated with a lower Systemic Inflammatory Grade ($p<0.001$), high subcutaneous fat index ($p<0.001$), high visceral fat area ($p<0.001$), normal/high skeletal muscle index ($p<0.001$) and normal/high skeletal muscle density ($p<0.001$).

For all patients of routine screening age (50-74 years) undergoing resectional surgery with curative intent on an elective basis for TNM Stage I-III colon cancer, screening diagnosis was associated with a lower Systemic Inflammatory Grade ($p<0.001$), high subcutaneous fat index ($p=0.002$), high visceral fat area ($p=0.007$), normal/high skeletal muscle index ($p<0.001$) and normal/high skeletal muscle density ($p=0.014$).

7.4 Discussion

The results of the present study show that during the study period, only 19% of colorectal cancer in the West of Scotland was diagnosed through screening and 50% of patients invited to screening fully participated in the screening process. Patients diagnosed through the bowel cancer screening programme were more likely to present electively with early-stage (TNM Stage I-II) disease and undergo curative resectional surgery with significantly better oncological outcomes than patients diagnosed outwith screening. Screening is not only associated with better tumour characteristics but is also associated with better host characteristics, particularly in terms of a lesser systemic inflammatory response and increased proportion of lean muscle and therefore there appears to be a role for screening both in screening the tumour and also in screening the host.

The present results show that despite the current stool-based bowel cancer screening programme being simple, safe and non-invasive, engagement with screening within the West of Scotland remains poor. Uptake to screening within Scotland is similar to that in England and Wales as reported in the National Bowel Cancer Audit 2020 – 60% and 57% respectively[316]. However, within the present study a higher proportion of patients were diagnosed through the Bowel Screening Programme than reported within the National Bowel Cancer Audit 2020 within England and Wales (19% versus 10%), likely due to the wider age range eligible for screening within Scotland compared to England and Wales (50-74 versus 60-74 years). Nonetheless, the proportion of patients diagnosed with colorectal cancer at TNM Stage I-II remains far short of the 75% target set within the NHS Long Term Plan[317], therefore, optimisation of services are required to meet this target. Within the present study, one in five patients had metastatic disease at the time of diagnosis and of those with full TNM staging, 50% of

patients had TNM Stage III-IV disease. The incidence of colorectal cancer (currently 1.9 million cases each year globally) has been predicted to double over the next 10-20 years[1]. A significant survival advantage was seen in patients diagnosed through screening (3-year CSS – 90% versus 58%, p<0.001). Optimisation of the screening service remains perhaps the most promising way of improving outcomes in patients with colorectal cancer.

Although traditionally considered a disease of high HDI (Human Development Index) nations, likely due to dietary and lifestyle factors, the incidence of colorectal cancer in low HDI countries has more recently been reported to be increasing, likely due to Western lifestyle changes and increasing life expectancy. Meanwhile, within some high HDI countries, the incidence has been reported to be decreasing, in part due to the introduction of screening programmes aimed not just at diagnosing colorectal cancer at an early malignant stage but also within the premalignant polyp phase[318]. Outcomes have been reported to be significantly worse in low compared to high HDI nations. This is, amongst other factors, the result of limited access to healthcare and late stage at diagnosis (in part due to the absence of screening programmes)[319]. As summarized in a recent review, the implementation of screening programmes within low HDI nations undoubtedly carries additional challenges[320]; however remains an opportunity to increase the proportion of patients diagnosed at early stage with improved oncological outcomes, particularly where access to adjuvant/palliative chemotherapy may be limited. Furthermore, although the establishment of such programmes will increase the burden on endoscopy services, increased detection and management of premalignant polyps may reduce the number of people requiring resectional surgery +/- adjuvant therapy. The present findings are therefore applicable to both high and low HDI nations.

In 1966, Wilson and Jungner described multiple factors that must be considered when stablishing a screening service, both in terms of the health condition screened for and the population in whom to screen.[138] Many of the factors lie outwith the scope of this study. Nonetheless, within the present study, 351 patients (5%) were diagnosed below the screening age of whom 79% were aged 40-49 years. It has been reported that an increasing number of younger people (age <50 years) are developing colorectal cancer[321,322], often with poorer outcomes and it would therefore seem reasonable to consider lowering the minimum age for screening with Scotland. Indeed, several sources including the American Cancer Society[323] and the US Preventative Services Task Force[324] advocate the inclusion of patients aged between either 45-50 or 40-50 years into bowel cancer screening. Previous research has suggested that the reduction of screening age from 50 to 45 years of age is cost effective[325] and avoids 4 cases of colorectal cancer, 2 colorectal cancer deaths and gains 14 quality-adjusted life years per 1000 people screened. However, this study was in the American population with a different healthcare system to the United Kingdom and may not be directly applicable elsewhere. Furthermore, a large proportion of patients diagnosed with bowel cancer were above the upper age limit for routine invitation to screening although these patients were still eligible to request screening tests. As described by Nee and Colleagues[326] the inclusion of older people within screening is more complex and the benefits of screening depend on several factors including comorbid and functional status. Within the present study, fewer than 10% of patients over 75 years returned a screening sample. Despite this, a large proportion of these patients subsequently underwent curative resectional surgery and it therefore seems reasonable that older

individuals in good health should be encouraged to continue to participate in screening.

Within the present study, non-return of screening sample was a major factor precluding screening diagnosis – fewer than 55% of patients invited for screening returned a screening sample and this remains below international guidelines[313]. The reason for non-engagement in screening is likely to be multifactorial. Although the precise reason for non-engagement requires more detailed qualitative investigation, the present study described several factors associated with non-return of screening test in particular: older age, male sex, less affluent socio-economic status, current smokers, patients with a low-normal BMI and patients with an increased comorbid status. Prior research has investigated factors influencing return versus non-return of bowel screening samples and factors including: lower educational achievement, lower socio-economic status, fear of cancer diagnosis, reluctance to handle faecal samples and a lack of knowledge regarding the benefits of early asymptomatic detection were reasons for non-engagement with screening[327-331]. It is of interest that this association with socio-economic status remains within the free at point of care National Health Service. The effect of sex on screening participation remains unclear. Although the present results show that females are more likely to engage with screening, a previous review by Mosquera and colleagues[332] reported significant variation between studies and offered several hypotheses for the discrepancies observed. Despite screening aiming to identify colorectal cancer within the asymptomatic population, there have been reports of a public perception that screening is only required if symptoms are experienced[333]. It seems likely that improved education may increase the participation rate within screening and prior research is supportive of this hypothesis[334]. The Scottish Bowel Screening

Programme has recently transitioned from using gFOBT (requiring two stool samples on three separate occasions) to FIT (requiring a single stool sample). This may result in an increased uptake to screening although this effect is likely to be modest[335]. Further measures are required to encourage patient participation, and these should be targeted at particular groups including those of increased socio-economic deprivation. However, there is potential to significantly improve screening uptake across the entire population and measures should not be restricted to such individuals. A recent study summarised barriers and facilitators to screening[336] and addressing these factors with measures including reminder letters and improved education is likely to improve screening participation.

The present results show that a significant proportion of screening tests returned within 2 years before colorectal cancer diagnosis were negative. Although some of these may represent true-negative tests (and therefore true interval cancers), it seems likely that the majority of these are false-negative results. It is recognised that gFOBT (used as the first-line investigation in the era of the present study) is less sensitive than FIT (first-line investigation since 2017), particularly in right-sided disease[337,338]. Therefore, it would be of interest to repeat the present study in the screening via FIT era. One would expect the false-negative rate to be significantly lower in such a study. Unlike Scotland, countries including Germany and the USA use periodic endoscopic evaluation in addition to stool sampling within their screening programmes. Should false-negative rates remain high within a population who had previously underwent screening via FIT such periodic endoscopic evaluation may be worth considering or a reduction in the abnormal threshold of FIT used for screening. The present results shown an association between right sided tumours and negative screening

results. This finding is in keeping with previous literature[339]. This may be the result of degradation of haemoglobin during colonic passage or due to blood from left sided lesions being more likely to be on the stool surface as opposed to mixed through the stool[340]. Within the present results, poorly differentiated tumours and extramural venous invasion were associated with cancers diagnosed outwith bowel screening. This is likely to be due to the increased proportion of right-sided cancers and more advanced disease within these patients. There may be other factors associated with the higher false negative rate of gFOBT/FIT tests in right sided cancers. Right and left sided colon cancers are now recognised to represent markedly different biological entities in terms of tumour characteristics and mutational factors. It may be that these factors impact on the fragility of a tumour and likelihood of bleeding and therefore positive stool sample. This association has not previously been investigated and would be of interest in future work.

Data, predominantly from the USA have described an association between ethnic minority status and reduced likelihood of participation within screening. Owing to the healthcare system in the USA, socio-economic deprivation may be a contributing factor in these studies; therefore the route to diagnosis of colorectal cancer across ethnicities was of interest in the free at point of care health service in Scotland. However, because of the small proportion of patients who were non-white British, it was not possible to accurately analyse this. 92% of the Scottish population in the 2011 census identified as white British. It has been shown that colorectal cancer is less common within several ethnic minority groups[341] (43); however, it is unclear whether this is sufficient to explain the lower proportion of patients diagnosed with colorectal cancer within this study. Notably, there was a significant quantity of missing ethnicity data raising the

possibility of reporting bias particularly as a recent study within Scotland did find lower screening uptake within ethnic minority populations[342]. Nonetheless, because of the small proportion of patients of ethnic minority status, the present study is likely underpowered to reliably make the comparison between ethnic minority status and screening involvement before cancer diagnosis.

The present study has several limitations. The cohort of patients included within the present study were from an era where gFOBT was used as the first-line screening test. Scotland has now transitioned from gFOBT to FIT although many countries worldwide still use gFOBT for screening. Although it would be of interest to repeat such a study in patients screened using FIT, the results of the present study remain applicable to current practice. However, there is likely to be a smaller proportion of "false negative" screening tests and potentially an improved uptake of screening as a result of this transition. Within the present study, we have analysed the results of the screening round within 2 years before diagnosis of colorectal cancer. In our comparison of factors associated with negative screening test results, negative results have been assumed to be false negatives. Bowel screening aims to detect not just carcinomas but additionally advanced polyps. Given the duration of the adenoma-carcinoma sequence, this assumption is likely to be predominantly correct; however, it is impossible to know which of these tests were false-negative results and which were true interval cancers. True interval cancers may be more aggressive in nature and this variation in disease biology may therefore impact on the survival difference seen between screening and non-screening cancers. Furthermore, the unadjusted difference in survival seen between screening and non-screening presentations may be confounded by other lifestyle related factors, age and co-morbidity. Given the association seen between screening test result and the type

of test used (gFOBT/FIT), this would be in keeping with the assumption that a significant proportion of negative FOBT tests were false negatives. FIT has been widely reported to have a higher sensitivity than gFOBT. However, given that the majority of patients who received a FIT test had a prior borderline gFOBT as opposed to being randomly allocated either gFOBT or FIT, this assumption may be biased. Finally, in the present study, the association between screening versus non-screening diagnosis and 3-year survival has been reported.

In conclusion, the present study shows that colorectal cancer diagnosed through screening is associated with improved oncological outcomes. This is due to both favourable tumour factors (earlier stage, elective presentations) and favourable host factors (less inflamed, higher lean muscle mass). However, less than one in five cases of colorectal cancer within the West of Scotland were diagnosed through screening. 37% of patients were not invited for screening, predominantly those above the age for routine invitation or within the 40-49 years age group. 29% of patients had not returned a screening sample, in particular: males with increased socio-economic deprivation or more comorbid patients. 13% of patients had returned a negative screening sample (likely false negative) within 2 years before diagnosis, in particular: female patients, patients with a BMI<30, patients with anaemia, right-sided tumours, patients who had a gFOBT test and patients with poorly differentiated tumours or tumours with extramural venous invasion. Further measures are required to educate the population about the benefits of screening to increase engagement with the screening process and to encourage patients aged 75+ years who are in otherwise good health to continue to participate in screening. Consideration should be given to extending screening to individuals aged between 40 and 50 years. Finally, further analysis should be

carried out within a FIT screening cohort to determine whether the false negative rate remains high.

7.5 Tables

Table 7-1 Association between screening diagnosis and tumour stage, mode of presentation, treatment type and survival

Variable	All patients	Non-screening diagnosis	Screening diagnosis	p
Total	6549	5332 (81%)	1217 (19%)	
Age (years)	6549	5332 (81%)	1217 (19%)	<0.001
<50	350 (5%)	350 (7%)	0 (0%)	
50-74	3943 (60%)	2727 (51%)	1216 (>99%)	
75+	2256 (34%)	2255 (42%)	1 (<1%)	
Sex	6549	5332 (81%)	1217 (19%)	<0.001
Male	3643 (56%)	2887 (54%)	756 (62%)	
Female	2906 (44%)	2445 (46%)	461 (38%)	
SIMD	6549	5332 (81%)	1217 (19%)	<0.001
1 (most deprived)	1871 (29%)	1570 (29%)	301 (25%)	
2	1509 (23%)	1251 (24%)	258 (21%)	
3	1129 (17%)	923 (17%)	206 (17%)	
4	1004 (15%)	782 (15%)	222 (18%)	
5 (least deprived)	1036 (16%)	806 (15%)	230 (19%)	
ASA classification	4440	3425 (77%)	1015 (23%)	<0.001
1	474 (11%)	330 (10%)	144 (14%)	
2	2342 (53%)	1706 (50%)	636 (63%)	
3	1395 (31%)	1171 (34%)	224 (22%)	
4	223 (5%)	213 (6%)	10 (1%)	
5	6 (<1%)	5 (<1%)	1 (<1%)	
Smoking	3523	2724 (77%)	799 (23%)	0.001
Non smoker	1638 (47%)	1256 (46%)	382 (48%)	
Ex-smoker	1353 (38%)	1025 (38%)	328 (41%)	
Smoker	532 (15%)	443 (16%)	89 (11%)	
BMI measurement	2498	1874 (75%)	624 (25%)	<0.001
<18.5	58 (2%)	51 (3%)	7 (1%)	
18.5-24.9	795 (32%)	644 (34%)	151 (24%)	
25-29.9	897 (36%)	679 (36%)	218 (35%)	
30-34.9	492 (20%)	337 (18%)	155 (25%)	
35+	256 (10%)	163 (9%)	93 (15%)	
Charlson score	2657	1990 (75%)	667 (25%)	<0.001
0	1561 (59%)	1104 (56%)	457 (69%)	
1	737 (28%)	572 (29%)	165 (25%)	
2	289 (11%)	255 (13%)	34 (5%)	
3+	70 (3%)	59 (3%)	11 (2%)	
Ethnicity	3341	2688 (81%)	653 (20%)	0.655
White British	3283 (98%)	2640 (98%)	643 (99%)	
Other	58 (2%)	48 (2%)	10 (2%)	
Preoperative anaemia	3051	2377 (78%)	674 (22%)	<0.001
No	1701 (56%)	1168 (49%)	533 (79%)	
Yes	1350 (44%)	1209 (51%)	141 (21%)	
Differentiation	5740	4564 (80%)	1176 (21%)	<0.001
Well-mod	4688 (82%)	3664 (80%)	1024 (87%)	
Poor	1052 (18%)	900 (20%)	152 (13%)	
EMVI	4350	3325 (76%)	1025 (24%)	<0.001
Negative	2579 (59%)	1856 (56%)	723 (71%)	
Positive	1771 (41%)	1469 (44%)	302 (30%)	
Tumour site	6549	5332 (81%)	1217 (19%)	0.450
Colon	4611 (70%)	3765 (71%)	846 (70%)	
Rectal	1938 (30%)	1567 (29%)	371 (31%)	

Colon tumour side	**4524**	**3684 (81%)**	**840 (19%)**	**<0.001**
Right	**2363 (52%)**	**2038 (55%)**	**325 (39%)**	
Left	**2161 (48%)**	**1646 (45%)**	**515 (61%)**	
Screening test type	**2229**	**1012 (45%)**	**1217 (55%)**	**<0.001**
gFOBT	**1188 (53%)**	**822 (81%)**	**366 (30%)**	
FIT	**1041 (47%)**	**190 (19%)**	**851 (70%)**	
TNM	**5402**	**4268 (79%)**	**1134 (21%)**	**<0.001**
I	**1195 (22%)**	**732 (17%)**	**463 (41%)**	
II	**1575 (29%)**	**1281 (30%)**	**294 (26%)**	
III	**1598 (30%)**	**1284 (30%)**	**314 (28%)**	
IV	**1034 (19%)**	**971 (23%)**	**63 (6%)**	
Metastatic at presentation	**6382**	**5175 (81%)**	**1207 (19%)**	**<0.001**
No	**5002 (78%)**	**3877 (75%)**	**1125 (93%)**	
Yes	**1380 (22%)**	**1298 (25%)**	**82 (7%)**	
Mode of presentation	**5193**	**4033 (78%)**	**1160 (22%)**	**<0.001**
Elective	**4307 (83%)**	**3161 (78%)**	**1146 (99%)**	
Emergency	**886 (17%)**	**872 (22%)**	**14 (1%)**	
Type of procedure	**6542**	**5325 (81%)**	**1217 (19%)**	**<0.001**
No procedure	**1516 (23%)**	**1452 (27%)**	**64 (5%)**	
Bypass/stent/defunctioning surgery	**358 (6%)**	**345 (7%)**	**13 (1%)**	
Local resection	**337 (5%)**	**199 (4%)**	**138 (11%)**	
Formal resection	**4331 (66%)**	**3329 (63%)**	**1002 (82%)**	
3-year survival (all patients)	**6549**	**5332**	**1217**	
OS	**58% (SE 1%)**	**51% (SE 1%)**	**86% (SE 1%)**	**<0.001**
CSS	**64% (SE 1%)**	**58% (SE 1%)**	**90% (SE 1%)**	**<0.001**

Table 7-2 Characteristics of patients not invited to participate in screening (n=2436)

Total number of patients	2436
Below screening age (<50)	351
18-29	24 (7%)
30-39	49 (14%)
40-49	277 (79%)
Above screening age (75+)	2035
75-79	543 (27%)
80-89	1311 (64%)
90+	181 (9%)
Unknown	51

Table 7-3 Association between clinicopathological characteristics and return vs non return of screening sample in patients invited to screening (n=4113)

Clinicopathological factor	Total n (%)	Returned screening test n (%)	Non-return of screening test n (%)	p
Total	4113	2230 (54%)	1883 (46%)	
Age	4113	2230 (54%)	1883 (46%)	<0.001
<65	1604 (39%)	859 (39%)	745 (40%)	
65-74	2026 (49%)	1155 (52%)	871 (46%)	
75+	483 (12%)	216 (10%)	267 (14%)	
Sex	4113	2230 (54%)	1883 (46%)	<0.001
Male	2422 (59%)	1252 (56%)	1170 (62%)	
Female	1691 (41%)	978 (44%)	713 (38%)	
SIMD	4113	2230 (54%)	1883 (46%)	<0.001
1 (most deprived)	1207 (29%)	559 (25%)	648 (34%)	
2	948 (23%)	474 (21%)	474 (25%)	
3	685 (17%)	371 (17%)	314 (17%)	
4	630 (15%)	390 (18%)	240 (13%)	
5 (least deprived)	643 (16%)	436 (20%)	207 (11%)	
ASA classification	3089	1784 (58%)	1305 (42%)	<0.001
1	348 (11%)	234 (13%)	114 (9%)	
2	1752 (57%)	1090 (61%)	662 (51%)	
3	884 (29%)	434 (24%)	450 (35%)	
4	101 (3%)	25 (1%)	76 (6%)	
5	4 (<1%)	1 (<1%)	3 (<1%)	
Smoking	2417	1413 (59%)	1004 (42%)	<0.001
Non smoker	1085 (45%)	670 (47%)	415 (41%)	
Ex-smoker	913 (38%)	568 (40%)	345 (34%)	
Smoker	419 (17%)	175 (12%)	244 (24%)	
BMI	1809	1093 (60%)	716 (40%)	0.007
<18.5	33 (2%)	13 (1%)	20 (3%)	
18.5-24.9	521 (29%)	293 (27%)	228 (32%)	
25-29.9	655 (36%)	401 (37%)	254 (36%)	
30-34.9	378 (21%)	242 (22%)	136 (19%)	
35+	222 (12%)	144 (13%)	78 (11%)	
Charlson score	1821	1108 (61%)	713 (39%)	0.030
0	1157 (64%)	729 (66%)	428 (60%)	
1	459 (25%)	271 (25%)	188 (26%)	
2	166 (9%)	86 (8%)	80 (11%)	
3+	39 (2%)	22 (2%)	17 (2%)	
Ethnicity	2123	1196 (56%)	927 (44%)	0.574
White British	2090 (98%)	1179 (99%)	911 (98%)	
Other	33 (2%)	17 (1%)	16 (2%)	

Table 7-4 Association between clinicopathological factors and screening test result in those who returned valid screening test (n=2229)

Clinicopathological factor	Total	Negative screening test n (%)	Positive screening test n (%)	p
Total	2229	844 (38%)	1385 (62%)	
Age	2229	844 (38%)	1385 (62%)	0.147
<65	859 (39%)	304 (36%)	555 (40%)	
65-74	1154 (52%)	452 (54%)	702 (51%)	
75+	216 (10%)	88 (10%)	128 (9%)	
Sex	2229	844 (38%)	1385 (62%)	<0.001
Male	1251 (56%)	402 (48%)	849 (61%)	
Female	978 (44%)	442 (52%)	536 (39%)	
SIMD	2229	844 (38%)	1385 (62%)	0.764
1 (most deprived)	558 (25%)	208 (25%)	350 (25%)	
2	474 (21%)	175 (21%)	299 (22%)	
3	371 (17%)	147 (17%)	224 (16%)	
4	390 (18%)	141 (17%)	249 (18%)	
5 (least deprived)	436 (20%)	173 (21%)	263 (19%)	
ASA classification	1784	644 (36%)	1140 (64%)	0.336
1	234 (13%)	80 (12%)	80 (12%)	
2	1090 (61%)	381 (59%)	381 (59%)	
3	434 (24%)	174 (27%)	174 (27%)	
4	25 (1%)	9 (1%)	9 (1%)	
5	1 (<1%)	0	0	
Smoking	1412	520 (37%)	892 (63%)	0.408
Non smoker	669 (47%)	246 (47%)	423 (47%)	
Ex-smoker	568 (40%)	202 (39%)	366 (41%)	
Smoker	175 (12%)	72 (14%)	103 (12%)	
BMI	1092	390 (36%)	702 (64%)	0.002
<18.5	13 (1%)	6 (2%)	7 (1%)	
18.5-24.9	293 (27%)	118 (30%)	175 (25%)	
25-29.9	400 (37%)	159 (41%)	241 (34%)	
30-34.9	242 (22%)	69 (18%)	173 (25%)	
35+	144 (13%)	38 (10%)	106 (15%)	
Charlson score	1108	372 (34%)	736 (66%)	0.002
0	729 (66%)	228 (61%)	501 (68%)	
1	271 (25%)	91 (25%)	180 (25%)	
2	86 (8%)	45 (12%)	41 (6%)	
3+	22 (2%)	8 (2%)	14 (2%)	
Preoperative anaemia	1198	442 (37%)	756 (63%)	<0.001
No	858 (72%)	276 (62%)	582 (77%)	
Yes	340 (28%)	166 (38%)	174 (23%)	
Differentiation	2110	778 (37%)	1332 (63%)	<0.001
Mod/well	1764 (84%)	604 (78%)	1160 (87%)	
Poor	346 (16%)	174 (22%)	172 (13%)	
EMVI	1788	633 (35%)	1155 (65%)	0.001
Negative	1189 (67%)	388 (61%)	801 (69%)	
Positive	599 (34%)	245 (39%)	354 (31%)	
Tumour site (for colon cancer)	1528	580 (38%)	948 (62%)	<0.001
Right	733 (48%)	359 (62%)	374 (40%)	
Left	795 (52%)	221 (38%)	574 (61%)	
Screening test type	2229	844 (38%)	1385 (62%)	<0.001
gFOBT	1188 (53%)	748 (89%)	440 (32%)	
FIT	1041 (47%)	96 (11%)	945 (68%)	

Table 7-5 A subgroup analysis of patients undergoing resectional surgery with curative intent for TNM I-III colon cancer. Association between screening versus non-screening diagnosis, Systemic Inflammatory Grade and CT-derived body composition

	Total	Non-Screening	Screening	p
Elective or emergency, any age				
SIG	1706	1344 (79%)	362 (21%)	<0.001
0	571 (34%)	384 (29%)	187 (52%)	
1	409 (24%)	300 (22%)	109 (30%)	
2	327 (19%)	273 (20%)	54 (15%)	
3	214 (13%)	207 (15%)	7 (2%)	
4	185 (11%)	180 (13%)	5 (1%)	
SFI	2313	1699 (74%)	614 (27%)	<0.001
Normal	470 (20%)	388 (23%)	82 (13%)	
High	1843 (80%)	1311 (77%)	532 (87%)	
VFA	2571	1916 (75%)	655 (26%)	<0.001
Normal	617 (24%)	517 (27%)	100 (15%)	
High	1954 (76%)	1399 (73%)	555 (85%)	
SMI	1785	1300 (73%)	485 (27%)	<0.001
Normal	826 (46%)	538 (41%)	288 (59%)	
Low	959 (54%)	762 (59%)	197 (41%)	
SMD	1790	1305 (73%)	485 (27%)	<0.001
Normal	556 (31%)	359 (28%)	197 (41%)	
Low	1234 (69%)	946 (73%)	288 (59%)	
Elective or emergency, age 50-74				
SIG	994	667 (67%)	327 (33%)	<0.001
0	382 (38%)	212 (32%)	170 (52%)	
1	251 (25%)	153 (23%)	98 (30%)	
2	179 (18%)	132 (20%)	47 (14%)	
3	107 (11%)	100 (15%)	7 (2%)	
4	75 (8%)	70 (11%)	5 (2%)	
SFI	1449	894 (62%)	555 (38%)	<0.001
Normal	264 (18%)	191 (21%)	73 (13%)	
High	1185 (82%)	703 (79%)	482 (87)	
VFA	1564	974 (62%)	590 (38%)	<0.001
Normal	329 (21%)	236 (24%)	93 (16%)	
High	1235 (79%)	738 (76%)	497 (84%)	
SMI	1167	729 (63%)	438 (38%)	<0.001
Normal	610 (52%)	343 (47%)	267 (61%)	
Low	557 (48%)	386 (53%)	171 (39%)	
SMD	1168	730 (63%)	438 (38%)	<0.001
Normal	419 (36%)	234 (32%)	185 (42%)	
Low	749 (64%)	496 (68%)	253 (58%)	
Elective, age 50-74				
SIG	799	477 (60%)	322 (40%)	<0.001
0	366 (46%)	198 (42%)	168 (52%)	
1	221 (28%)	125 (26%)	96 (30%)	
2	136 (17%)	90 (19%)	46 (14%)	
3	48 (6%)	41 (9%)	7 (2%)	
4	28 (4%)	23 (5%)	5 (2%)	
SFI	1270	722 (57%)	548 (43%)	0.002
Normal	212 (17%)	141 (20%)	71 (13%)	
High	1058 (83%)	581 (81%)	477 (87%)	
VFA	1356	774 (57%)	582 (43%)	0.007
Normal	257 (19%)	166 (21%)	91 (16%)	
High	1099 (81%)	608 (79%)	491 (84%)	
SMI	1024	592 (58%)	432 (42%)	<0.001
Normal	562 (55%)	297 (50%)	265 (61%)	
Low	462 (45%)	295 (50%)	167 (39%)	

SMD	1025	593 (58%)	432 (42%)	0.014
Normal	394 (38%)	209 (35%)	185 (43%)	
Low	631 (62%)	384 (65%)	247 (57%)	

8 Chapter 8 – An Investigation Into the Association Between Tumour Mutational Status, Mode of Presentation and Outcomes in Patients Undergoing Curative Surgery for Colon Cancer

8.1 Introduction

Tumour development and progression is the result of a series of complex interactions between the tumour and the host involving multiple genetic events and cell signalling pathways[343]. As described within Chapter 1, colorectal cancer most commonly develops through the Chromosomal Instability (CIN) pathway[343] as first described by Fearon and Vogelstein[9]. APC mutations (prevalence 30-70%), P53 mutations (prevalence 50-75%), KRAS mutations (prevalence 30-50%) and PIK3CA mutations (prevalence 20%) make up the most commonly observed genetic mutations within this pathway with subsequent effects on cell proliferation, survival and induction of apoptosis[344]. BRAF mutations (prevalence 7-10%) are associated with the formation of serrated polyps, with tumours arising via the CIMP and MSI pathways and are more common within right-sided colon cancer[345].

The prognostic effect of BRAF mutational status within non-metastatic colorectal cancer remains unclear[346,347]. KRAS mutational status has been associated with adverse oncological outcomes in both metastatic and non-metastatic disease[346-348], however research into KRAS mutant colorectal cancer has historically been constrained due to challenges associated with creating KRAS mutant animal

models[349] although such models are now available. Until recently, KRAS mutant colorectal cancer has been considered undruggable however more recently G12C inhibitors (Sotorasib/Adagrasib) have been developed and trials are ongoing[350,351].

As described previously, an elevated systemic inflammatory response is associated with adverse outcomes in patients with colon cancer. The systemic inflammatory response has been associated with factors including TNM Stage and several studies[35,139,352] have suggested a potential association between mismatch repair status (via the MSI pathway) and the systemic inflammatory response, however the precise interaction between tumour and host remains poorly understood. KRAS mutations are recognised to be more common within right-sided colon cancer. A previous study by Patel and colleagues reported an association between right-sided colon cancer and an elevated systemic inflammatory response although did not include KRAS status[353]. Two previous reviews have described an inflammatory phenotype of KRAS mutational status, predominantly within lung and pancreatic cancer but also within colorectal cancer[354,355]. The association between KRAS mutational status and markers of the systemic inflammatory response within non-metastatic colorectal cancer has not been widely studied however a single study of 337 patients reported a lower average preoperative CRP (7.07 versus 10.61, p=0.020) within KRAS mutant colorectal cancer[356]. Furthermore, a recent mouse model of KRAS mutant colorectal cancer reported increased colonic inflammation and cachexia within the KRAS mutant group[349]. Within other cancer types including pancreatic cancer, KRAS mutational status has been associated with increased inflammatory markers including IL-6.

The literature review presented within Chapter 2 did not identify any literature investigating the association between mode of presentation and mutational status in colorectal cancer. It may be that mutational status, including KRAS mutant status, may be associated with an increased inflammatory response, rapid tumour development and emergency presentation. The present study aims firstly to determine whether mutational status is associated with other clinicopathological factors and oncological outcomes in a cohort of patients undergoing elective resectional surgery for colon cancer and secondly to determine whether there is an association between mutational status and mode of presentation in a cohort of patients undergoing either elective or emergency resectional surgery with curative intent for colon cancer.

8.2 Methods

The patient population included within the present study was obtained from the amalgamation of two datasets:

(1) A single centre dataset of patients from the Western Infirmary, Glasgow diagnosed with colorectal cancer between January 2000 and December 2008 with mutational status analysed retrospectively

(2) The West of Scotland Managed Clinical Network (MCN) dataset as described within Chapter 3 – a subgroup of patients diagnosed with colorectal cancer within the West of Scotland from January 2011 – December 2014 with mutational status analysed prospectively

These datasets were well matched for the included clinicopathological factors including mutational status and it was therefore appropriate to combine both datasets.

Patients undergoing curative resectional surgery for TNM I-III colon cancer were included as described in Chapters 3 and 4. Tumours were staged using the AJCC TNM classification system 5th and 6th editions for the 2000-2008 and 2011-2014 cohorts respectively. The preoperative systemic inflammatory response was stratified using Systemic Inflammatory Grade as described within Chapter 5. Overall and cancer-specific survival were defined as previously described. To reduce confounding factors, the initial analysis between mutational status, clinicopathological factors and survival analysis was performed in elective patients only.

For the analysis of Klinrtrup-Makinen grade within the 2000-2008 cohort, whole Haematoxylin and Eosin (H&E) stained sections taken from the point of deepest invasion were scored manually using NDP view (Hamamatsu) after scanning slides onto a server using the Hamamatsu NanoZoomer at x20 magnification (Welwyn Garden City, UK). Briefly, KM was scored semi-quantitatively at the tumour's invasive margin as weak (no inflammatory cells present or sporadic patches of cells) or strong (presence of a continuous band or cup-like infiltrate of inflammatory cells with evidence of tumour nest destruction).

Mutational status within the MCN cohort had been analysed as part of the Cancer Research UK Stratified Medicine Programme as previously described and the results were obtained from electronic patient records. A small proportion of patients from this cohort had retrospective BRAF/KRAS analysis following development of metastatic disease. For BRAF, mutational analysis was carried out on codons 599, 600 and 601. For KRAS, mutational analysis was carried out on codons 12, 13, 61 and 146. For PIK3CA, mutational analysis was carried out on exons 9 and 20. For TP53, mutational analysis was carried out on exons 4-9.

For the 2000-2008 cohort, mutational analysis was carried out by K. Pennel and the Glasgow Precision Oncology Laboratory as described in the acknowledgements section. KRAS/BRAF/APC/P53/PIK3CA mutational status was assessed using a targeted capture sequencing. RNA Baits (Agilent) were utilised to capture a custom in-house designed panel of 151 cancer-associated genes. DNA was extracted from formalin fixed paraffin embedded sections from patients and standardized to a concentration of 4ng/µl. Targeted capture libraries were prepared from 150-200ng DNA. Sequencing was performed using an Illumina HiSeq 4000. For KRAS, mutational analysis was carried out on codons

12, 13, 19, 59, 61, 117 and 146. For BRAF, mutational analysis was carried out on codons 483, 594, 600 and 601.

8.2.1 Statistical Analysis

The relationship between mutational status and clinicopathological characteristics was analysed using the Chi squared test. Three-year overall and cancer specific survival was calculated using the life table function of SPSS as previously described. Statistical significance was calculated using the log-rank test. Survival analysis was carried out using Cox's proportional hazards model to calculate Hazard Ratios (HRs) and 95% confidence intervals (95% CIs). Variables with a p-value of <0.1 on univariate analysis were entered into a multivariate model using the backwards conditional method in which variables with a significance of $p \geq 0.10$ were removed from the model in a stepwise fashion. Overall and cancer-specific survival has been shown graphically on Kaplan-Meier curves with 30-day mortality included.

Statistical analysis was carried out using IBM SPSS Statistics for Windows Version 28 (IBM Corporation, Armonk, New York, USA). A two-tailed p-value of <0.05 has been considered significant throughout.

8.3 Results

8.3.1 Demographics

368 patients were identified who were suitable for inclusion within this study, 267 of whom had undergone surgery on an elective basis. Of elective patients, the majority were aged 65+ (74%) and had TNM II/III disease (37%/53% respectively). 56% of patients had right-sided disease. For mutational status, 45% of patients had a KRAS mutation, 17% had a BRAF mutation, 17% had a PIK3CA mutation, 64% had a P53 mutation and 74% had an APC mutation. 45%/40%/15% has a Systemic Inflammatory Grade of 0/1-2/3-4 respectively. Within the whole cohort there were 5 postoperative deaths (2%). After exclusion of these, 3-year overall/cancer-specific survival was 74%/79% respectively.

8.3.2 Association Between APC Mutational Status and Clinicopathological Factors

APC mutational status was available for 96 elective patients, 71 (74%) of whom had an APC mutation. The association between APC mutational status and clinicopathological factors is shown in Table 8-1. APC mutational status was associated with moderately-well differentiated tumours (p=0.003) and BRAF wild-type tumours (p=0.006).

A trend was observed between APC mutational status and favourable 3-year cancer-specific survival (67% versus 81%, p=0.070) and overall survival (61% versus 78%, p=0.051). This is shown graphically in Figure 8-1.

8.3.3 Association Between P53 Mutational Status and Clinicopathological Factors

P53 mutational status was available for 117 elective patients, 75 (64%) of whom had a P53 mutation. The association between P53 mutational status and clinicopathological characteristics is shown in Table 8-2. P53 mutational status was associated with KRAS wild-type tumours (p=0.002) and PIK3CA wild-type tumours (p=0.003). A trend was observed between P53 mutational status and TNM Stage II disease (p=0.091) and extramural venous invasion (p=0.061).

P53 mutational status was not significantly associated with 3-year cancer-specific survival (82% versus 93%, p=0.947) or overall survival (76% versus 85%, p=0.405). This is shown graphically in Figure 8-2.

8.3.4 Association Between KRAS Mutational Status and Clinicopathological Factors

KRAS mutational status was available for 267 elective patients, 121 (45%) of whom had a KRAS mutation. The association between KRAS mutational status and clinicopathological characteristics is shown in Table 8-3. KRAS mutant status was associated with right-sided tumour location (p=0.013), moderately-well differentiated tumours (p=0.011), BRAF wild-type tumours (p<0.001), PIK3CA mutant tumours (p=0.027) and P53 wild-type tumours (p=0.002). A trend was

observed between KRAS mutant status and female patients (p=0.074) and Systemic Inflammatory Grade (p=0.072).

KRAS mutant status was associated with adverse 3-year cancer specific survival (82% versus 74%, p=0.006) and overall survival (78% versus 69%, p=0.070). This is shown graphically in Figure 8-3.

8.3.5 Association Between BRAF Mutational Status and Clinicopathological Factors

BRAF mutational status was available for 263 elective patients, 45 (17%) of whom had a BRAF mutation. The association between BRAF mutational status and clinicopathological characteristics is shown in Table 8-4. BRAF mutant status was associated with female patients (p=0.015), right-sided tumours (p<0.001), APC wild-type tumours (p=0.006) and KRAS wild-type tumours (p<0.001). A trend was observed between BRAF mutant status and increased socio-economic deprivation (p=0.052) and poorly differentiated tumours (p=0.067).

A significant association was observed between BRAF mutational status and improved 3-year cancer specific survival (78% versus 84%, p=0.021) but no association was seen for overall survival (73% versus 80%, p=0.201). This is shown graphically in Figure 8-4.

8.3.6 Association Between PIK3CA Mutational Status and Clinicopathological Factors

PIK3CA mutational status was available for 117 elective patients, 20 (17%) of whom had a PIK3CA mutation. The association between PIK3CA mutational status and clinicopathological characteristics is shown in Table 8-5. PIK3CA mutational status was associated with patients aged 65-74 (p=0.045), KRAS mutant tumours (p=0.027) and P53 wild-type tumours (p=0.003). A trend was observed between PIK3CA mutational status and right-sided tumours (p=0.079) and low Klintrup grade (p=0.055).

PIK3CA mutational status was not associated with 3-year cancer specific survival (95% versus 75%, p=0.407) or overall survival (83% versus 75%, p=0.452). This is shown graphically in Figure 8-5.

8.3.7 Association Between KRAS/BRAF Mutational Status and Overall/Cancer Specific Survival

The association between KRAS and BRAF status and cancer-specific/overall survival (elective patients only) after adjustment for other clinicopathological factors is shown in Table 8-6.

For cancer specific survival: TNM Stage (p<0.001), differentiation (p<0.001), Systemic Inflammatory Grade (p=0.003), BRAF mutational status (p=0.025) and KRAS mutational status (p=0.007) were significant on univariate analysis. When those factors significant on univariate analysis (p<0.01) were entered into the

multivariate model: TNM Stage (HR 2.92, 95% CI 1.79-4.74, p<0.001), Systemic Inflammatory Grade (HR 1.34, 95% CI 1.10-1.64, p=0.004) and KRAS mutational status (HR 1.64, p=0.050) remained associated with cancer specific survival.

For overall survival: age (p=0.001), TNM Stage (p=0.005), differentiation (p=0.004), Systemic Inflammatory Grade (p<0.001) and KRAS mutational status (p=0.073) were significant on univariate analysis. When those factors significant on univariate analysis were entered into the multivariate model: age (HR 1.39, 95% CI 1.05-1.83, p=0.022), TNM Stage (HR 1.50, 95% CI 1.08-2.08, p=0.016) and Systemic Inflammatory Grade (HR 1.25, 95% CI 1.07-2.08, p=0.005) remained associated with overall survival. A trend was observed between KRAS mutational status and adverse overall survival (HR 1.47, 95% CI 0.96-2.24, p=0.079).

8.3.8 Association Between Mode of Presentation and Mutational Status

The association between mode of presentation and mutational status is shown in Table 8-7. 74% of elective patients versus 75% of emergency patients had an APC mutation (p=0.932). 64% of elective patients versus 50% of emergency patients had a P53 mutation (p=0.251). 45% of elective patients versus 54% of emergency patients had a KRAS mutation (p=0.163). 17% of elective patients and 16% of emergency patients had a BRAF mutation (p=0.710). 17% of elective patients and 28% of emergency patients had a PIK3CA mutation (p=0.277).

8.4 Discussion

The results of the present study show that within a cohort of patients undergoing elective curative surgery for TNM Stage I-III colon cancer, amongst the common mutations known to be associated with the development and progression of colorectal cancer (KRAS/BRAF/P53/PIK3CA/APC) there is a consistent association between mutational status and tumour sidedness but there were no other consistent associations between mutational status and tumour or host factors. Only KRAS mutational status was associated with adverse cancer-specific and overall survival independent of TNM Stage and systemic inflammation. Within the combined elective and emergency cohort, no statistically significant association was seen between mode of presentation and mutational status.

The frequency of mutations within the present dataset is in keeping with previously published results validating the mutational data[357]. KRAS and BRAF mutations have traditionally been considered mutually exclusive[358]. Within the present results, KRAS/BRAF co-mutant status while uncommon was observed in a small number of cases (n=6). More recently, this co-mutation although uncommon has been reported[359,360] and the present results are in keeping with this co-mutation being rare, albeit still observed. Other associations between observed co-mutations were in keeping with the existing literature in terms of KRAS/PIK3CA[361-363], KRAS/P53[364] and PIK3CA/P53[363]. Further investigation of the effect of these co-mutations on outcomes would be of interest within a large dataset.

The present results show that KRAS mutant status was associated with adverse cancer-specific survival (82% versus 74%) and overall survival (78% versus 69%) and this remained significant after adjustment for other common

clinicopathological factors. KRAS mutant colorectal cancer is widely accepted to be associated with adverse outcomes within the context of metastatic disease[365,366]. Within the context of non-metastatic disease, the effect of KRAS mutation on outcomes has been less well studied. Several studies[367,368], including an Australian Study by Prabhakaran and colleagues, reported an independent association between KRAS mutant status and distal recurrence (OR 11.04, $p<0.001$) within a cohort of 670 patients undergoing resectional surgery for TNM Stage I-III colorectal cancer. KRAS mutant status has previously been reported to be associated with right-sided tumour location and the present results are consistent with this[366,369]. The relationship between tumour and host is complex and as previously described it is recognised that an elevated systemic inflammatory response is associated with adverse outcomes following potentially curative surgery for colorectal cancer. Prior research has suggested an inflammatory phenotype of KRAS mutant colorectal cancer[349,354,370]. Within the present study, a trend was observed between KRAS mutant status and patients with Systemic Inflammatory Grade 1-2 ($p=0.072$). Further work is required to establish whether the presence of KRAS mutant disease drives this systemic inflammatory response.

In the present study, BRAF mutant colorectal cancer was strongly associated with right-sided disease and this is consistent with the published literature[371,372]. On unadjusted analysis, BRAF mutant status was associated with improved 3-year cancer specific survival (78% versus 84%, $p=0.021$) however no significant effect of BRAF mutation on either cancer-specific or overall survival was observed after adjustment for other clinicopathological factors. Within the literature, BRAF mutation has been associated with adverse outcomes[373] however again this research has predominantly been within metastatic disease. Nonetheless, a

recent meta-analysis did find an association between BRAF mutant status and adverse overall and disease-free survival[350] however in a previous cohort study of 228 patients with TNM Stage II/III colon cancer no association was observed between BRAF status and outcomes[374]. BRAF mutational status is recognised to be associated with microsatellite instability and could not be accounted for within the present results. MSI predicts improved outcomes and this may explain the present findings. The association between BRAF mutational status and outcomes within non-metastatic colon cancer requires further investigation in a cohort with known mismatch repair status.

The present results did not show a significant association between any of the included mutations and mode of presentation. A trend was seen between emergency presentation and P53 wild-type, KRAS mutant and PIK3CA mutant colon cancer. No prior studies were identified in Chapter 2 investigating the association between mode of presentation and mutational status within colorectal cancer. Numbers within the present study were small and further investigation of the association between mutational status, mode of presentation and outcomes in TNM Stage I-III colorectal cancer is required. KRAS mutant colorectal cancer as described above has been associated with adverse outcomes and possibly an elevated systemic inflammatory response. If this is the case, this elevated inflammatory response may drive rapid tumour growth and may predispose to increased evasion of screening diagnosis and increased likelihood of emergency presentation.

The present study is limited by its retrospective observational nature in terms of missing data. Mutational status (aside from BRAF/KRAS) and Klintrup Grade was only available for a relatively small number of patients and therefore to avoid

loss of power other mutations were not included within the multivariate survival analysis. Furthermore, there is a recognised association between BRAF mutant tumours and mismatch repair (MMR) status however MMR data was not available for the present cohort. The present study utilised two patient cohorts from distinct time periods to maximise power. Overall, these cohorts were well matched and were therefore combined however the later cohort (2011-2014) were younger at presentation and more likely to present electively, likely due to the introduction of bowel screening. For this reason and to reduce potential for bias, the majority of the analysis including survival analysis was carried out in elective patients only. Furthermore, although the methods for mutational analysis were consistent within each cohort, it is possible that there are differences in mutational analysis between cohorts. Therefore, further studies would ideally be carried out in a large prospective cohort. Finally, within the time period studied, the SCOT study was ongoing within this population investigating the effect of 3 versus 6 months of adjuvant chemotherapy in colon cancer. The SCOT study reported broadly similar outcomes in the 3 versus 6 month groups therefore the effect of this is expected to be limited however it is possible that within the included time period there was a transition from the use of 5-flurouracil chemotherapy to oxaliplatin.

Further prospective work is required analysing mutational status, mismatch repair status and associations with mode of presentation, local/systemic inflammatory responses and outcomes in patients with non-metastatic colon cancer. A previous review summarised the possible effect of mutational status on response to adjuvant therapy and further analysis of this would be appropriate as it may lead to the development of prevision medicine within the adjuvant setting[375], either around choice of adjuvant chemotherapeutic agents

or immunotherapy. Indeed, the ATOMIC trial[376] studying the effect of adjuvant chemotherapy +/- anti PD-1 therapy within mismatch repair deficient TNM Stage III colon cancer is ongoing.

To date, immunotherapy has predominantly targeted the adaptive immune system with targets including IL-1a and PD-1/PD-L1[377-379]. Indeed, within advanced cancer, such therapies have revolutionised patient care. The innate immune system remains another target and the literature to date around this has been comprehensively summarised in a recent review[380]. Furthermore, literature examining the effect of an elevated systemic inflammatory response on the efficacy of immunotherapy remains limited. However, several studies examining the effect of neoadjuvant immunotherapy in the context of oesophageal cancer reported a better response to immunotherapy in patients with an elevated systemic inflammatory response[381,382]. Whether the innate inflammatory response is related to tumour mutational status is largely unknown and is a clear area of interest for future research. If a link was identified between mutational status and the innate immune response this may help to target additional treatment.

In conclusion, the present results shown an association between common genetic mutations and tumour sidedness and an association between KRAS mutational status, Systemic Inflammatory Grade and adverse outcomes after adjustment for other common clinicopathological factors. There may be an association between mode of presentation and KRAS mutant disease that may in part explain the adverse outcomes observed in emergency presentations of colon cancer, however further investigation into this association is required and such studies

should include common mutations, mismatch repair status and the local/systemic inflammatory response within a large cohort.

8.5 Tables

Table 8-1 Association between APC mutational status and clinicopathological characteristics

	Total	APC-Wild	APC-Mutant	P
Age	96	25 (26%)	71 (74%)	0.036
<65	15 (16%)	0	15 (21%)	
65-74	33 (34%)	9 (36%)	24 (34%)	
75+	48 (50%)	16 (64%)	32 (45%)	
Sex	96	25 (26%)	71 (74%)	0.896
Male	45 (47%)	12 (48%)	33 (47%)	
Female	51 (53%)	13 (52%)	38 (54%)	
SIMD				
1 (most deprived)				
2				
3				
4				
5 (least deprived)				
Smoking				
Non smoker				
Ex-smoker				
Smoker				
ASA				
1				
2				
3				
4				
Preop anaemia				
No				
Yes				
TNM Stage	96	25 (26%)	71 (74%)	0.222
1	5 (5%)	1 (4%)	4 (6%)	
2	36 (38%)	6 (24%)	30 (42%)	
3	55 (57%)	18 (72%)	37 (52%)	
T Stage	96	25 (26%)	71 (74%)	0.332
1	2 (2%)	1 (4%)	1 (1%)	
2	6 (6%)	2 (8%)	4 (6%)	
3	53 (55%)	10 (40%)	43 (61%)	
4	35 (37%)	12 (48%)	23 (32%)	
N Stage	96	25 (26%)	71 (74%)	0.182
0	42 (44%)	7 (28%)	35 (49%)	
1	36 (38%)	12 (48%)	24 (34%)	
2	18 (19%)	6 (24%)	12 (17%)	
Tumour site	96	25 (26%)	71 (74%)	0.509
Right	60 (63%)	17 (68%)	43 (61%)	
Left	26 (38%)	8 (32%)	28 (39%)	
Differentiation	96	25 (26%)	71 (74%)	0.003
Mod-well	85 (89%)	18 (72%)	67 (94%)	
Poor	11 (12%)	7 (28%)	4 (6%)	
EMVI				
Negative				
Positive				
APC				
Wild				
Mutant				
BRAF	96	25 (26%)	71 (74%)	0.006
Wild	76 (79%)	15 (60%)	61 (86%)	
Mutant	20 (21%)	10 (40%)	10 (14%)	
KRAS	96	25 (26%)	71 (74%)	0.649

Wild	50 (52%)	14 (56%)	36 (51%)	
Mutant	46 (48%)	11 (44%)	35 (49%)	
PIK3CA				
Wild				
Mutant				
P53				
Wild				
Mutant				
mGPS	64	17 (27%)	47 (73%)	0.725
0	39 (61%)	9 (53%)	30 (64%)	
1	12 (19%)	4 (24%)	8 (17%)	
2	13 (20%)	4 (24%)	9 (19%)	
NLR	71	17 (24%)	54 (76%)	0.876
<3	37 (52%)	8 (47%)	29 (54%)	
3-5	18 (25%)	5 (29%)	13 (24%)	
5+	16 (23%)	4 (24%)	12 (22%)	
SIG	63	16 (25%)	47 (75%)	0.147
0	25 (40%)	5 (31%)	20 (43%)	
1	14 (22%)	5 (31%)	9 (19%)	
2	8 (13%)	0	8 (17%)	
3	13 (21%)	4 (25%)	9 (19%)	
4	3 (5%)	2 (13%)	1 (2%)	
SIG collapsed	63	16 (25%)	47 (75%)	0.427
0	25 (40%)	5 (31%)	20 (43%)	
1-2	22 (35%)	5 (31%)	17 (36%)	
3-4	16 (25%)	6 (38%)	10 (21%)	
Postop death (30 days)	93	25 (27%)	68 (73%)	0.496
No	88 (95%)	23 (92%)	65 (96%)	
Yes	5 (5%)	2(8%)	3 (4%)	
3-year survival (Exc 30-day mort)	88	23	65	
CSS	78% (SE 5%)	67% (SE 10%)	81% (SE 5%)	0.070
OS	74% (SE 5%)	61% (SE 10%)	78% (SE 5%)	0.051

Table 8-2 Association between p53 mutational status and clinicopathological characteristics

	Total	P53-Wild	P53-Mutant	P
Age	117	42 (36%)	75 (64%)	0.688
<65	30 (26%)	9 (21%)	21 (28%)	
65-74	47 (40%)	17 (41%)	30 (40%)	
75+	40 (34%)	16 (38%)	24 (32%)	
Sex	117	42 (36%)	75 (64%)	0.483
Male	58 (50%)	19 (45%)	39 (52%)	
Female	59 (50%)	23 (55%)	36 (48%)	
SIMD	96	31 (32%)	65 (68%)	0.597
1 (most deprived)	34 (35%)	11 (36%)	23 (35%)	
2	21 (22%)	4 (13%)	17 (26%)	
3	9 (9%)	4 (13%)	5 (8%)	
4	15 (16%)	6 (19%)	9 (4%)	
5 (least deprived)	17 (18%)	6 (19%)	11 (17%)	
Smoking	96	31 (32%)	65 (68%)	0.957
Non smoker	41 (43%)	13 (42%)	28 (43%)	
Ex-smoker	41 (43%)	13 (42%)	28 (43%)	
Smoker	14 (15%)	5 (16%)	9 (14%)	
ASA	95	31 (33%)	64 (67%)	0.351
1	0	0	0	
2	73 (77%)	26 (84%)	47 (73%)	
3	19 (20%)	5 (16%)	14 (22%)	
4	3 (3%)	0	3 (5%)	
Preop anaemia	94	31 (33%)	63 (67%)	0.923
No	60 (64%)	20 (65%)	40 (64%)	
Yes	34 (36%)	11 (36%)	23 (37%)	
TNM Stage	117	42 (36%)	75 (64%)	0.091
1	21 (18%)	11 (26%)	10 (13%)	
2	53 (45%)	14 (33%)	39 (52%)	
3	43 (37%)	17 (41%)	26 (35%)	
T Stage	117	42 (36%)	75 (64%)	0.171
1	8 (7%)	4 (10%)	4 (5%)	
2	16 (14%)	9 (21%)	7 (9%)	
3	69 (59%)	23 (55%)	46 (61%)	
4	24 (21%)	6 (14%)	18 (24%)	
N Stage	117	42 (36%)	75 (64%)	0.783
0	74 (63%)	25 (60%)	49 (65%)	
1	29 (25%)	11 (26%)	18 (24%)	
2	14 (12%)	6 (14%)	8 (11%)	
Tumour site	117	42 (36%)	75 (64%)	0.968
Right	61 (52%)	22 (52%)	39 (52%)	
Left	56 (48%)	20 (48%)	36 (48%)	
Differentiation	117	42 (36%)	75 (64%)	0.777
Mod-well	107 (92%)	38 (91%)	69 (92%)	
Poor	10 (9%)	4 (10%)	6 (8%)	
EMVI	96	31 (32%)	65 (68%)	0.061
Negative	55 (57%)	22 (71%)	33 951%)	
Positive	41 (43%)	9 (29%)	32 (49%)	
Klintrup Grade	20	14 (70%)	6 (30%)	0.769
Low	11 (55%)	8 (57%)	3 (50%)	
High	9 (45%)	6 (43%)	3 (50%)	
APC				
Wild				
Mutant				
BRAF	117	42 (36%)	75 (64%)	0.960
Wild	95 (81%)	34 (81%)	61 (81%)	
Mutant	22 (19%)	8 (19%)	14 (19%)	
KRAS	117	42 (36%)	75 (64%)	0.002
Wild	67 (57%)	16 (38%)	51 (68%)	

Mutant	50 (43%)	26 (62%)	24 (32%)	
PIK3CA	117	42 (36%)	75 (64%)	0.003
Wild	97 (83%)	29 (69%)	68 (91%)	
Mutant	20 (17%)	13 (31%)	7 (9%)	
P53				
Wild				
Mutant				
mGPS	84	31 (37%)	53 (63%)	0.808
0	63 (75%)	22 (71%)	41 (77%)	
1	14(17%)	6 (19%)	8 (15%)	
2	7 (8%)	3 (10%)	4 (8%)	
NLR	112	39 (35%)	73 (65%)	0.420
<3	66 (59%)	26 (67%)	40 (55%)	
3-5	31 (28%)	8 (21%)	23 (32%)	
5+	15 (13%)	5 (13%)	10 (14%)	
SIG	80	28 (35%)	52 (65%)	0.465
0	39 (49%)	16 (57%)	23 (44%)	
1	26 (33%)	6 (21%)	20 (39%)	
2	6 (8%)	2 (7%)	4 (8%)	
3	6 (8%)	2 (7%)	4 (8%)	
4	3 (4%)	2 (7%)	1 (2%)	
SIG collapsed	80	28 (35%)	52 (65%)	0.304
0	39 (49%)	16 (57%)	23 (44%)	
1-2	32 (40%)	8 (29%)	24 (46%)	
3-4	9 (11%)	4 (14%)	5 (10%)	
Postop death (30 days)	116	41 (35%)	75 (65%)	-
No	116	41	75	
Yes	0			
3-year survival (Exc 30-day mort)	116	41	75	
CSS	89% (SE 3%)	82% (se 6%)	93% (SE 3%)	0.947
OS	82% (SE 4%)	76% (SE 7%)	85% (SE 4%)	0.405

Table 8-3 Association between KRAS mutational status and clinicopathological characteristics

	Total	KRAS-Wild	KRAS-Mutant	P
Age	267	146 (55%)	121 (45%)	0.998
<65	68 (26%)	37 (25%)	31 (26%)	
65-74	102 (38%)	56 (38%)	46 (38%)	
75+	97 (36%)	53 (36%)	44 (36%)	
Sex	267	146 (55%)	121 (45%)	0.074
Male	133 (50%)	80 (55%)	53 (44%)	
Female	134 (50%)	66 (45%)	68 (56%)	
SIMD	150	87 (58%)	63 (42%)	0.567
1 (most deprived)	43 (29%)	25 (29%)	18 (29%)	
2	39 (26%)	25 (29%)	14 (22%)	
3	19 (13%)	8 (9%)	11 (18%)	
4	22 (15%)	12 (14%)	10 (16%)	
5 (least deprived)	27 (18%)	17 (20%)	10 (16%)	
Smoking	146	83 (57%)	63 (43%)	0.179
Non smoker	73 (50%)	36 (43%)	37 (59%)	
Ex-smoker	52 (36%)	33 (40%)	19 (30%)	
Smoker	21 (14%)	14 (17%)	7 (11%)	
ASA	147	84 (57%)	63 (43%)	0.318
1	9 (5%)	3 (4%)	5 (8%)	
2	105 (71%)	60 (71%)	45 (71%)	
3	31 (21%)	18 (21%)	13 (21%)	
4	3 (2%)	3 (4%)	0	
Preop anaemia	146	84 (58%)	62 (43%)	0.249
No	88 (60%)	54 (64%)	34 (55%)	
Yes	58 (40%)	30 (36%)	28 (45%)	
TNM Stage	267	146 (55%)	121 (45%)	0.627
1	27 (10%)	17 (12%)	10 (8%)	
2	99 (37%)	52 (36%)	47 (39%)	
3	141 (53%)	77 (53%)	64 (53%)	
T Stage	267	146 (55%)	121 (45%)	0.805
1	11 (4%)	5 (3%)	6 (5%)	
2	24 (9%)	15 (10%)	9 (7%)	
3	147 (55%)	80 (55%)	67 (55%)	
4	85 (32%)	46 (32%)	39 (32%)	
N Stage	267	146 (55%)	121 (45%)	0.976
0	127 (48%)	69 (47%)	58 (48%)	
1	81 (30%)	44 (30%)	37 (31%)	
2	59 (22%)	33 (23%)	26 (22%)	
Tumour site	265	144 (54%)	121 (46%)	0.013
Right	149 (56%)	71 (49%)	78 (65%)	
Left	116 (44%)	73 (51%)	43 (36%)	
Differentiation	267	146 (55%)	121 (45%)	0.011
Mod-well	229 (86%)	118 (81%)	111 (92%)	
Poor	38 (14%)	28 (19%)	10 (8%)	
EMVI	150	87 (58%)	63 (42%)	0.801
Negative	72 (48%)	41 (47%)	31 (49%)	
Positive	78 (52%)	46 (53%)	32 (51%)	
Klintrup Grade	115	80 (70%)	35 (30%)	0.888
Low	58 (50%)	40 (50%)	18 (51%)	
High	57 (50%)	40 (50%)	17 (49%)	
APC	96	50 (52%)	46 (48%)	0.649
Wild	25 (26%)	14 (28%)	11 (24%)	
Mutant	71 (74%)	36 (72%)	35 (76)	
BRAF	263	144 (55%)	119 (45%)	<0.001
Wild	218 (83%)	105 (73%)	113 (95%)	
Mutant	45 (17%)	39 (27%)	6 (5%)	
KRAS				

Wild				
Mutant				
PIK3CA	117	67 (57%)	50 (43%)	0.027
Wild	97 (83%)	60 (90%)	37 (74%)	
Mutant	20 (17%)	7 (10%)	13 (26%)	
P53	117	57 (57%)	50 (43%)	0.002
Wild	42 (36%)	16 (24%)	26 (52%)	
Mutant	75 (64%)	51 (76%)	24 (48%)	
mGPS	181	91 (50%)	90 (50%)	0.671
0	126 (70%)	66 (73%)	60 (67%)	
1	34 (19%)	15 (17%)	19 (21%)	
2	21 (12%)	10 (11%)	11 (12%)	
NLR	235	126 (54%)	109 (46%)	0.837
<3	134 (57%)	74 (59%)	60 (55%)	
3-5	63 (27%)	32 (25%)	31 (228%)	
5+	38 (16%)	20 (16%)	18 (17%)	
SIG	176	89 (51%)	87 (49%)	0.206
0	79 (45%)	46 (52%)	33 (38%)	
1	46 (26%)	20 (23%)	26 (30%)	
2	24 (14%)	8 (9%)	16 (18%)	
3	20 (11%)	11 (12%)	9 (10%)	
4	7 (4%)	4 (5%)	3 (3%)	
SIG collapsed	176	89 (51%)	87 (49%)	0.072
0	79 (45%)	46 (52%)	33 (38%)	
1-2	70 (40%)	28 (32%)	42 (48%)	
3-4	27 (15%)	15 (17%)	12 (14%)	
Postop death (30 days)	263	145 (55%)	118 (45%)	0.259
No	258 (98%)	141 (97%)	117 (99%)	
Yes	5 (2%)	4 (3%)	1 (1%)	
3-year survival (Exc 30-day mort)	258	141	117	
CSS	79% (se 3%)	82% (SE 3%)	74% (SE 4%)	0.006
OS	74% (SE 3%)	78% (SE 3%)	69% (SE 4%)	0.070

Table 8-4 Association between BRAF mutational status and clinicopathological characteristics

	Total	BRAF-Wild	BRAF-Mutant	P
Age	263	218 (83%)	45 (17%)	0.865
<65	64 (24%)	54 (25%)	10 (22%)	
65-74	102 (39%)	83 (38%)	19 (42%)	
75+	97 (37%)	81 (37%)	16 (36%)	
Sex	263	218 (83%)	45 (17%)	0.015
Male	131 (50%)	116 (53%)	15 (33%)	
Female	132 (50%)	102 (47%)	30 (67%)	
SIMD	146	122 (84%)	24 (16%)	0.052
1 (most deprived)	42 (29%)	29 (24%)	13 (54%)	
2	37 (25%)	33 (27%)	4 (17%)	
3	18 (12%)	16 (13%)	2 (8%)	
4	22 (15%)	19 (16%)	3 (13%)	
5 (least deprived)	27 (19%)	25 (21%)	2 (8%)	
Smoking	142	118 (83%)	24 (17%)	0.894
Non smoker	70 (49%)	58 (49%)	12 (50%)	
Ex-smoker	52 (37%)	44 (37%)	8 (33%)	
Smoker	20 (14%)	16 (14%)	4 (17%)	
ASA	143	119 (83%)	24 (17%)	0.360
1	8 (6%)	8 (7%)	0	
2	102 (71%)	86 (72%)	16 (67%)	
3	30 (21%)	23 (19%)	7 (29%)	
4	3 (2%)	2 (2%)	1 (4%)	
Preop anaemia	142	119 (84%)	23 (16%)	0.610
No	87 (61%)	74 (62%)	13 (57%)	
Yes	55 (39%)	45 (38%)	10 (44%)	
TNM Stage	263	218 (83%)	45 (17%)	0.400
1	27 (10%)	20 (9%)	7 (16%)	
2	98 (37%)	81 (37%)	17 (38%)	
3	138 (53%)	117 (54%)	21 (47%)	
T Stage	263	218 (83%)	45 (17%)	0.143
1	11 (4%)	10 (5%)	1 (2%)	
2	24 (9%)	16 (7%)	8 (18%)	
3	147 (56%)	125 (57%)	22 (49%)	
4	81 (31%)	67 (31%)	14 (31%)	
N Stage	263	218 (83%)	45 (17%)	0.301
0	126 (48%)	102 (47%)	24 (53%)	
1	79 (30%)	64 (29%)	15 (33%)	
2	58 (22%)	52 (24%)	6 (13%)	
Tumour site	261	216 (83%)	45 (17%)	<0.001
Right	146 (56%)	103 (48%)	43 (96%)	
Left	115 (44%)	113 (52%)	2 (4%)	
Differentiation	263	218 (83%)	45 (17%)	0.067
Mod-well	227 (86%)	192 (88%)	35 (78%)	
Poor	36 (14%)	26 (12%)	10 (22%)	
EMVI	146	122 (84%)	24 (16%)	0.298
Negative	71 (49%)	57 (47%)	14 (58%)	
Positive	75 (51%)	65 (53%)	10 (42%)	
Klintrup Grade	115	80 (70%)	35 (30%)	0.306
Low	95 (83%)	68 (85%)	27 (77%)	
High	20 (17%)	12 (15%)	8 (23%)	
APC	96	76 (79%)	20 (21%)	0.006
Wild	25 (26%)	15 (20%)	10 (50%)	
Mutant	71 (74%)	61 (80%)	10 (50%)	
BRAF				
Wild				
Mutant				
KRAS	263	218 (83%)	45 (17%)	<0.001

Wild	144 (55%)	105 (48%)	39 (87%)	
Mutant	119 (45%)	113 (52%)	6 (13%)	
PIK3CA	117	95 (81%)	22 (19%)	0.633
Wild	97 (83%)	78 (82%)	19 (86%)	
Mutant	20 (17%)	17 (18%)	3 (14%)	
P53	117	95 (81%)	22 (19%)	0.960
Wild	42 (36%)	34 (36%)	8 (36%)	
Mutant	75 (64%)	61 (64%)	14 (64%)	
mGPS	180	152 (84%)	28 (16%)	0.262
0	126 (70%)	110 (72%)	16 (57%)	
1	33 (18%)	26 (17%)	7 (25%)	
2	21 (12%)	16 (11%)	5 (18%)	
NLR	231	194 (84%)	37 (16%)	0.308
<3	132 (57%)	108 (56%)	24 (65%)	
3-5	61 (26%)	55 (28%)	6 (16%)	
5+	38 (17%)	31 (16%)	7 (19%)	
SIG	175	147 (84%)	28 (16%)	0.857
0	79 (45%)	67 (46%)	12 (43%)	
1	45 (26%)	38 (26%)	7 (25%)	
2	24 (14%)	21 (14%)	3 (11%)	
3	20 (11%)	16 (11%)	4 (14%)	
4	7 (4%)	5 (3%)	2 (7%)	
SIG collapsed	175	147 (84%)	28 (16%)	0.627
0	79 (45%)	67 (46%)	12 (43%)	
1-2	69 (39%)	59 (40%)	10 (36%)	
3-4	27 (15%)	21 (14%)	6 (21%)	
Postop death (30 days)	259	214 (83%)	45 (17%)	0.876
No	254 (98%)	210 (98%)	44 (98%)	
Yes	5 (2%)	4 (2%)	1 (2%)	
3-year survival (Exc 30-day mort)	254	210	44	
CSS	79% (SE 3%)	78% (SE 3%)	84% (SE 6%)	0.021
OS	74% (SE 3%)	73% (SE 3%)	80% (SE 6%)	0.201

Table 8-5 Association between PIK3CA mutational status and clinicopathological characteristics

	Total	PIK3CA-Wild	PIK3CA-Mutant	P
Age	117	79 (83%)	20 (17%)	0.045
<65	30 (26%)	27 (28%)	3 (15%)	
65-74	47 (40%)	34 (35%)	13 (65%)	
75+	40 (34%)	36 (37%)	4 (20%)	
Sex	117	97 (83%)	20 (17%)	0.347
Male	58 (50%)	50 (52%)	8 (40%)	
Female	59 (50%)	47 (49%)	12 (60%)	
SIMD	96	82 (85%)	14 (15%)	0.771
1 (most deprived)	34 (35%)	29 (35%)	5 (36%)	
2	21 (22%)	17 (21%)	4 (29%)	
3	9 (9%)	8 (10%)	1 (7%)	
4	15 (16%)	12 (15%)	3 (21%)	
5 (least deprived)	17 (18%)	16 (20%)	1 (7%)	
Smoking	96	82 (85%)	14 (15%)	0.662
Non smoker	41 (43%)	34 (42%)	7 (50%)	
Ex-smoker	41 (43%)	35 (43%)	6 (43%)	
Smoker	14 (15%)	13 (16%)	1 (7%)	
ASA	95	82 (86%)	13 (14%)	0.686
1	0	0	0	
2	73 (77%)	62 (76%)	11 (85%)	
3	19 (20%)	17 (21%)	2 915%)	
4	3 (3%)	3 (4%)	0	
Preop anaemia	94	81 (86%)	13 (14%)	0.853
No	60 (64%)	52 (64%)	8 (62%)	
Yes	34 (36%)	29 (36%)	5 (39%)	
TNM Stage	117	97 (83%)	20 (17%)	0.341
1	21 918%)	19 (20%)	2 (10%)	
2	53 (45%)	45 (46%)	8 (40%)	
3	43 (37%)	33 (34%)	10 (50%)	
T Stage	117	97 (83%)	20 (17%)	0.608
1	8 (7%)	8 (8%)	0	
2	16 (14%)	13 (13%)	3 (15%)	
3	69 (59%)	56 (58%)	13 (65%)	
4	24 (21%)	20 (21%)	4 (20%)	
N Stage	117	97 (83%)	20 (17%)	0.393
0	74 (63%)	64 (66%)	10 (50%)	
1	29 (25%)	22 (23%)	7 (35%)	
2	14 (12%)	11 (11%)	3 (15%)	
Tumour site	117	97 (83%)	20 (17%)	0.079
Right	61 (52%)	47 (49%)	14 (70%)	
Left	56(48%)	20 (52%)	6 (30%)	
Differentiation	117	97 (83%)	20 (17%)	0.799
Mod-well	107 (92%)	89 (92%)	18 (90%)	
Poor	10 (9%)	8 (8%)	2 (10%)	
EMVI	96	82 (85%)	14 (15%)	0.567
Negative	55 (57%)	46 (56%)	9 (64%)	
Positive	41 (43%)	36 (44%)	5 (36%)	
Klintrup Grade	20	14 (70%)	6 (30%)	0.055
Low	14 (70%)	8 (57%)	6 (100%)	
High	6 (30%)	6 (43%)	0	
APC				
Wild				
Mutant				
BRAF	117	97 (83%)	20 (17%)	0.633
Wild	95 (81%)	78 (80%)	17 (85%)	
Mutant	22 (19%)	19 (20%)	3 (15%)	
KRAS	117	97 (83%)	20 (17%)	0.027

Wild	67 (57%)	60 (62%)	7 (35%)	
Mutant	50 (43%)	37 (38%)	13 (65%)	
PIK3CA				
Wild				
Mutant				
P53	117	97 (83%)	20 (17%)	0.003
Wild	42 (36%)	29 (30%)	13 (65%)	
Mutant	75 (64%)	68 (70%)	7 (35%)	
mGPS	84	66 (79%)	18 (21%)	0.719
0	63 (75%)	50 (76%)	13 (72%)	
1	14 (17%)	10 (15%)	4 (22%)	
2	7 (8%)	6 (9%)	1 (6%)	
NLR	112	93 (83%)	19 (17%)	0.516
<3	66 (59%)	54 (58%)	12 (63%)	
3-5	31 (28%)	25 (27%)	6 (32%)	
5+	15 (13%)	14 (15%)	1 (5%)	
SIG	80	63 (79%)	17 (21%)	0.623
0	39 (49%)	32 (51%)	7 (41%)	
1	26 (33%)	18 (29%)	8 (47%)	
2	6 (8%)	5 (8%)	1 (6%)	
3	6 (8%)	5 (8%)	1 (6%)	
4	3 (4%)	3 (5%)	0	
SIG collapsed	80	63 (79%)	17 (21%)	0.425
0	39 (49%)	32 (51%)	7 (41%)	
1-2	32 (40%)	23 (37%)	9 (53%)	
3-4	9 (11%)	8 (13%)	1 (6%)	
Postop death (30 days)	116	96 (83%)	20 (17%)	-
No	116	96	20	
Yes				
3-year survival (Exc 30-day mort)	116	96	20	
CSS	89% (SE 3%)	92% (SE 3%)	75% (SE 10%)	0.407
OS	82% (SE 4%)	83% (SE 4%)	75% (SE 10%)	0.452

Table 8-6 - Association between KRAS/BRAF status and overall/cancer specific survival after adjustment for other clinicopathological factors

Variable	Cancer specific survival				Overall survival			
	UVA		MVA		UVA		MVA	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Age	0.98 (0.75-1.27)	0.861	-	-	1.44 (1.15-1.80)	0.001	1.39 (1.05-1.83)	0.022
Sex	1.02 (0.68-1.51)	0.937	-	-	1.12 (0.81-1.55)	0.506	-	-
SIMD	0.97 (0.81-1.16)	0.761	-	-	0.99 (0.84-1.15)	0.845	-	-
ASA	0.68 (0.38-1.22)	0.198	-	-	1.21 (0.78-1.88)	0.388	-	-
TNM Stage	2.55 (1.73-3.75)	<0.001	2.92 (1.79-4.74)	<0.001	1.45 (1.12-1.87)	0.005	1.50 (1.08-2.08)	0.016
Tumour site	0.90 (0.60-1.35)	0.615	-	-	0.89 (0.64-1.25)	0.507	-	-
Differ	2.28 (1.40-3.70)	<0.001	-	0.089	1.89 (1.23-2.89)	0.004	-	0.130
BRAF	0.46 (0.23-0.91)	0.025	-	0.179	0.75 (0.48-1.17)	0.205	-	-
KRAS	1.75 (1.17-2.61)	0.007	1.64 (1.00-2.71)	0.050	1.35 (0.97-1.86)	0.073	1.47 (0.96-2.24)	0.079
SIG	1.34 (1.11-1.62)	0.003	1.34 (1.10-1.64)	0.004	1.33 (1.14-1.55)	<0.001	1.25 (1.07-2.08)	0.005

Table 8-7 Association between mutational status and mode of presentation

Mutation	Total	Elective	Emergency	P
APC	155	96 (62%)	59 (38%)	0.932
Wild	40 (26%)	25 (26%)	15 (25%)	
Mutant	115 (74%)	71 (74%)	44 (75%)	
P53	135	117 (87%)	18 (13%)	0.251
Wild	51 (38%)	42 (36%)	9 (50%)	
Mutant	84 (62%)	75 (64%)	9 (50%)	
KRAS	368	267 (73%)	101 (27%)	0.163
Wild	193 (52%)	146 (55%)	47 (47%)	
Mutant	175 (48%)	121 (45%)	54 (54%)	
BRAF	360	263 (73%)	97 (27%)	0.710
Wild	300 (83%)	218 (83%)	82 (85%)	
Mutant	60 (17%)	45 (17%)	15 (16%)	
PIK3CA	135	117 (87%)	18 (13%)	0.277
Wild	110 (82%)	97 (83%)	13 (72%)	
Mutant	25 (19%)	20 (17%)	5 (28%)	

8.6 Figures

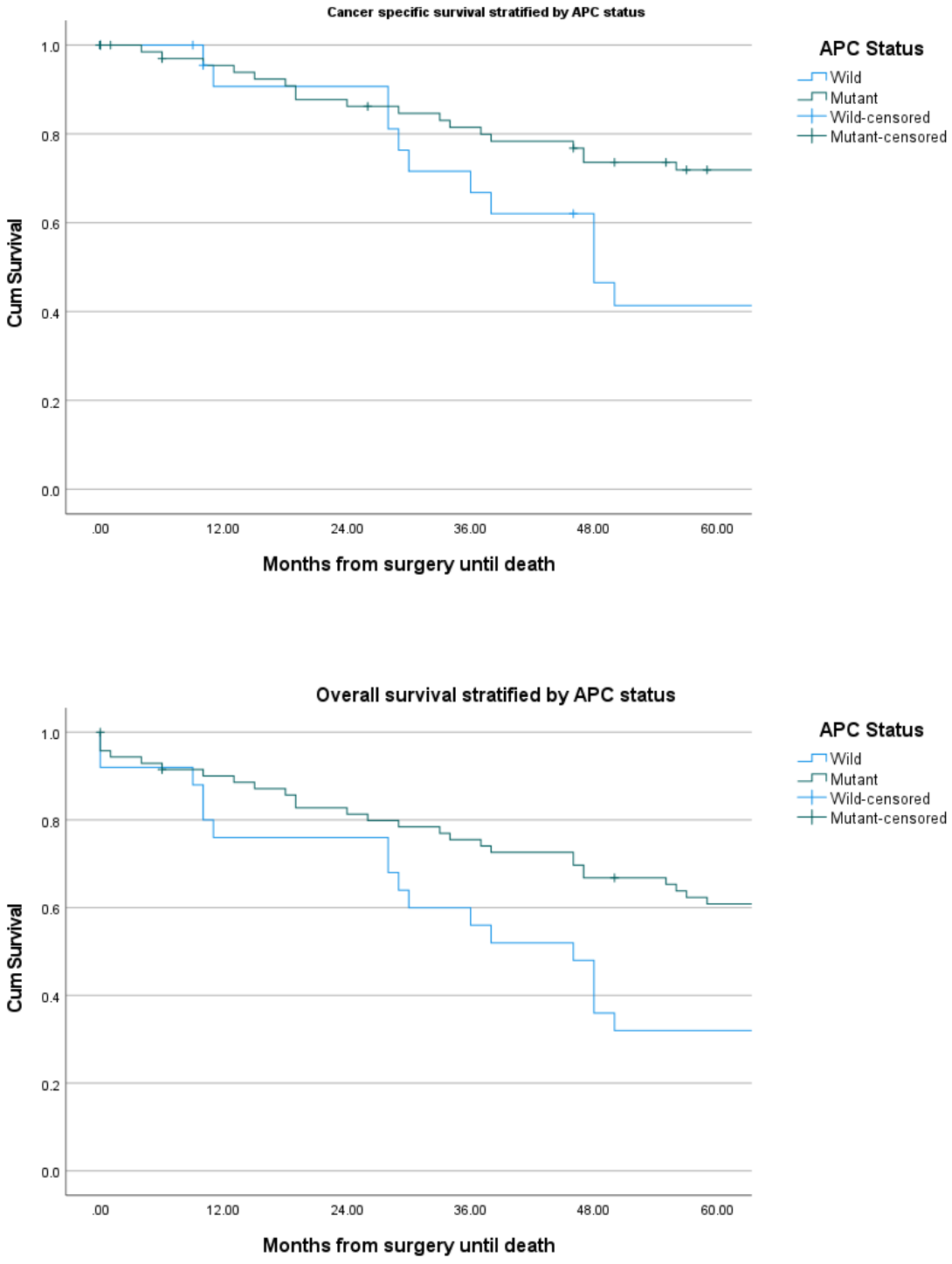


Figure 8-1 Cancer-specific (top) and overall survival (bottom) stratified by APC mutant status

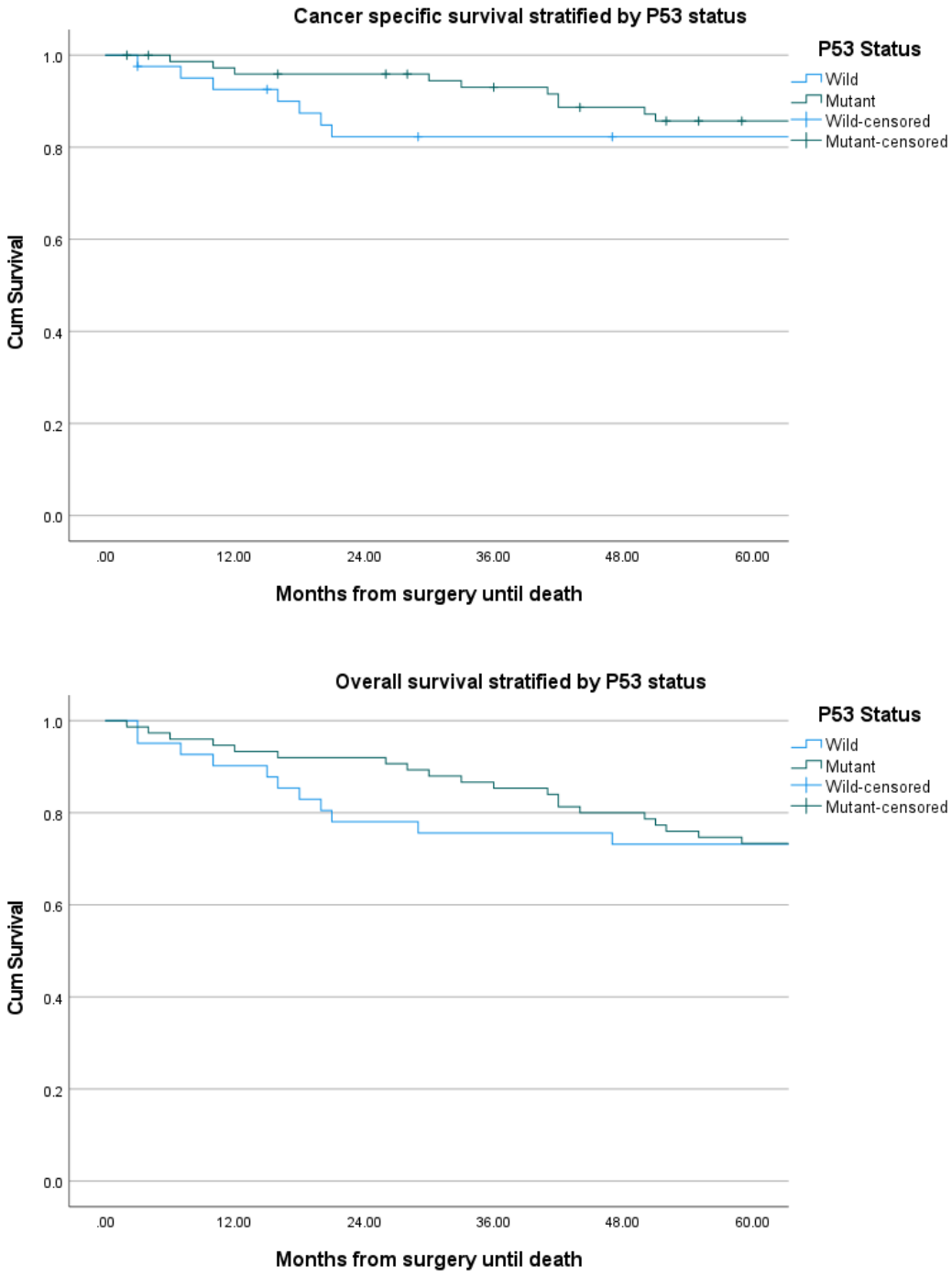


Figure 8-2 Cancer-specific (top) and overall survival (bottom) stratified by P53 mutant status

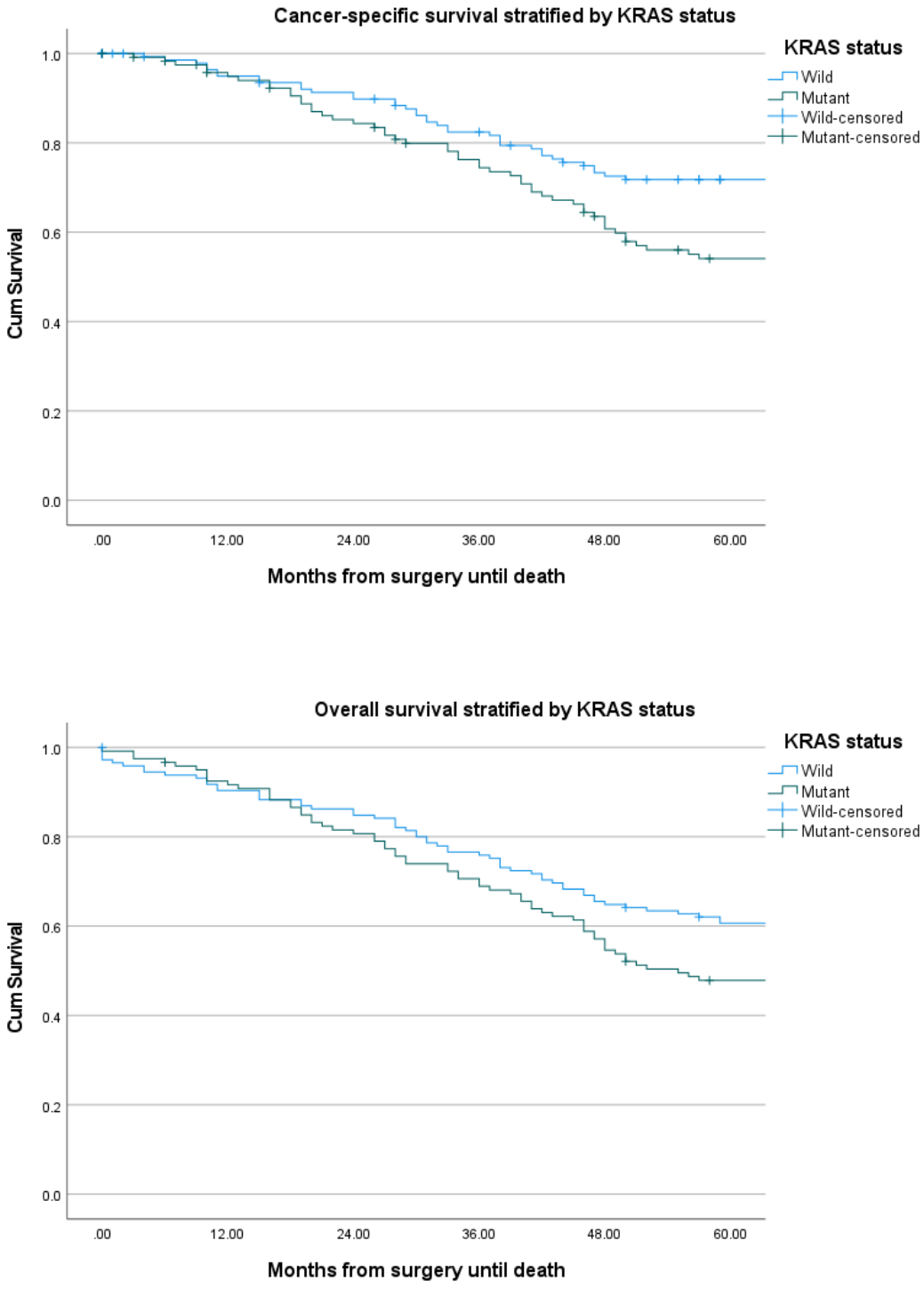


Figure 8-3 Cancer-specific (top) and overall survival (bottom) stratified by KRAS mutant status

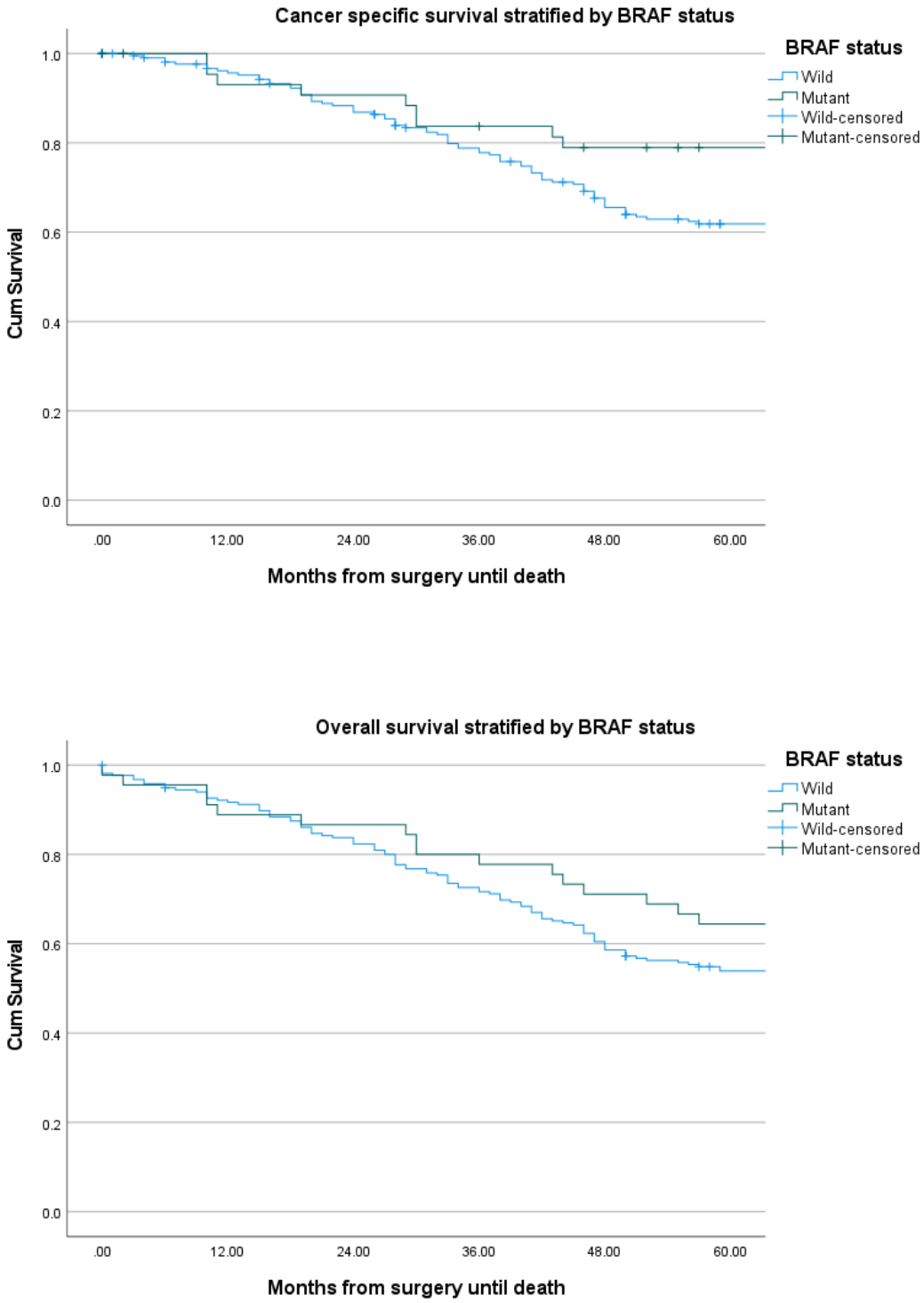


Figure 8-4 Cancer-specific (top) and overall survival (bottom) stratified by BRAF mutant status

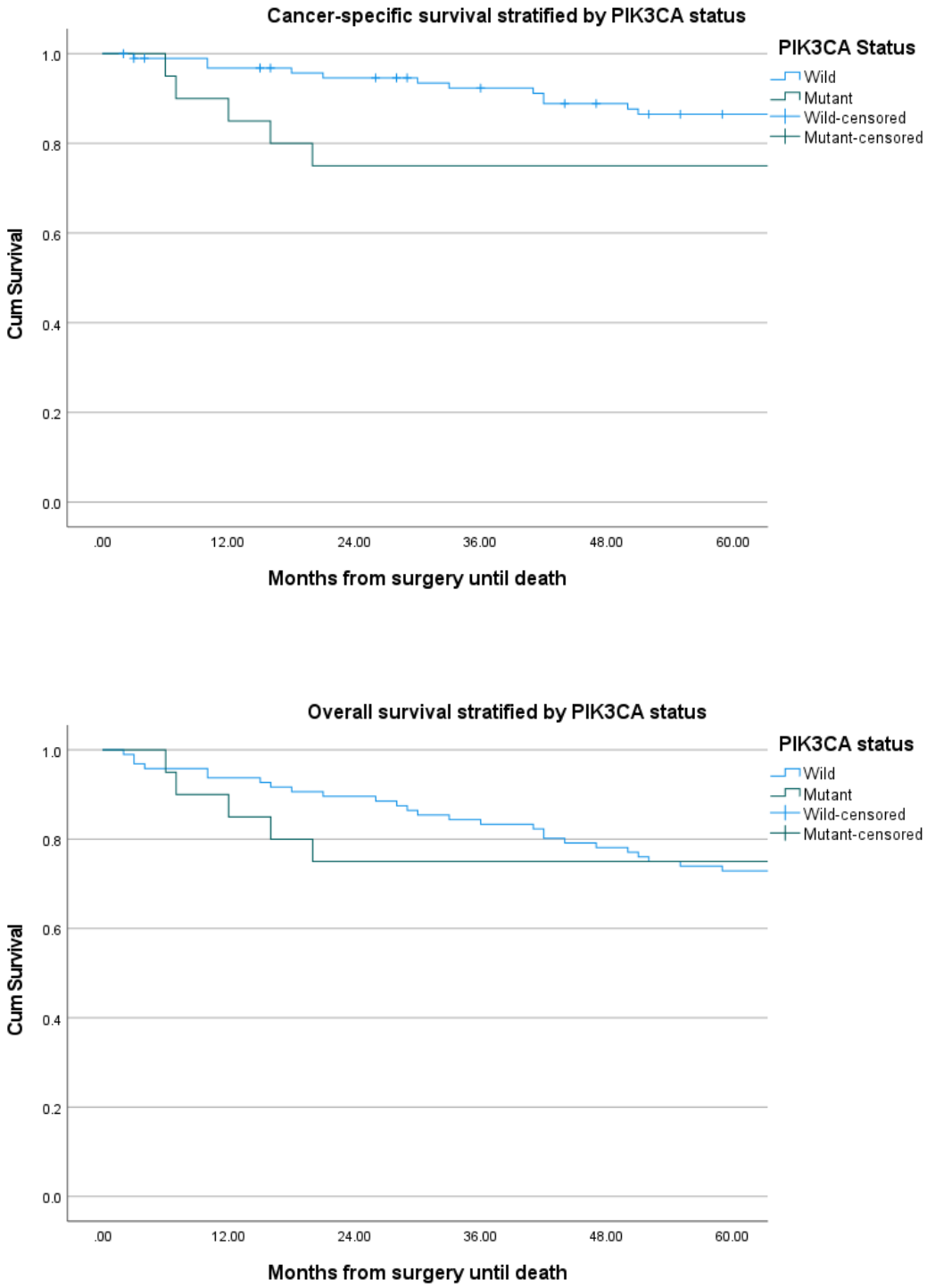


Figure 8-5 Cancer-specific (top) and overall survival (bottom) stratified by PIK3CA mutant status

9 Chapter 9 - Emergency Presentation as a Marker of High Risk TNM Stage II Colon Cancer

9.1 Introduction

As described in Chapter 1 and highlighted in a recent review[383], the management of TNM Stage II colon cancer is more complex than the management of TNM Stage I or TNM Stage III disease. The use of adjuvant chemotherapy within TNM Stage III disease is well established however the beneficial effect of adjuvant chemotherapy in TNM Stage II disease is less clear. However, trials including the QUASAR trial[185] have reported improved oncological outcomes following adjuvant chemotherapy in terms of recurrence (RR 0.78, 95% CI 0.66-0.93) and overall survival (RR 0.84, 95% CI 0.68-1.00), albeit with only modest effect. This has led to the subclassification of TNM Stage II disease into high risk or low risk. High risk clinicopathological features include emergency presentation, T4 disease, <12 nodes in the resection specimen, poorly differentiated tumours and the presence of margin involvement or extramural venous invasion. Clinical guidelines including those by the National Institute of Clinical Excellence (NICE)[257], The Association of Coloproctology of Great Britain and Ireland (ACPGBI)[184] and the American Society of Colon and Rectal Surgeons (ASCRS)[147] recommend the consideration of those patients with high risk features for adjuvant chemotherapy.

As described within Chapter 5, an increased preoperative systemic inflammatory response is associated with adverse short-term and long-term outcomes independent of TNM Stage. Emergency presentation is currently considered a high-risk factor in TNM Stage II disease however an elevated preoperative systemic inflammatory response is not an established risk factor. Within Chapter

5, it was shown that across TNM I-III colon cancer emergency presentation no longer remained significant for oncological outcomes after adjustment for other factors including the preoperative systemic inflammatory response.

The aim of the present study was to analyse the effects of emergency presentation on short-term and long-term oncological outcomes when controlled for other factors including the established features of high-risk TNM Stage II colon cancer and the preoperative systemic inflammatory response within a cohort of patients undergoing resectional surgery with curative intent for TNM Stage II colon cancer.

9.2 Methods

Patients undergoing curative surgery for TNM Stage I-III colon cancer in the West of Scotland were identified as previously described within Chapters 3 and 4. Patients undergoing curative surgery for TNM Stage II colon cancer on either an elective or emergency basis as previously defined were selected for inclusion within the present study.

Tumour factors, host factors, short-term and long-term survival was defined as described in Chapters 3 and 4. The preoperative systemic inflammatory response was stratified using Systemic Inflammatory Grade as described within Chapter 5.

9.2.1 Statistical Analysis

The relationship between clinicopathological characteristics and mode of presentation was examined using the Chi-squared test. The relationship between clinicopathological characteristics and postoperative mortality was examined using binary logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs). Variables with a p-value of <0.1 on univariate analysis were entered into a multivariate model using the backwards conditional method.

Overall and cancer specific survival has been carried out excluding postoperative deaths using Cox's proportional hazards model to calculate hazard ratios (HRs) and 95% confidence intervals (95% CIs). Variables with a p-value of <0.1 on univariate analysis were entered into a multivariate model using the backwards conditional method. Adjuvant chemotherapy was included in the multivariate model regardless of significance on univariate analysis. The life table function of

SPSS was used to calculate 3-year overall and cancer specific survival. Results have been displayed as percentage 3-year overall/cancer specific survival and percentage standard error (SE). Survival has been displayed graphically using Kaplan-Meier Graphs.

Statistical analysis was carried out using IBM SPSS statistics for Windows Version 25 (IBM Corporation, Armonk, New York, USA). A p-value of ≤ 0.05 was considered statistically significant throughout.

9.3 Results

9.3.1 All Patients

6549 patients were identified who had been diagnosed with colorectal cancer in the West of Scotland from January 2011 to December 2014. Of these, 1161 patients underwent resectional surgery with curative intent for TNM Stage II disease and met the inclusion criteria for this study.

The majority of patients were male (53%), aged >65 (74%) and underwent an elective (80%) R0 resection (99%). 28%/24%/21%/14%/13% of patients had a preoperative Systemic Inflammatory Grade of 0/1/2/3/4 respectively.

The median follow-up of survivors was 69 months (range 45-95 months). 38 patients (3%) died within 30 days of surgery. After exclusion of postoperative deaths there were 328 deaths of which 43% were cancer related.

9.3.2 Association Between Clinicopathological Factors and Mode of Presentation in TNM Stage II Colon Cancer

The association between clinicopathological factors and mode of presentation is shown in Table 9-1. Emergency presentation was associated with age<65 or >74 ($p=0.004$), female sex ($p=0.031$), socio-economic deprivation ($p<0.001$), current smokers ($p<0.001$), increased ASA classification ($p<0.001$), T4 disease ($p<0.001$), extramural venous invasion ($p<0.001$), positive margins ($p=0.019$), increased SIG ($p<0.001$), the use of adjuvant chemotherapy ($p=0.002$) and postoperative

mortality (p<0.001). After exclusion of 30-day mortality, emergency presentation was associated with adverse 3-year cancer-specific survival (84% versus 94%, p<0.001) and overall survival (77% versus 87%, p<0.001).

9.3.3 Association Between Clinicopathological Factors and Postoperative Mortality in TNM Stage II Colon Cancer

The association between clinicopathological factors including mode of presentation and 30-day mortality in patients undergoing curative surgery for TNM Stage II colon cancer is shown in Table 9-2.

On univariate analysis: older age (p<0.001), emergency presentation (p<0.001), ASA classification (p<0.001) and SIG (p<0.001) were associated with 30-day mortality. No association was seen between postoperative mortality and sex (p=0.530), SIMD (p=0.751), smoking (p=0.210), tumour site (p=0.842), T Stage (p=0.261), lymph node yield (p=0.137), tumour differentiation (p=0.526), EMVI (p=0.537) or margin involvement (p=0.650). On multivariate analysis, age (OR 2.11, p=0.014), ASA classification (OR 2.17, p=0.003) and SIG (OR 1.37, p=0.002) remained associated with postoperative mortality.

9.3.4 Association Between Clinicopathological Factors Including Mode of Presentation and Long-Term Outcomes in TNM Stage II Colon Cancer

The association between clinicopathological factors including mode of presentation and long-term oncological outcomes after exclusion of postoperative deaths is shown in Table 9-3.

For cancer specific survival: age ($p<0.001$), sex ($p=0.060$), mode of presentation ($p<0.001$), smoking ($p=0.008$), ASA classification ($p=0.007$), T Stage ($p<0.001$), lymph node yield ($p=0.046$), EMVI ($p=0.007$), margin involvement ($p<0.001$) and Systemic Inflammatory Grade ($p<0.001$) were significant on univariate analysis. No association was seen between SIMD ($p=0.120$), tumour site ($p=0.242$), tumour differentiation ($p=0.477$) or adjuvant chemotherapy ($p=0.203$) and cancer specific survival. When those factors significant on univariate analysis (and adjuvant chemotherapy) were entered into the multivariate model: mode of presentation (HR 1.57, $p=0.070$), T Stage (HR 2.72, $p<0.001$), margin involvement (HR 3.01, $p=0.014$), SIG (HR 1.18, $p=0.065$) and adjuvant chemotherapy (HR 0.48, $p=0.008$) remained associated with cancer specific survival.

For overall survival: age ($p<0.001$), SIMD ($p=0.006$), mode of presentation ($p<0.001$), smoking ($p<0.001$), ASA classification ($p<0.001$), T Stage ($p<0.001$), lymph node yield ($p<0.001$), EMVI ($p=0.005$), margin involvement ($p=0.001$), SIG ($p<0.001$) and adjuvant chemotherapy were significant on univariate analysis. No association was seen between sex ($p=0.723$), tumour site ($p=0.155$) or differentiation ($p=0.845$) and overall survival. When those factors significant on

univariate analysis were entered into the multivariate model: age (HR 1.45, p<0.001), ASA classification (HR 1.30, p=0.016), T Stage (HR 1.41, p=0.036), lymph node yield (HR 1.48, p=0.031), margin involvement (HR 2.27, p=0.042), SIG (HR 1.26, p<0.001) and adjuvant chemotherapy (HR 0.53, p=0.007) remained associated with overall survival.

9.3.5 3-Year Overall Survival Stratified by Systemic Inflammatory Grade and Number of High-Risk Features

3-year overall survival stratified by both the number of high-risk factors of TNM Stage II disease and Systemic Inflammatory Grade is shown in Table 9-4 for the whole cohort and an elective presentation only subgroup. Within the whole cohort this is displayed graphically in Figure 9-1.

In both elective and emergency patients, 3-year overall survival was 84%. In patients with no high-risk factors, 3-year overall survival was 95%/89%/85%/73%/83% (p=0.045) for SIG O/1/2/3/4 respectively. In patients with one high risk factor, 3-year overall survival was 91%/86%/79%/84%/76% (p=0.006) for SIG 0/1/2/3/4 respectively. In patients with two or more high risk factors, 3-year overall survival was 92%/87%/81%/66%/55% (p<0.001) for SIG 0/1/2/3/4 respectively.

In elective patients only, 3-year overall survival was 86%. In patients with no high-risk factors, 3-year overall survival was 95%/91%/88%/62% (p=0.016) for SIG O/1/2/3 respectively (fewer than 10 patients in SIG 4 subgroup therefore survival analysis not performed). In patients with one high risk factor, 3-year

overall survival was 92%/86%/82%/86%/71% (p<0.001) for SIG 0/1/2/3/4 respectively. In patients with two or more high risk factors, 3-year overall survival was 91%/88%/83%/62%/50% (p=0.002) for SIG 0/1/2/3/4 respectively.

9.3.6 3-Year Cancer-Specific Survival Stratified by Systemic Inflammatory Grade and Number of High-Risk Features

3-year cancer-specific survival stratified by both the number of high-risk factors of TNM Stage II disease and Systemic Inflammatory Grade is shown in Table 9-5 for all patients and elective patients only and in Figure 9-1 for all patients.

In both elective and emergency patients, 3-year cancer-specific survival was 91%. In patients with no high-risk factors, 3-year cancer-specific survival was 96%/97%/91%/91%/92% (p=0.011) for SIG 0/1/2/3/4 respectively. In patients with one high risk factor, 3-year cancer-specific survival was 97%/97%/88%/94%/86% (p=0.133) for SIG 0/1/2/3/4 respectively. In patients with two or more high risk factors, 3-year cancer-specific survival was 94%/94%/83%/78%/70% (p=0.073) for SIG 0/1/2/3/4 respectively.

In elective patients only, 3-year cancer-specific survival was 94%. In patients with no high-risk factors, 3-year cancer-specific survival was 96%/96%/92%/92% (p=0.553) for SIG O/1/2/3 respectively (fewer than 10 patients in SIG 4 subgroup therefore survival analysis not performed). In patients with one high risk factor, 3-year cancer-specific survival was 99%/98%/95%/95%/85% (p=0.049) for SIG 0/1/2/3/4 respectively. In patients with two or more high risk factors, 3-year

cancer-specific survival was 94%/97%/83%/85%/62% (p=0.146) for SIG 0/1/2/3/4 respectively.

9.4 Discussion

The results of the present study show that within a large regional cohort of patients who underwent curative resection for TNM Stage II colon cancer, after adjustment for other factors including the preoperative systemic inflammatory response as measured by Systemic Inflammatory Grade, emergency presentation was not independently associated with postoperative mortality, cancer specific survival or overall survival. Furthermore, the preoperative systemic inflammatory response was independently associated with significantly worse overall and cancer-specific survival in both the whole cohort and the elective only cohort, including those patients with no other high-risk features who are not currently candidates for adjuvant chemotherapy.

A number of clinicopathological factors are currently used to define high risk TNM Stage II colon cancer and are therefore key in the clinical decision-making regarding adjuvant chemotherapy. The effect of adjuvant chemotherapy in TNM Stage II disease remains uncertain however both the QUASAR trial[185] and a recent meta-analysis[186] reported improved survival with adjuvant chemotherapy in selected cases. This is reflected in several current guidelines[147,184,257]. With only a moderate benefit of adjuvant chemotherapy being seen within the aforementioned studies, there remains a need to optimise the indications for adjuvant treatment for TNM Stage II disease, particularly because this early-stage disease is likely to become more prevalent with ongoing measures to improve bowel screening uptake and sensitivity.

The majority of the current literature reports an independent association between emergency presentation and worse overall/cancer-specific survival[126,127,129,226] although this was not seen in the present study. Contrary to

the majority of the pre-existing literature, the present study is specific for TNM Stage II disease and controls for the preoperative systemic inflammatory response.

The relevance of the systemic inflammatory response in TNM Stage II colon cancer is not limited to emergency presentations. In the elective cohort, 28%/21%/9%/8% of patients had a SIG of 1/2/3/4 respectively. When considered alongside the established high-risk features of TNM Stage II disease, those patients with no high-risk features (and therefore not currently deemed to be candidates for adjuvant chemotherapy) and an elevated preoperative SIR have significant worse outcomes than those patients with established high-risk features but a normal preoperative SIR (who are candidates for adjuvant therapy).

There is now good evidence that the perioperative systemic inflammatory response has prognostic value. Therapeutic strategies to attenuate this response have the potential to improve both short-term and long-term outcomes in patients. Recently, the use of corticosteroids to attenuate the systemic inflammatory response has received worldwide attention within the context of COVID-19 – the RECOVERY trial reported a significant improvement in 28-day survival following administration of dexamethasone[384]. Thus far, few trials have examined the effect of dexamethasone within colon cancer, other than in the reduction of postoperative nausea and vomiting. However, a meta-analysis of gastrointestinal cancers reported a reduction in the postoperative systemic inflammatory response and a reduction in both overall and infective complications in those patients who received preoperative corticosteroids[49]. Similar findings were reported in a recent observational study[385]. While these

studies predominantly included elective surgery, patients undergoing emergency surgery could potentially have a greater magnitude of benefit from preoperative corticosteroids given the elevated systemic inflammatory response observed within this cohort. As described subsequently in Chapter 10, a UK wide survey has reported equipoise for further investigation into the impact of single dose perioperative dexamethasone administration on outcomes in colorectal cancer. Other emerging treatments in colorectal cancer include immunotherapy[386] however, to date, immunotherapy has mainly been restricted to advanced disease. Perioperative use of immunotherapy within colorectal cancer has yet to be explored but may be beneficial, particularly in those patients with an elevated preoperative SIR.

In the present study, poorly differentiated tumours were not associated with worse overall or cancer-specific survival on either univariate or multivariate analysis. Two recent reviews[186,387] reported no survival benefit with adjuvant chemotherapy for poorly differentiated tumours in TNM Stage II disease. The justification in considering poor differentiation as a high-risk feature within TNM Stage II colon cancer is therefore questionable given that tumour differentiation does not appear to be independently associated with adverse outcomes in TNM Stage II colon cancer after adjustment for other clinicopathological factors.

This study has limitations due to its retrospective nature. Preoperative CRP was not measured routinely in all centres hence the presence of missing data for a significant proportion of patients. Nonetheless the sample size remained large and would limit the degree of bias. Importantly, the present findings can be readily tested using routinely collected data. Given the retrospective, observational nature of this study, adjuvant chemotherapy was given according

to existing guidelines, therefore not to the inflamed but otherwise low risk Stage II patients. This may partially account for the adverse outcomes seen in inflamed but otherwise low risk patients. To account for this, adjuvant chemotherapy was included within the multivariate model regardless of significance on univariate analysis. Finally, the definition of emergency presentation in the literature is variable between studies. Within the present study, emergency presentation was defined as an unplanned admission requiring definitive treatment within 72 hours of presentation. This is the most common definition used in the literature however other definitions do exist. This adds weight to the argument that the more objectively measured SIR should be used as a marker of high risk TNM Stage II disease rather than the more subjective emergency presentation.

In conclusion, the present study shows the preoperative systemic inflammatory response (as measured by SIG) to be an independent predictor of poorer short-term and long-term outcomes in TNM Stage II colon cancer and indeed has a greater impact on long-term outcomes than emergency presentation which did not retain independent significance for overall/cancer specific survival despite being considered a high-risk factor. Future work in the form of a prospective trial is required to include the preoperative systemic inflammatory response as an indicator of high-risk stage II disease and therefore as a potential indicator for chemotherapy in patients with TNM stage II colon cancer.

9.5 Tables

Table 9-1 Association between mode of presentation and clinicopathological factors in patients undergoing resectional surgery with curative intent for TNM Stage II colon cancer

Variable	Total	Elective	Emergency	P
Total	1161	935 (81%)	226 (20%)	
Age	1161	935 (81%)	226 (20%)	0.004
<65	307 (26%)	235 (25%)	72 (32%)	
65-74	394 (34%)	338 (36%)	56 (25%)	
75+	460 (40%)	362 (39%)	98 (43%)	
Sex	1161	935 (81%)	226 (20%)	0.031
Male	614 (53%)	509 (54%)	105 (47%)	
Female	547 (47%)	426 (46%)	121 (54%)	
SIMD	1161	935 (81%)	226 (20%)	<0.001
1 (most deprived)	335 (29%)	245 (26%)	90 (40%)	
2	245 (21%)	202 (22%)	43 (19%)	
3	226 (20%)	180 (19%)	46 (20%)	
4	169 (15%)	151 (16%)	18 (8%)	
5 (least deprived)	186 (16%)	157 (17%)	29 (13%)	
Smoking	1092	892 (82%)	200 (18%)	<0.001
Non smoker	498 (46%)	418 (47%)	80 (40%)	
Ex-smoker	410 (38%)	343 (39%)	67 (34%)	
Smoker	184 (17%)	131 (15%)	53 (27%)	
ASA	1110	900 (81%)	210 (19%)	<0.001
1	88 (8%)	76 (8%)	12 (6%)	
2	594 (54%)	513 (57%)	81 (39%)	
3	372 (34%)	278 (31%)	94 (45%)	
4	54 (5%)	33 (4%)	21 (10%)	
5	2 (<1%)	0	2 (1%)	
Tumour site	1155	931 (81%)	224 (19%)	0.285
Right	681 (59%)	556 (60%)	125 (56%)	
Left	474 (41%)	375 (40%)	99 (44%)	
T Stage	1161	935 (81%)	226 (20%)	<0.001
3	856 (74%)	742 (79%)	114 (50%)	
4	305 (26%)	193 (21%)	112 (50%)	
Lymph node yield	1160	934 (81%)	226 (20%)	0.700
12+	960 (83%)	771 (83%)	189 (84%)	
<12	200 (17%)	163 (18%)	37 (16%)	
Differentiation	1161	935 (81%)	226 (20%)	0.425
Mod/well	961 (83%)	778 (83%)	183 (81%)	
Poor	200 (17%)	157 (17%)	43 (19%)	
EMVI	1134	909 (80%)	225 (20%)	<0.001
Negative	661 (58%)	559 (62%)	102 (45%)	
Positive	473 (42%)	350 (39%)	123 (55%)	
Margin involvement	1152	928 (81%)	224 (19%)	0.019
R0	1132 (99%)	916 (99%)	216 (96%)	
R1	20 (2%)	12 (1%)	8 (4%)	
SIG	759	550 (73%)	209 (28%)	<0.001
0	209 (28%)	192 (35%)	17 (8%)	
1	184 (24%)	152 (28%)	32 (15%)	
2	162 (21%)	117 (21%)	45 (22%)	
3	108 (14%)	47 (9%)	61 (29%)	
4	96 (13%)	42 (8%)	54 (26%)	
Adjuvant chemotherapy	1155	932 (81%)	223 (19%)	0.002
No	899 (78%)	743 (80%)	156 (70%)	
Yes	256 (22%)	189 (20%)	67 (30%)	

Postoperative mortality	1161	935 (81%)	226 (20%)	<0.001
No	1123 (97%)	916 (98%)	207 (92%)	
Yes	38 (3%)	19 (2%)	19 (8%)	
3-year survival	1123	916	207	
CSS	92% (SE 1%)	94% (SE 1%)	84% (SE 3%)	<0.001
OS	85% (SE 1%)	87% (SE 1%)	77% (SE 3%)	<0.001

Table 9-2 Association between clinicopathological factors including mode of presentation and postoperative mortality in patients undergoing resectional surgery with curative intent for TNM Stage II colon cancer

Variable	Univariate analysis		Multivariate analysis	
Age	2.89 (1.67-5.00)	<0.001	2.11 (1.16-3.83)	0.014
Sex	0.81 (0.42-1.56)	0.530	-	-
SIMD	0.96 (0.77-1.21)	0.751	-	-
Mode of presentation	4.43 (2.30-8.51)	<0.001	-	0.143
Smoking	1.38 (0.84-2.27)	0.210	-	-
ASA	2.90 (1.84-4.56)	<0.001	2.17 (1.29-3.65)	0.003
Tumour site	0.94 (0.48-1.81)	0.842	-	-
T Stage	1.48 (0.75-2.93)	0.261	-	-
Lymph node yield	1.75 (0.84-3.67)	0.137	-	-
Differentiation	1.29 (0.58-2.86)	0.526	-	-
EMVI	0.81 (0.41-1.58)	0.537	-	-
Margin involvement	1.60 (0.21-12.30)	0.650	-	-
SIG	1.62 (1.25-2.09)	<0.001	1.37 (1.05-1.79)	0.022

Table 9-3 Association between clinicopathological characteristics including mode of presentation and long-term outcomes in patients undergoing resectional surgery with curative intent for TNM Stage II colon cancer

Variable	Cancer specific survival				Overall survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	P	HR (95% CI)	p
Age	1.48 (1.19-1.84)	<0.001	-	0.124	1.85 (1.59-2.15)	<0.001	1.45 (1.18-1.78)	<0.001
Sex	1.38 (0.99-1.92)	0.060	-	0.441	1.04 (0.84-1.29)	0.723	-	-
SIMD	0.91 (0.81-1.03)	0.120	-	-	0.90 (0.83-0.97)	0.006	-	0.633
Mode of presentation	2.71 (1.92-3.83)	<0.001	1.57 (0.96-2.54)	0.070	1.74 (1.36-2.23)	<0.001	-	0.516
Smoking	1.36 (1.08-1.71)	0.008	-	0.192	1.29 (1.11-1.50)	<0.001	-	0.236
ASA classification	1.39 (1.09-1.78)	0.007	-	0.768	1.81 (1.55-2.10)	<0.001	1.30 (1.05-1.61)	0.016
Tumour site	0.82 (0.58-1.15)	0.242	-	-	0.85 (0.68-1.06)	0.155	-	-
T Stage	3.55 (2.55-4.95)	<0.001	2.72 (1.69-4.40)	<0.001	1.95 (1.55-2.44)	<0.001	1.41 (1.02-1.94)	0.036
Lymph node yield	1.50 (1.01-2.22)	0.046	-	0.280	1.54 (1.19-1.99)	<0.001	1.48 (1.04-2.11)	0.031
Diff	1.16 (0.77-1.77)	0.477	-	-	0.97 (0.73-1.30)	0.845	-	-
EMVI	1.59 (1.14-2.23)	0.007	-	0.741	1.37 (1.10-1.70)	0.005	-	0.337
Margin involvement	4.63 (2.27-9.46)	<0.001	3.01 (1.25-7.22)	0.014	2.73 (1.50-4.98)	0.001	2.27 (1.03-5.01)	0.042
SIG	1.44 (1.25-1.65)	<0.001	1.18 (0.99-1.41)	0.065	1.36 (1.24-1.49)	<0.001	1.26 (1.13-1.40)	<0.001
Adjuvant chemotherapy	0.76 (0.51-1.16)	0.203	0.48 (0.28-0.83)	0.008	0.41 (0.30-0.58)	<0.001	0.53 (0.34-0.84)	0.007

Table 9-4 3-year overall survival stratified by Systemic Inflammatory Grade and number of high-risk factors in patients undergoing resectional surgery with curative intent for TNM Stage II colon cancer

3-year cancer specific survival									
High risk factors	Total		0		1		2+		
All patients									
High risk factors	n	%3yr OS (%SE)	n	%3yr OS (%SE)	n	%3yr OS (%SE)	n	%3yr OS (%SE)	p
Total	711	84% (1%)	228	89% (2%)	269	84% (2%)	214	77% (3%)	0.004
0	198	93% (2%)	83	95% (2%)	79	91% (3%)	36	92% (5%)	0.643
1	178	87% (3%)	63	89% (4%)	63	86% (4%)	52	87% (5%)	0.450
2	152	82% (3%)	48	85% (5%)	52	79% (6%)	52	81% (5%)	0.318
3	101	74%% (4%)	22	73% (9%)	38	84% (6%)	41	66% (7%)	0.066
4	82	68% (5%)	12	83% (11%)	37	76% (7%)	33	55% (9%)	0.371
p	<0.001		0.045		0.006		<0.001		
Elective only									
High risk factors	n	%3yr OS (%SE)	n	%3yr OS (%SE)	n	%3yr OS (%SE)	n	%3yr OS (%SE)	p
Total	524	86% (2%)	190	89% (2%)	206	86% (2%)	128	81% (3%)	0.139
0	183	93% (2%)	75	95% (3%)	75	92% (3%)	33	91% (5%)	0.776
1	147	88% (3%)	57	91% (4%)	50	86% (5%)	40	88% (5%)	0.240
2	110	85% (3%)	41	88% (5%)	39	82% (6%)	30	83% (7%)	0.641
3	47	72% (7%)	13	62% (13%)	21	86% (8%)	13	62% (13%)	0.063
4	37	65% (8%)	4	-	21	71% (10%)	12	50% (14%)	0.652
p	<0.001		0.016		<0.001		0.002		

Table 9-5 3-year cancer-specific survival stratified by Systemic Inflammatory Grade and number of high-risk factors in patients undergoing resectional surgery with curative intent for TNM Stage II colon cancer

3-year cancer specific survival									
High risk factors	Total		0		1		2+		
All patients									
SIG	n	%3yr OS (%SE)	n	%3yr OS (%SE)	n	%3yr OS (%SE)	n	%3yr OS (%SE)	p
Total	711	91% (1%)	228	95% (2%)	269	93% (2%)	214	84% (3%)	<0.001
0	198	96% (1%)	83	96% (2%)	79	97% (2%)	36	94% (4%)	0.883
1	178	96% (2%)	63	97% (2%)	63	97% (2%)	52	94% (3%)	0.011
2	152	87% (3%)	48	91% (4%)	52	88% (5%)	52	83% (5%)	0.275
3	101	87% (3%)	22	91% (6%)	38	94% (4%)	41	78% (7%)	0.035
4	82	80% (5%)	12	92% (8%)	37	86% (6%)	33	(70% (8%)	0.365
p	<0.001		0.011		0.133		0.073		
Elective only									
SIG	n	%3yr OS (%SE)	n	%3yr OS (%SE)	n	%3yr OS (%SE)	n	%3yr OS (%SE)	p
Total	524	94% (1%)	190	95% (2%)	206	96% (1%)	128	89% (3%)	0.001
0	183	97% (1%)	75	96% (2%)	75	99% (1%)	33	94% (4%)	0.616
1	147	97% (1%)	57	96% (3%)	50	98% (2%)	40	97% (3%)	0.007
2	110	91% (3%)	41	92% (4%)	39	95% (4%)	30	83% (7%)	0.212
3	47	91% (4%)	13	92% (7%)	21	95% (5%)	13	85% (10%)	0.410
4	37	79% (7%)	4	-	21	85% (8%)	12	62% (15%)	0.581
p	0.004		0.553		0.049		0.146		

9.6 Figures

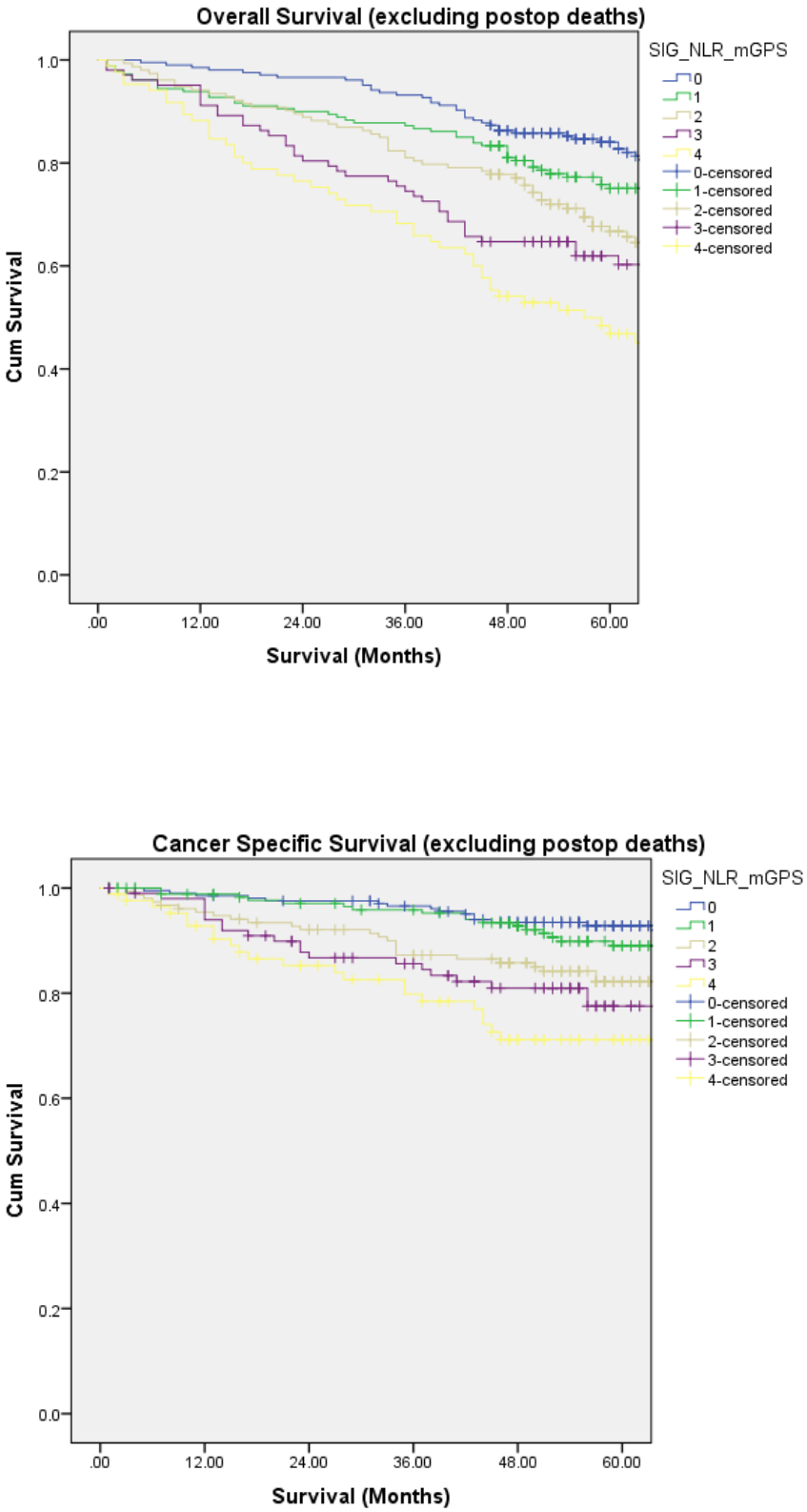


Figure 9-1 Overall and cancer specific survival stratified by Systemic Inflammatory Grade

10 Chapter 10 – Attitudes Towards the Use of Perioperative Steroids in Resectional Colorectal Cancer Surgery in the UK

10.1 Introduction

As previously described, the relationship between an increased perioperative systemic inflammatory response and likelihood of postoperative complications has been well documented in the medical literature[47,388,389] as has the relationship between the postoperative systemic inflammatory response, postoperative complications and long-term oncological outcomes and survival[42,47,390]. As described within previous chapters, patients undergoing surgery for colorectal cancer on an emergency basis have an elevated pre/postoperative systemic inflammatory response and adverse short-term and long-term outcomes when compared to patients undergoing surgery on an elective basis.

A previous retrospective propensity matched observational study, from our department that included patients undergoing elective resectional surgery for colorectal cancer, demonstrated a reduction in both the magnitude of the postoperative systemic inflammatory response and the overall complication rate in those patients who received single dose dexamethasone on induction of anaesthesia[385]. While a recent randomised controlled trial[391] documented the beneficial effect of single dose dexamethasone on postoperative nausea and vomiting, it did not measure the systemic inflammatory response. The administration of preoperative corticosteroids appears to be safe, with a

previous meta-analysis[49] not demonstrating any association between preoperative corticosteroid administration and an increased risk of complications including anastomotic leaks.

This questionnaire-based study aimed to examine both attitudes towards and current practice of perioperative steroid administration in resectional colorectal surgery. This would improve knowledge of current perioperative steroid use and perceived benefits and risk of this adjunct to anaesthesia. It would also help to assess whether there is current equipoise to carry out further research in this area, including the effect of perioperative steroid use on the postoperative systemic inflammatory response, morbidity and mortality within the context of curative colorectal cancer surgery. This may be of particular interest in the high-risk emergency group of patients who have raised pre/postoperative systemic inflammatory responses and adverse short-term and long-term outcomes when compared to elective patients.

10.2 Methods

This study utilised an internet based survey which was generated on the SurveyMonkey website[392] and included nine questions regarding the use of perioperative steroids in resectional colorectal cancer surgery (Table 10-1).

Once this survey was generated, the link to it was publicised on our department's Twitter feed. Additionally, a list of email addresses was obtained for surgeons and anaesthetists who have published in this area and the access link was circulated to them. As only a minority of participants were from outside the United Kingdom, we decided to exclude these to provide insight into current use of and attitudes towards perioperative steroid administration in the United Kingdom.

The survey was circulated in February 2019, closed for responses in March 2019 and no incentives were used to encourage participation. This study has been registered with the Research Registry – unique identifier "researchregistry5124". There are no conflicts of interest or sources of funding to declare. All responses to this survey were anonymous. Given the nature of this study (anonymous questionnaire), ethical approval for this study was not required.

10.2.1 Statistical Analysis

Numerical data has been displayed as numbers and/or percentages to the nearest whole number. The variation in responses between surgeons and anaesthetists have been compared using the Chi squared test with a two-tailed

p-value of <0.05 being considered statistically significant. Data was analysed and graphs were created using Microsoft Office and IBM SPSS Statistics Version 24.

10.3 Results

Overall, 100 people responded to this survey. 97 people answered Queston 1, 76% (n=74) of whom worked in the UK. Only the responses from those who worked in the UK were included in further analysis.

74 people answered Question 2. 54% of respondents were Consultant Anaesthetists, 22% Consultant Colorectal Surgeons, 11% Anaesthetic Trainees, 9% Surgical Trainees and 4% Consultant Non-Colorectal Surgeons.

70 people answered Question 3. 54% of respondents give some patients steroids in the perioperative period, 23% give all patients steroids in the perioperative period, 14% do not give any patients steroids in the perioperative period and 9% of respondents were unsure whether their patients receive steroids or not. 48 people provided a free text comment regarding choice of steroids with greater than 90% using dexamethasone. The majority of these who specified a dose administer between 3.3mg and 8mg of dexamethasone perioperatively.

70 people answered Question 4. Of those whose patients receive steroids, the decision regarding perioperative steroid use was made by anaesthetists in 75% of cases, is protocol driven in 12% of cases, is made by a combination of surgeons and anaesthetists in 11% of cases and is made by surgeons in 2% of cases. The remainder do not use perioperative steroids.

70 people answered Question 5. Of those who give perioperative steroids, 90% of respondents administer steroids intraoperatively or on induction of anaesthesia. 5% give steroids preoperatively and 5% give steroids postoperatively.

67 people answered Question 6 (Figure 10-1). 63% of respondents would be reluctant to give steroids to insulin-controlled diabetics, 45% to those deemed at high risk of wound infection, 43% to other diabetics, 16% to emergency cases and 6% to patients with renal failure. 10% would be reluctant to give steroids to other patients including those who were septic or at high risk of delirium.

67 people answered Question 7 (Figure 10-2). 94% of respondents think that perioperative steroids reduce postoperative nausea and vomiting, 27% think that they reduce the surgical stress response, 10% think that they reduce overall complications, 6% think that they have no beneficial effect, 4% think that they improve long term survival, 3% think that they reduce anastomotic leak rate and 3% think that they reduce postoperative mortality. 9% of respondents think that they have other beneficial effects which, based on free text responses, were predominantly analgesia effects.

66 people answered Question 8 (Figure 10-3). 55% of respondents would be concerned about uncontrolled diabetes/hyperglycaemia, 29% about increased wound complications, 15% about increased psychiatric/mood disturbance, 11% about insomnia, 8% about increased anastomotic leak rate, 5% about increased adrenal complications and 5% about increased gastric complications. 6% had other concerns and based on free text comments this was predominantly concern over long-term oncological outcomes.

60 people answered Question 9 (Figure 10-4). 87% of respondents think that there would be sufficient equipoise for a trial in this area. 58% think there would be sufficient equipoise for a 3-armed trial (no steroids versus low dose steroids versus high dose steroids), 32% for comparison of steroids versus no steroids and 13% for low versus high dose steroids. 13% of respondents did not think that there would be sufficient equipoise for a trial in this area.

As shown in Table 10-2, when responses of surgeons (any grade) were compared to anaesthetists (any grade), significantly more anaesthetists were concerned about giving steroids to non-insulin-controlled diabetics (58% versus 14%, $p=0.001$) and insulin dependent diabetics (80% versus 27%, $p<0.001$). Significantly more anaesthetists were concerned about uncontrolled diabetes/hyperglycaemia following steroid administration (73% versus 14%, $p<0.001$) and a higher proportion of surgeons were concerned about the effect of steroids on anastomotic leak rate (18% versus 2%, $p=0.021$). Significantly more surgeons than anaesthetists had either no concerns or other concerns regarding steroid administration (55% versus 18%, $p=0.002$).

10.4 Discussion

The present study was predominantly completed by Consultant Anaesthetists working in the United Kingdom. The majority of respondents gave some/all of their patients intraoperative steroids with the decision of whether to administer steroids being at the discretion of the anaesthetist in most cases. Reduction of postoperative nausea and vomiting was the primary aim of perioperative steroid administration. Reluctance to administer steroids was particularly notable for those patients who are diabetic, particularly insulin dependent and those at higher risk of wound infection. This study suggests that there is interest in carrying out a randomised controlled trial examining the impact of dexamethasone on the postoperative systemic inflammatory response and complications following colorectal resection with respondents indicating that a three-armed trial comparing no steroids versus low dose steroids versus high dose steroids would be the preferred format for this.

Based on this survey, there is concern regarding the use of perioperative single dose dexamethasone within the diabetic cohort of patients, particularly those with insulin dependent diabetes. Two recent randomised controlled trials[393,394] have reported a significant increase in blood glucose levels following dexamethasone in both diabetic and non-diabetic patients, although there was no significant difference in the size of the effect between diabetics/non-diabetics in either study. A recent Cochrane review[395] similarly reported increased blood glucose levels following dexamethasone administration, however evidence was limited and there was no evidence of increased adverse outcomes as a result of this although diabetic patients were excluded from the majority of trials.

A previous meta-analysis[49] analysed the impact of corticosteroids on both postoperative complications and the postoperative systemic inflammatory response. It reported a significant reduction in both overall complications and the postoperative systemic inflammatory response in those patients receiving preoperative corticosteroids although a significant reduction in infective complications was seen following surgery for liver but not colorectal malignancy. Similarly, a recent propensity matched cohort study[385] that included patients undergoing surgery for colorectal cancer, reported a significantly lower postoperative systemic inflammatory response and overall complications in those patients receiving dexamethasone. A further randomised trial[396]of 73 patients undergoing maxillofacial surgery, reported a significant reduction in postoperative CRP rise within the cohort receiving preoperative dexamethasone.

While a recent large multicentre randomised trial (DREAMS)[391] reported a significant reduction in postoperative nausea and vomiting in patients undergoing elective bowel surgery who received single dose perioperative dexamethasone, it did not investigate the difference in postoperative systemic inflammatory response between groups. Although not limited to colorectal surgery, the PACMAN trial[397] is currently underway and will include surgical complications. However, while CRP levels will be collected, postoperative levels of inflammation are not included as either primary or secondary outcomes. The PADDI trial[398] is currently underway and will include surgical site infection as a primary outcome, however this trial neither includes postoperative inflammation as a primary outcome, nor is limited to colorectal resections.

A previous systematic review by Watt and Colleagues[171] examined the objective evidence for reduction of the postoperative systemic inflammatory response

through the use of the Enhanced Recovery After Surgery (ERAS) pathway within colorectal cancer. Minimally invasive surgery represented the only factor identified to objectively influence the postoperative systemic inflammatory response. Although outwith the scope of the literature review presented in Chapter 2, previous literature has reported an association between emergency presentation and less frequent use of minimally invasive surgery[210,237]. It seems clear that in some emergency presentations, minimally invasive surgery would be neither appropriate, safe or technically feasible however where possible minimally invasive techniques should be utilised. Indeed, previous literature has reported improved short-term and long-term outcomes of laparoscopic surgery in emergency colorectal surgery[399,400]. Any future trial on the use of medication to attenuate the systemic inflammatory response must therefore adjust for surgical approach.

Limited literature exists reporting the effect of steroid use on long-term disease-free survival. One study comparing 515 patients with TNM Stage I-III rectal cancer did report, on multivariate analysis, improved disease-free and overall survival in those patients receiving intravenous dexamethasone. A follow-up study[401] of a previously conducted small trial of 43 patients undergoing colonic resection, also reported a higher rate of distant recurrence in patients receiving dexamethasone. However, a recently conducted large propensity matched cohort study[402] of 2729 patients undergoing breast cancer surgery, did not find an association between perioperative dexamethasone administration and increased recurrence or mortality. Furthermore, an observational study[403] of 679 patients undergoing pancreaticoduodenectomy for cancer, reported improved overall survival in patients given intraoperative dexamethasone.

Although the present study has focussed on the potential for using perioperative corticosteroids to attenuate the perioperative systemic inflammatory response, other pharmacological agents including non-steroidal anti-inflammatory drugs (NSAIDS) and COX-2 inhibitors may also offer potential benefit. Concerns have previously been raised with regard to the potential association between perioperative NSAID use and increased anastomotic leak rate. The literature has varied to this regard[404-406] however a recent multicentre study of over 4000 patients that examined the role of NSAIDs in reducing postoperative ileus in patients undergoing elective colorectal surgery did not show an association between NSAID use and increased anastomotic leak rate[407]. Previous research has suggested that there may be an association between NSAID and/or aspirin administration and reduced cancer recurrence[408], [409]. The association between perioperative NSAID administration and the postoperative systemic inflammatory response has not been investigated and would be of interest in future work.

The present study has several limitations. This survey is small, particularly for the subgroup analysis comparing responses between surgeons and anaesthetists. To encourage participation in the survey we intentionally kept survey length short and questions simple. Furthermore, medical professionals who have a greater interest in either perioperative steroid use and evidence based medical practice or have stronger opinions either for or against perioperative steroid use were more likely to respond therefore this may bias results. To mitigate against this we attempted to recruit participants through other avenues including relevant societies however this was not feasible due to cost implications or the policies of relevant organisations.

In summary, this study has suggested that while most patients currently receive postoperative steroids with the primary aim of reducing postoperative nausea and vomiting (PONV) they are not used routinely for all patients. Furthermore, no consensus exists as to the correct dose, even in the context of the prevention of PONV. On the basis of the results of this study, there would be interest in carrying out a randomised controlled trial in patients undergoing resectional surgery for colorectal cancer, with a three-armed RCT comparing no steroids versus low dose steroids versus high dose steroids being the most popular choice of design. Ideally, surgical and anaesthetic technique would be otherwise standardised. In our opinion, such a study should include postoperative complications as the primary outcome and a measure of the postoperative systemic inflammatory response (eg CRP or poGPS) as a secondary outcome. If included, diabetic patients and those at increased risk of wound infection would need close monitoring to ensure that they did not have an unacceptably increased risk of complications. Additionally, long-term follow-up of patients included in such a trial would be important to identify whether perioperative single dose steroid administration alters disease-free survival, although if not powered for this outcome then it may remain an area of uncertainty. Finally, subgroup analysis of the effect of perioperative dexamethasone within a cohort of patients undergoing resectional surgery for colorectal cancer on an emergency basis would be of interest.

10.5 Tables

Table 10-1 Questions included in online survey

Question 1: In which country/region do you work in?	
United Kingdom	Australia
Europe	Other (please specify)
USA	
Question 2: What is your grade and speciality?	
Anaesthetist (Consultant)	Consultant Surgeon (Non-Colorectal)
Anaesthetist (Trainee)	Career Grade Surgeon
Anaesthetist (Other)	Surgical Trainee
Consultant Surgeon (Colorectal)	Other (please specify)
Question 3: Do any of your patients receive steroids in the perioperative period? If yes, please specify the drug and dose or unknown if unsure.	
Yes (all)	No
Yes (some)	Unsure
Question 4: If you answered yes to Question 3 who makes the decision regarding administration of steroids? If you answered no to Question 3 please select N/A	
Surgeon	Part of ERAS or similar protocol
Anaesthetist	N/A
Combination	
Question 5: If you answered yes to Question 3 when are steroids given to patients? If you answered no to Question 3 please select N/A	
Preoperatively	Postoperatively
Intraoperatively/on induction of anaesthesia	N/A
Question 6: Are there any groups of patients to whom you would be reluctant to give perioperative steroids? (Select all that apply)	
Diabetics (diet/tablet controlled)	High risk of wound infection
Diabetics (insulin controlled)	Emergency cases
Renal failure	Other (please specify)
Question 7: Do you think that single dose steroids given perioperatively for colorectal cancer are associated with? (Select all that apply)	
Reduced postoperative nausea/vomiting	Reduced postoperative mortality
Reduced overall complications	Improved long term survival
Reduced anastomotic leaks	None of the above
Reduced surgical stress response	Other (please specify)
Question 8: Do you have concerns regarding the use of perioperative single dose steroids for patients undergoing colorectal cancer resection? (Select all that apply)	
Diabetes/hyperglycaemia	Adrenal complications
Increased wound complications	Gastric complications
Increased anastomotic leak rate	Renal failure
Psychiatric/mood problems	No concerns
Insomnia	Other (please specify)
Question 9: If a trial was set up examining steroid administration at induction of anaesthesia for colorectal resection, with the aim of addressing the effect on the postoperative systemic inflammatory response and complications, do you think there would be sufficient equipoise to recruit for the following: (Please select all that you feel would be of interest)	
2-armed trial – steroids vs no steroids	3-armed trial – no steroids vs low dose steroids vs high dose steroids
2-armed trial – low vs high dose steroids	Insufficient equipoise for a trial in this area

Table 10-2 Responses to views of perioperative steroids in surgeons (any grade) compared to anaesthetists (any grade)

	Surgeon	Anaesthetist	P
Groups of patients reluctant to give steroids			
Non-insulin dependent diabetes	3 (14%)	26 (58%)	0.001
Insulin dependent diabetes	6 (27%)	36 (80%)	<0.001
Renal failure	2 (9%)	2 (4%)	0.451
High risk wound infection	7 (32%)	21 (47%)	0.247
Emergency cases	1 (5%)	0 (0%)	0.150
Other	2 (9%)	3 (7%)	0.723
Associations of steroids			
Reduced postop nausea/vomiting	19 (86%)	44 (98%)	0.064
Reduced overall complications	3 (14%)	4 (9%)	0.551
Reduced anastomotic leaks	1 (5%)	1 (2%)	0.600
Reduced surgical stress response	8 (36%)	10 (22%)	0.220
Reduced postop mortality	1 (5%)	1 (2%)	0.600
Improved long term survival	2 (9%)	1 (2%)	0.202
None of the above	1 (5%)	0 (0%)	0.150
Other	0 (0%)	3 (7%)	0.215
Concerns regarding steroids			
Diabetes/hyperglycaemia	3 (14%)	32 (73%)	<0.001
Increased wound complications	4 (18%)	15 (34%)	0.178
Increased anastomotic leak rate	4 (18%)	1 (2%)	0.021
Psychiatric/mood problems	1 (5%)	9 (21%)	0.089
Insomnia	3 (14%)	4 (9%)	0.572
Adrenal complications	1 (5%)	2 (5%)	1
Gastric complications	2 (9%)	1 (2%)	0.210
Renal failure	0	0	X
Other	12 (55%)	8 (18%)	0.002
No concerns	12 (55%)	8 (18%)	0.002
Equipoise for trial			
Steroids vs no steroids	5 (25%)	14 (34%)	0.469
Low vs high dose steroids	5 (25%)	2 (4.9%)	0.021
No steroids vs low dose vs high dose	14 (70%)	22 (53.7%)	0.223
No equipoise for trial	3 (15%)	4 (9.8%)	0.546

10.6 Figures

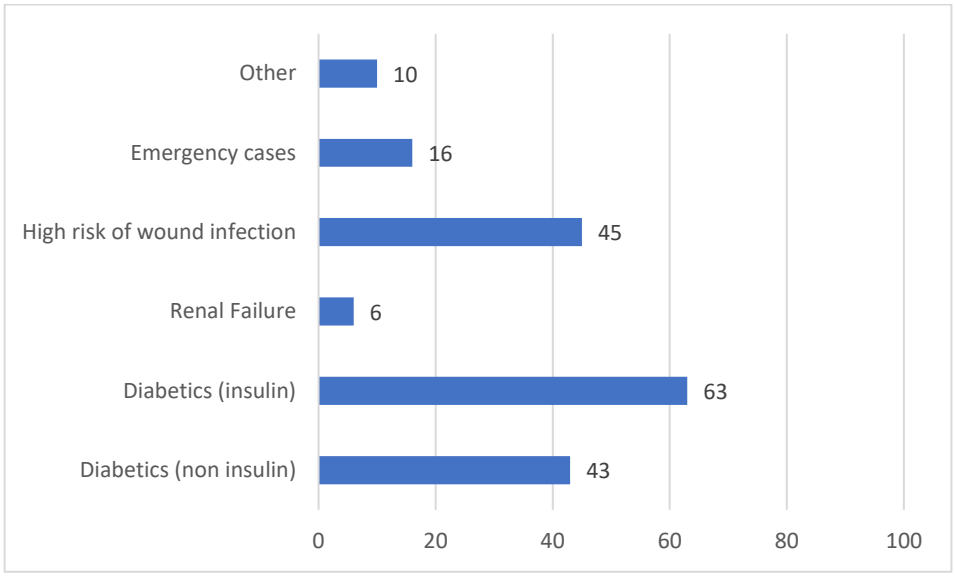


Figure 10-1 Are there any groups of patients to whom you would be reluctant to give perioperative steroids?

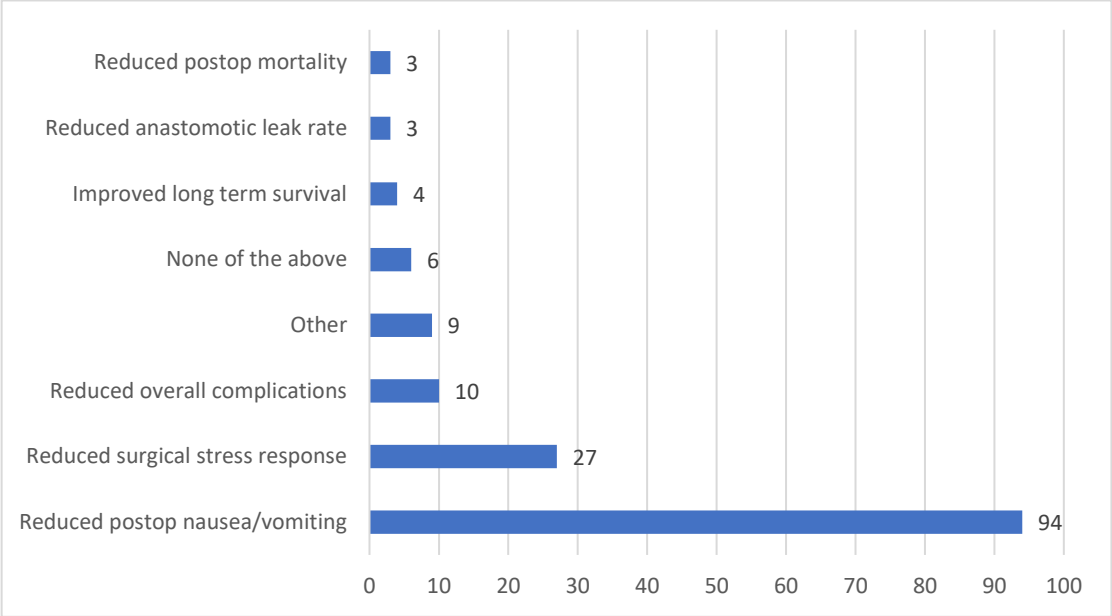


Figure 10-2 Do you think that single dose steroids given perioperatively for colorectal cancer are associated with:

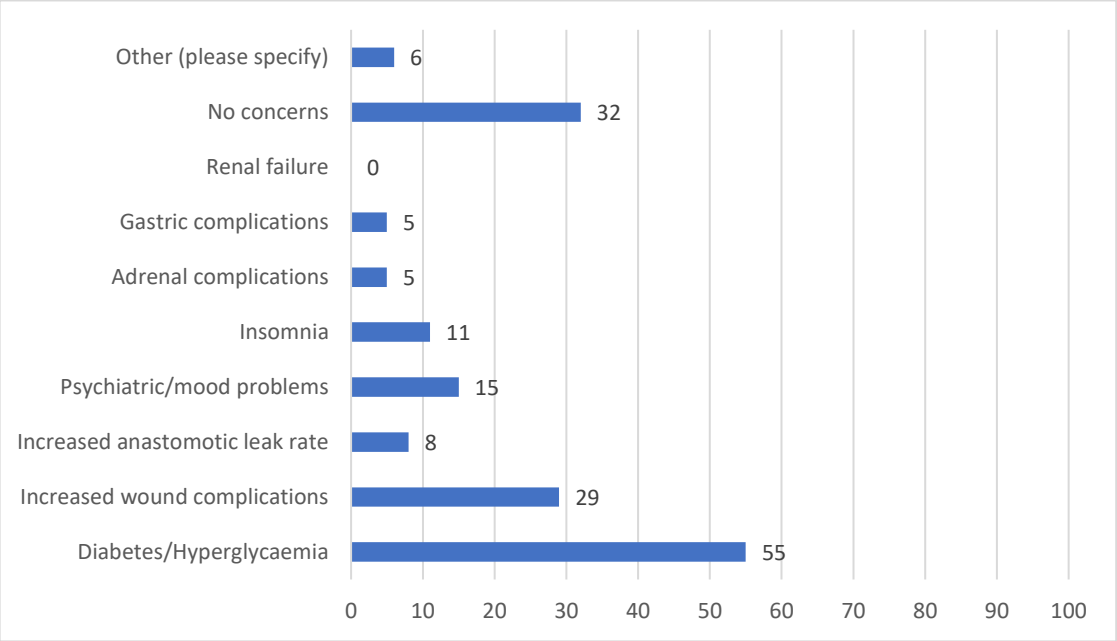


Figure 10-3 Do you have any concerns regarding the use of perioperative single dose steroids for patients undergoing colorectal cancer resection?

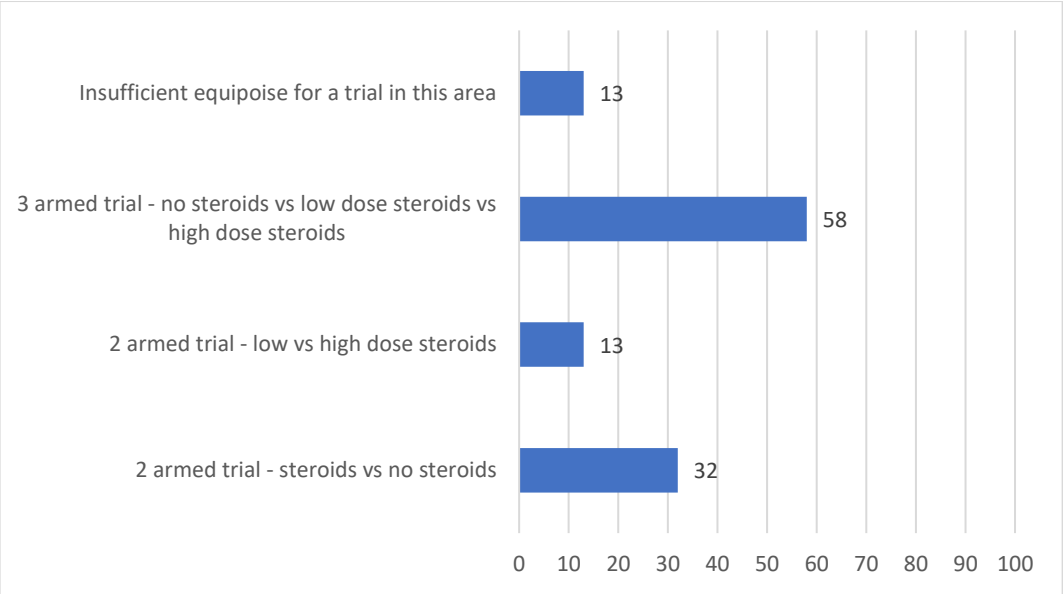


Figure 10-4 If a trial was set up examining steroids administered at induction of anaesthesia, do you think there would be sufficient equipoise to assess the following?

11 Conclusions and Future Work

11.1 Chapter by Chapter Summary

At the beginning of this period of research, it was clear that, based on pre-existing literature, patients presenting on an emergency basis with colorectal cancer were widely reported to have adverse short-term and long-term outcomes in comparison to patients undergoing investigation and treatment on a planned (elective) basis. This had been shown to be the case both on unadjusted survival analysis and after adjustment for basic clinicopathological factors including disease stage. Indeed, within TNM Stage II colorectal cancer, emergency presentation is considered to be a high-risk feature that may merit adjuvant chemotherapy. However, it was hypothesised that emergency presentation per se was not the independent factor associated with adverse outcomes within this high-risk group of patients. Rather, it seemed likely that a combination of tumour, host, perioperative and other factors may differ between elective and emergency presentations of colorectal cancer and these differences may account for the adverse outcomes observed.

The literature comparing elective and emergency presentations of colorectal cancer in terms of tumour, host and other factors had not been previously comprehensively summarised. Therefore, this thesis started with a systematic review and meta-analysis of the pre-existing literature as reported within Chapter 2. However, it was apparent that existing studies were heterogenous and although a comparison of unadjusted data was possible, and in some cases suitable for comparison in a meta-analysis, it was not feasible to compare

adjusted associations or outcomes. However, based on the comparison of unadjusted associations, it was clear that multiple tumour and host factors differed between elective and emergency presentations of colorectal cancer. Furthermore, within this systematic review and meta-analysis, a number of factors recognised to be important in the development and progression of colorectal cancer, including the systemic inflammatory response and mutational status had not previously been compared.

In Chapter 3, the association between mode of presentation and basic demographic factors was examined, including longitudinal change, tumour site (colon/rectum) and the presence of metastatic disease within a regional cohort of all patients diagnosed with colorectal cancer within the West of Scotland. In keeping with the findings of Chapter 2, an association was seen between emergency presentation, colon cancer and increased metastatic disease at diagnosis. On subgroup analysis of all patients undergoing resectional surgery with curative intent for TNM I-III colon cancer, emergency presentation was associated with adverse short-term and long-term outcomes even after adjustment for TNM Stage. This chapter (and the majority of this thesis) utilised a regional database of patients diagnosed with colorectal cancer in the West of Scotland between January 2011 and December 2014 therefore the need to broadly compare mode of presentation and outcomes prior to more detailed investigation was essential to confirm the rationale for this thesis. This regional database included approximately 50% of the population of Scotland and can therefore be assumed to be representative of colorectal cancer across Scotland. It was clear that there was a strong association between emergency presentation and colon cancer therefore, for the majority of this thesis, more in-depth investigation has been carried out only in patients undergoing resectional

surgery with curative intent for TNM I-III colon cancer. Nonetheless, further research into the association between tumour and host factors and short-term and long-term outcomes would be relevant to other patient subgroups identified within this chapter including rectal cancer, patients undergoing local (endoscopic) management of polyp cancers and patients with advanced (metastatic) disease. No longitudinal change was seen in the proportion of patients presenting as an emergency however the study period was relatively short (4 years) and conducted in a population with an already established bowel screening programme that was not significantly modified during the study period. Therefore, it is not unexpected that no longitudinal change was observed.

In Chapter 4, the association between mode of presentation and major clinicopathological factors including co-morbidity was examined in patients undergoing resectional surgery for TNM I-III colon cancer. The results of Chapter 4 confirm an independent association between younger age, higher ASA classification, smoking status, lower BMI, more advanced T Stage and emergency presentation of colon cancer and moreover, these factors were associated with short-term and/or long-term outcomes. Nonetheless, after adjustment for these factors, emergency presentation retained independent association with both short-term and long-term survival therefore it seemed likely that other factors were associated with mode of presentation and outcomes. More detailed examination of such factors has been carried out in subsequent chapters. It was of interest that younger patients (aged under 50) were more likely to present on an emergency basis. It may be that this is a result of non-inclusion within the bowel screening programme or due to delays in presentation, referral or investigation due to lower likelihood of colorectal cancer within the younger

population. However, recently an increased incidence of colorectal cancer has been observed within younger patients (under 50 years) and this has been associated with adverse outcomes[410]. Therefore, further research is warranted comparing younger patients (under 50 years) to the over 50s population to determine whether these patients are predisposed to emergency presentation due to differing tumour, host or other characteristics. ASA, but not Charlson Index was associated with emergency presentation. ASA is a subjective assessment that is likely to encompass a number of factors including age, acute illness, medical co-morbidities and frailty[411]. In terms of medical co-morbidities, elective and emergency presentations were broadly similar. However, Diabetes Mellitus appeared to be protective against emergency presentation. On further analysis of diabetic characteristics, no clear association was found between preoperative HbA1c or treatment type (diet/tablet/insulin). This association may be due to the incidental identification of anaemia during routine blood tests as part of ongoing diabetic follow up and subsequent diagnosis of colorectal cancer on an elective basis. Alternatively, regular engagement between patients with Diabetes Mellitus and healthcare practitioners as part of routine diabetes follow up may result in the reporting and subsequent investigation of symptoms that would have otherwise gone unreported. Although a similar pattern may have been expected in other co-morbidities including chronic kidney disease or ischaemic heart disease, it seems likely that patients with diabetes have more regular ongoing follow up. Validation of this observation within a different cohort would be of interest and additionally further analysis of this finding in terms of reasons for referral/investigation. However, this observation did not contribute to the adverse outcomes observed in emergency presentations.

In Chapter 5, the association between mode of presentation and the preoperative systemic inflammatory response was examined. As described in Chapter 1, the importance of the systemic inflammatory response in the development and progression of colorectal cancer is clear. The results of Chapter 5 show that the effect of the systemic inflammatory response within two different organ systems, as measured by the modified Glasgow Prognostic Score and Neutrophil-Lymphocyte Ratio, were independently associated with overall survival and thus combined into an overall Systemic Inflammatory Grade (SIG). After adjustment for the factors identified within Chapter 4, SIG remained independently associated with emergency presentation and furthermore with both short-term and long-term survival. Indeed, although emergency presentation remained independently associated with short-term survival after adjustment for SIG, emergency presentation did not remain significant for long-term survival. It is therefore clear that the systemic inflammatory response is a significant contributor to the disparity in outcomes seen between elective and emergency presentations of TNM I-III colon cancer. The precise relationship between the tumour and host remains poorly understood and further work in this field is required. Furthermore, although this chapter investigated the preoperative systemic inflammatory response, the utility of independent measurements of the systemic inflammatory response in the postoperative environment (for example utilising the postoperative Glasgow Prognostic Score and NLR) to better stratify outcomes should be considered. The systemic inflammatory response has clear prognostic implications in both elective and emergency presentations of colon cancer. Further work should be undertaken to investigate the effects on outcomes of modulating the

perioperative systemic inflammatory response in patients undergoing curative treatment for colon cancer.

In Chapter 6, the association between mode of presentation and CT-derived body composition was examined. The loss of lean muscle mass is recognised to be associated with a number of disease processes including cancer and closely linked to the systemic inflammatory response. As reported within Chapter 5, there is a clear association between emergency presentation and an elevated systemic inflammatory response when stratified using serological measurements. However, serological measurements of the systemic inflammatory response are unable to differentiate between short-term inflammation (within hours to days prior to emergency presentation) and long-term inflammation (within weeks to months prior to emergency presentation). It is unlikely that a significant loss of lean muscle mass occurs within hours-days prior to emergency presentation. The results of Chapter 6 show that emergency presentation is indeed associated with a loss of lean muscle mass as measured by skeletal muscle index. This would suggest that patients presenting as an emergency with colon cancer have a chronically elevated systemic inflammatory response in comparison to those patients presenting electively and this inflamed state may predispose these patients to presenting emergently. Prehabilitation is of current interest in patients undergoing resectional surgery with curative intent for colorectal cancer. However, it remains to be seen whether a relatively short period of increased physical activity can reverse the chronic muscle loss observed in these patients, likely associated with an increased metabolic state. The results of Chapter 6 show that a reduction in skeletal muscle mass (skeletal muscle index) is common and adversely prognostic and, additionally, a loss of skeletal muscle density is associated with adverse outcomes. This loss of skeletal muscle density,

widely assumed to be the result of fat infiltration into muscle remains incompletely understood and further investigation is required. To date, interest in CT-derived body composition has been predominantly limited to the research environment. However, particularly with the increasing availability of artificial-intelligence based methods of body composition analysis, the prognostic role of CT-derived body composition may become more widely used within the clinical setting[412]. Within the present investigation only fat and muscle mass/density were examined however other CT-derived markers including liver density/volume and aortic calcification[413] have been shown to be prognostic and further investigation of these factors including their relationship with mode of presentation is required.

In Chapter 7, the participation of patients diagnosed with colorectal cancer within the West of Scotland in the most recent round of bowel screening (within two years prior to diagnosis) was analysed. Less than 20% of colorectal cancer within the West of Scotland was diagnosed through screening. Failure to diagnose through screening was predominantly a result of non-invitation to screening (37% of all patients diagnosed with colorectal cancer), non-return of screening test (46% of all patients invited to screening) or negative screening result (38% of all patients who returned a screening test). It seems likely that increasing engagement with the bowel cancer screening programme and optimisation of screening to reduce false negative tests is perhaps the most promising way to improve outcomes in patients diagnosed with colorectal cancer by increasing the proportion of patients diagnosed with and treated for colorectal cancer on an elective basis at an early disease stage. This study included a cohort of patients undergoing screening using gFOBT. Within Scotland, screening using gFOBT has now been replaced with FIT. Carrying out a

similar study in patients screened using FIT would audit current practice and help to guide the need for optimisation of the screening programme with increased identification of early-stage disease in the elective setting.

In Chapter 8, the association between tumour mutational status, mode of presentation and outcomes in patients undergoing curative resectional surgery for TNM I-III colon cancer was examined, As described in Chapter 1, colorectal cancer most commonly develops through a series of genetic mutations. KRAS mutational status been shown to be associated with adverse oncological outcomes, particularly in advanced (metastatic) disease. The results of Chapter 8 show that KRAS mutational status is also associated with adverse outcomes in patients undergoing resectional surgery with curative intent for non-metastatic disease. The present study did not show a significant association between mutational status and mode of presentation however patient numbers were small and further research is required is warranted in this field. Furthermore, the precise association between tumour and host remains poorly understood however the present results suggest a possible link between KRAS mutational status and the systemic inflammatory response. Further, prospective research, is required in this area. More recently, advances in circulating tumour DNA (ctDNA) have facilitated the development of ctDNA based genomic profiling. This has been summarised in a recent comprehensive review[414]. The utility of this within colorectal cancer remains unclear, in particular due to the simplicity of endoscopic investigation with tissue sampling for colorectal cancer. Nonetheless, results within gastrointestinal cancer, including assessment of KRAS and BRAF status appear promising and this is an area of further interest.

In Chapter 9, the role of emergency presentation as a high-risk factor in TNM Stage II colon cancer was examined in addition to other established high-risk features and the systemic inflammatory response. The results of Chapter 9 show that after adjustment for the other high-risk factors and for adjuvant chemotherapy, emergency presentation did not remain associated with adverse outcomes. Indeed, the results show that SIG is more strongly associated with adverse outcomes than some of the other established factors. On the basis of this, re-evaluation of the current high-risk features should be carried out, with consideration given to the role of adjuvant therapy in patients with an elevated preoperative systemic inflammatory response.

In Chapter 10, the attitudes towards corticosteroid administration in the perioperative management of patients undergoing resectional surgery for colorectal cancer were examined in a national survey. The results show that corticosteroids were frequently administered with the primary objective of reducing postoperative nausea and vomiting. Previous cohort studies have examined the use of corticosteroids in the perioperative setting and have reported a potential reduction in the postoperative systemic inflammatory response and improved short-term outcomes. The results of this survey show that there would be interest in conducting a randomised clinical trial examining the impact of single dose corticosteroid administration at induction of anaesthesia in patients undergoing resectional surgery for colorectal cancer. Attenuation of this response is applicable both to the elective and emergency subgroups of patients. Given the association between emergency presentation and elevated systemic inflammatory response, the effect on outcomes of perioperative corticosteroid administration may be greater in the emergency cohort. A recent multicentre cohort study[415] of over 30,000 patients undergoing

resectional surgery for solid organ tumours reported a decreased one year mortality and cancer recurrence in patients receiving single-dose intraoperative dexamethasone. Although dexamethasone administration was associated with an increased risk of postoperative hyperglycaemia, no increased risk of surgical site infections was identified. Therefore, this may be a safe, simple way to improve patient outcomes however data from clinical trials is required.

In summary, there are multiple differences between elective and emergency presentations of colon cancer in terms of tumour, host, perioperative and other factors. At the time of starting this period of research we hypothesised that emergency presentation per se was not the cause of adverse oncological outcomes, rather a combination of these other clinicopathological factors underpinned the adverse outcomes observed. The results presented within this thesis are supportive of this hypothesis, however further research is required as outlined above. Furthermore, this thesis focussed on long-term oncological outcomes. Further work is required to investigate the associations between mode of presentation and short-term outcomes.

11.2 Highlights

- This thesis, for the first time, comprehensively summarises the literature to date, comparing the association between mode of presentation and tumour/host factors in colorectal cancer

- This thesis shows, for the first time, that the systemic inflammatory response can be better stratified using both differential white cell count and acute phase protein based markers and combined these into an overall systemic inflammatory grade (SIG). As such, this is a novel way of stratifying prognosis in patients with colorectal cancer and has potential to form the basis for clinical decision making around additional therapies. These could include the recognition of the systemic inflammatory response as a high risk feature within TNM Stage II colon cancer and, as such, an indication for adjuvant chemotherapy. It may also be a basis on which to give other therapies including corticosteroids and NSAIDs and potentially the selection of particular adjuvant chemotherapy/immunotherapy regimens that may be more effective in patients with an elevated systemic inflammatory response.

- There are multiple differences between elective and emergency presentations of colon cancer in terms of tumour and host factors. To date, emergency presentation has been widely reported to be independently associated with adverse short-term and long-term survival in patients undergoing resectional surgery with curative intent for colon cancer. However, the results reported within this thesis show that, after adjustment for factors including systemic inflammatory grade, emergency presentation no longer retains independent prognostic significance for

oncological outcomes. It is therefore clear that in addition to other factors for example T Stage and ASA classification, the systemic inflammatory response is a major factor that underpins the adverse outcomes seen in patients undergoing resectional surgery with curative intent for TNM I-III colon cancer on an emergency basis

- The present results show that patients undergoing resectional surgery with curative intent for colon cancer on an emergency basis have a lower lean skeletal muscle mass than those presenting electively. Given the known association with the systemic inflammatory response this suggests that the elevated systemic inflammatory response seen in emergency patients is not acute at time of presentation. Instead, it suggests that they had a chronically inflamed state that may have predisposed them to more rapid tumour growth and emergency presentation

- The present results show that within a free at point of care health service with an established bowel screening programme, the proportion of patients diagnosed through screening remains small. The results have highlighted several key areas to increase the proportion of patients diagnosed through screening

11.3 Future Work

This thesis has highlighted a number of areas that would be of interest for future work. These include:

- Further detailed investigation into the association between perioperative factors (including surgical approach, surgeon subspecialty, the postoperative systemic inflammatory response and postoperative complications), mode of presentation and long-term outcomes in patients undergoing resectional surgery with curative intent for colon cancer

- Analysis of the route to diagnosis of colorectal cancer within a patient cohort undergoing screening using FIT testing and a comparison with the present results of patients who underwent screening using FOBT

- Further investigation into diabetes and mode of presentation – why is diabetes protective against emergency presentation?

- There are a number of areas of interest within adjuvant chemotherapy:

    - The association between mode of presentation and adjuvant chemotherapy administration (including time to commencing chemotherapy, type of chemotherapy given, number of cycles given)

    - The association between CT-derived body composition and chemotherapy toxicity and need for dose reduction – should muscle mass/density be accounted for when calculating chemotherapy dose as opposed to BMI or body surface area

- Investigation of the association between T Stage, tumour size and the systemic inflammatory response

- The association between consensus molecular subtypes and mode of presentation of colon cancer

- The association between mode of presentation and frailty in patients with colon cancer

- The association between mutational status, and the local/systemic inflammatory response and outcomes in colon cancer

- The potential to stratify the postoperative systemic inflammatory response using both the differential white cell count and acute-phase protein based scores/ratios (for example both the postoperative NLR and poGPS)

- The association between the systemic inflammatory response, circulating tumour cells and recurrence patterns in patients undergoing resectional surgery with curative intent for colon cancer

- The introduction of routine evaluation for the preoperative systemic inflammatory response in patients with colorectal cancer. SIG is easy to calculate however the addition of SIG to one of the widely available online calculators (for example http://www.mdcalc.com) may encourage its routine use

12 Reference List

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