Outcomes of English Colorectal Cancer Care:

Observation, Quantification and Comparison of Outcomes

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The candidate confirms that the work submitted is their own and that appropriate credit has been given where reference has been made to the work of others.

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2. Abstract

Colorectal cancer is the fourth most common cancer in England, but English colorectal cancer outcomes have traditionally lagged behind those of similar income level countries. Reasons behind these poor outcomes are multi-factorial but include high numbers of elderly patients presenting with advanced disease and a stubbornly high rate of emergency admissions. Recent years have seen significant changes in the National Health Service's approach to cancer treatment, alongside the development of population-level databases.

This study uses population-level data, obtained through the National Cancer Data Repository to investigate how short-term outcomes of colorectal cancer patients within the English NHS between 1998 and 2010 have changed. Further, it seeks to evaluate the impact of the NHS Bowel Cancer Screening Program and novel technologies such as laparoscopic surgery and endoluminal stents on those outcomes.

Risks factors for emergency colorectal cancer admission such as older age and increased co-morbidity remain although short-term mortality rates (30 and 90-day) appear to be falling. Length of stay for colorectal cancer patients fell markedly over the study period, aided by the introduction of laparoscopic surgery, whilst those who engaged in the screening program were seen to have a greater likelihood of presenting electively and with early stage disease. Endoluminal stents have a clear, but as yet undefined role to play in the management of the colorectal cancer patient, but do appear to offer certain advantages to selected patients.

Population-level data allows evaluation of interventions in healthcare and comparison of international outcomes. English colorectal cancer outcomes improved over the study period reported here, but are still not at the level of our European and international neighbours. There remains much work to do to improve these outcomes; it is likely that population-level data will play a pivotal role in this.

3. Table of Contents

3.1 List of Figures

3.2 List of Tables

4. Abbreviations

Abbreviation	Meaning
5-FU	5-Fluorouracil
AIDS	Acquired Immunodeficiency Syndrome
BCSP	Bowel Cancer Screening Project
CEPOD	Confidential Enquiry into Perioperative Deaths
CLASICC	Conventional versus Laparoscopically Assisted Surgery in Colorectal Cancer
COLOR	Colorectal Cancer Laparoscopic or Open Resection
CONCORD	Cancer Survival in Five Continents
CPEX	Cardio-Pulmonary Exercise Testing
CRC	Colorectal Cancer
CREST	ColoRectal Endoscopic Stenting Trial
DCO	Death Certificate Only
DNA	Deoxyribonucleic Acid
ECRIC	Eastern Cancer Registration and Information Centre
EPIC	European Prospective Investigation into Cancer and Nutrition
ESCO	Colonic stenting as a bridge to surgery versus emergency surgery for malignant colonic obstruction: results of a multicentre randomised controlled trial
EUROCARE	European Cancer Registry
FAP	Familial Adenomatous Polyposis
FIT	Faecal Immunochemical Test
FOBT	Faecal Occult Blood Test
GP	General Practitioner
GY	Gray
HES	Hospital Episode Statistics
HNPCC	Hereditary Non-Polyposis Colorectal Cancer
ICBP	International Cancer Benchmarking Project
ICD	International Classification of Diseases
IMD	Index of Multiple Deprivation

IQR	Inter-Quartile Range
LCRT	Long Course Chemo-Radiotherapy
NAEDI	National Awareness and Early Diagnosis Initiative
NBOCAP	National Bowel Cancer Audit Project
NCDR	National Cancer Data Repository
NCIN	National Cancer Intelligence Network
NCRAS	National Cancer Registration and Analysis Service
NHS	National Health Service
NHSBCSP	National Health Service Bowel Cancer Screening Project
NICE	National Institute for Clinical Excellence
NSAID	Non-Steroidal Anti-Inflammatory Drug
NSWCCR	New South Wales Central Cancer Registry
NYCRIS	North Yorkshire Cancer Registry and Information Service
ONS	Office for National Statistics
OPCS	Office of Population and Census Surveys
PHE	Public Health England
SCRT	Short Course Pre-operative Radiotherapy
SEER	Surveillance Epidemiology and End Result
SEMS	Self-Expanding Metal Stent
TNM	Tumour Nodes Metastasis
TWW	Two Week Wait
UK	United Kingdom
USA	United States of America

5. Introduction and Literature Review

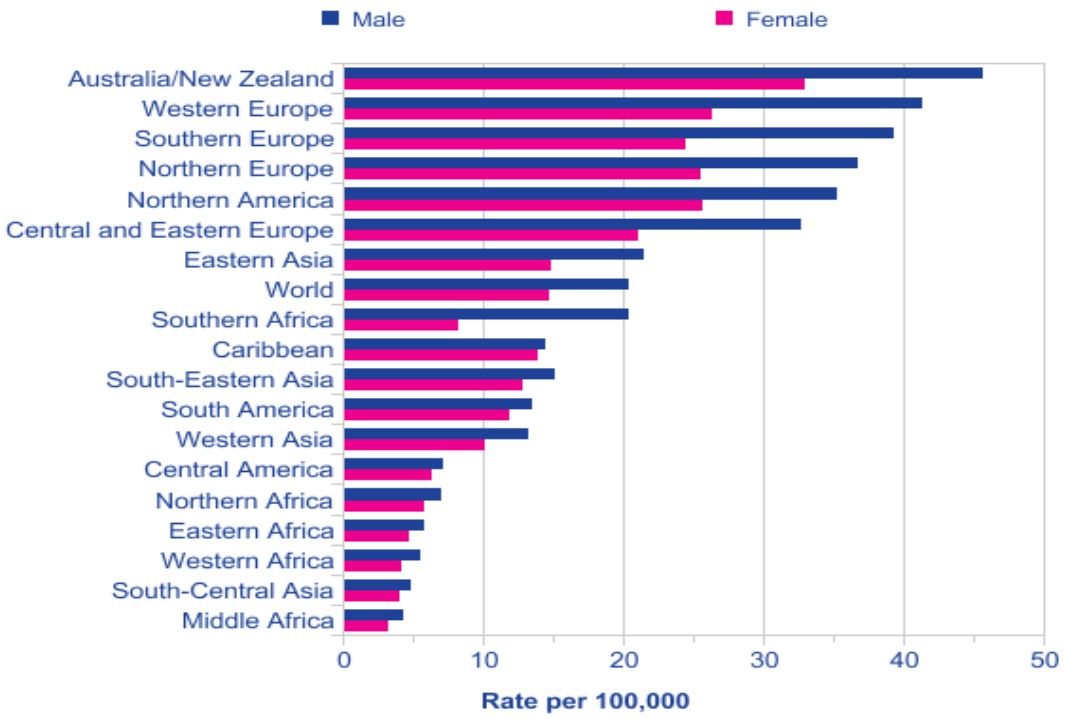
5.1. Colorectal Cancer: Incidence, Aetiology, Risk Factors and Staging

Approximately 330,000 people are diagnosed with an invasive cancer within the United Kingdom (UK) each year and 50% of people alive in the UK today can expect to be diagnosed with cancer at some point during their life[1]. Since 2011, cancer has overtaken heart disease and stroke as the most common cause of death within the UK, accounting for 1 in 4 deaths (~160,000 deaths per year)[1]. The burden of disease cancer represents to the National Health Service (NHS) is huge. As the number of older people within the United Kingdom and England continues to increase, the on-going diagnosis and management of cancer is likely to be one of the major health issues that must be dealt with by future UK governments, allied healthcare workers and clinicians.

Colorectal cancer (bowel cancer) is the fourth most common cancer in the UK and the third most common worldwide, behind breast and lung cancer[2,3]. There are approximately 40,000 new cases of colorectal cancer (CRC) diagnosed in the UK each year, of which roughly half will be alive at five years following diagnosis[3]. Nevertheless in 2012 alone, CRC accounted for the deaths of 8795 men and 7392 women in the UK[2].

The incidence of colorectal cancer exhibits significant geographical variation but has been steadily rising throughout Europe and the UK since the 1970's, with countries that 'westernise' rapidly seeing an attendant rise in rates of colorectal cancer[4].

5.1.2. Figure 1: World Age-Standardised Incidence Rates per 100,000 Population of Colorectal Cancer[4]



Worldwide, the highest incidence of CRC is in Australia/ New Zealand and the lowest in Africa[4]. Within Europe, Slovakia has the highest incidence of CRC with 90.7 cases in men per 100,000, whilst in comparison, Greece has the lowest incidence with 23.7 cases per 100,000[4].

Approximately two thirds of cases are cancers of the colon and one-third cancers of the rectum. There is a roughly equal incidence of colon cancer between men and women, but rectal cancer occurs more commonly in men, with 63% of cases of rectal cancer occurring in males[4].

The incidence of colorectal cancer is strongly related to age and weakly to socioeconomic deprivation[5–7]. In 2007-9, 72% of cases of CRC in the UK occurred in those aged over 65 and whilst CRC is 11% more common in the most socially deprived men compared with the most affluent, there is no significant difference for women[4].

In terms of prevalence, current estimates are that 3.26 million people (worldwide) were still alive up to five years after their diagnosis of colorectal cancer in 2008; UK prevalence rates are set out below[4]:

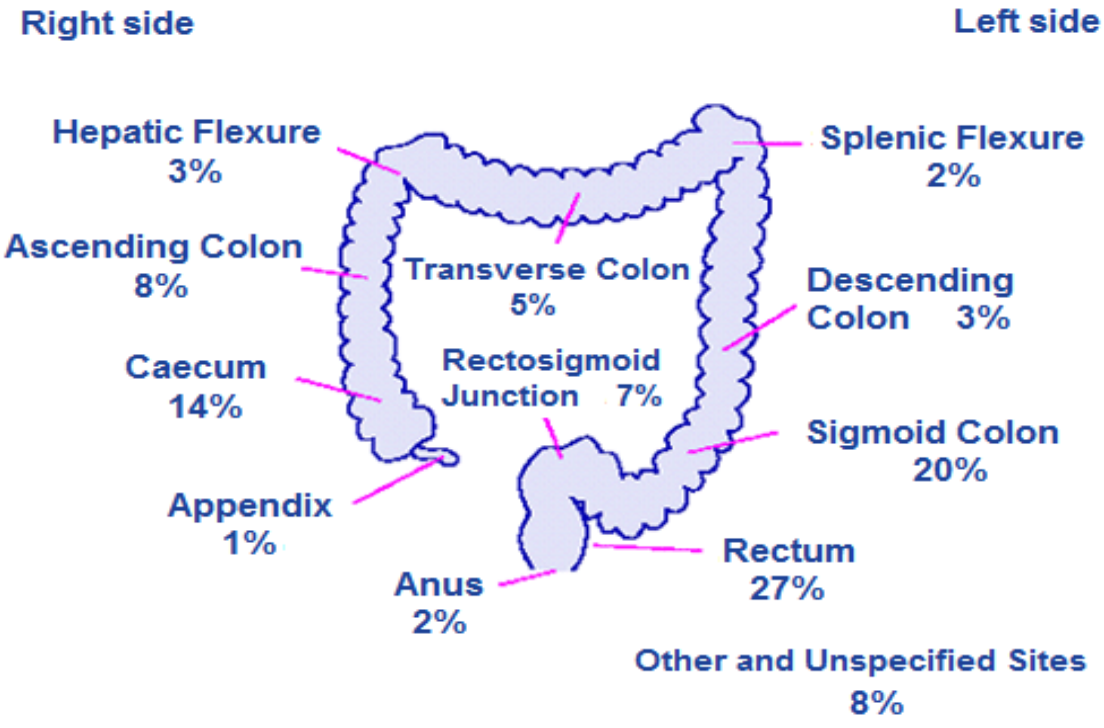
5.1.3. Figure 2: Bowel Cancer (C18-C20), One, Five and Ten Year Cancer Prevalence, UK, 31st December 2006[4]

	1 Year Prevalence	5 Year Prevalence	10 Year Prevalence
Male	14,635	51,183	78,483
Female	11,415	40,594	65,075
Persons	26,050	91,777	143,558

Whilst the exact aetiology of colorectal cancer remains unknown, in over 90% cases, the morphology of CRC is that of adenocarcinoma (including mucinous or colloid adenocarcinomas) arising from adenomatous polyps[4]. Signet-ring carcinomas, adenosquamous, medullary and other rare morphologies do occur, however, their incidence is minimal in comparison with adenocarcinoma.[4]

CRC occurs most commonly on the left-hand side of the large bowel (splenic flexure, descending and sigmoid colon, rectum with approximately 60% of tumours being 'left sided'[4].

5.1.4. Figure 3: Bowel Cancer (C18-21), Percentage Distribution of Cases within the Large Bowel, Great Britain, 2007-2009[4]



Colorectal cancer is thought to arise from a series of genetic 'hits' within specific oncogenes and tumour suppressor genes, resulting in the development of the adenoma-carcinoma sequence. At least 4 successive 'hits' are required to ensure progression to carcinoma, with the tumour suppressor genes *APC*, *SMAD4* and *TP53* and the oncogene *KRAS* being the prime targets for these 'hits'[8]. Eighty-five per cent of cases of colorectal cancers are classified as 'sporadic' however, and direct initiating factors for these 'hits' remain unknown[8].

Of the remaining 15% of cases, some clearly defined risk factors are apparent. Genetic factors in the forms of familial colorectal cancer (those who have a first degree relative affected <45 years of age, or two first degree relatives affected), Familial Adenomatous Polyposis (FAP), Hereditary Non-Polyposis Colorectal Cancer (HNPCC or Lynch Syndrome), Peutz-Jeghers syndrome and juvenile polyposis are well documented[9]. Inflammatory bowel disease (Ulcerative Colitis and to a lesser extent Crohn's disease) and the Acquired Immune Deficiency Syndrome (AIDS) are well recognised as risk factors for colorectal cancer[9]. Other risk factors identified but without a clear causal relationship include age, previous polyps/ colorectal cancer, race, type 2 diabetes, diet, lifestyle, obesity, smoking and excess alcohol consumption[10–12]. Non-Steroidal Anti-Inflammatory Drugs (NSAIDS) have been noted, through their inhibitory effect on cyclo-oxygenase-2 (and subsequent toxic effect on gastro-epithelial cells), to have a chemopreventive effect on adenoma formation as far back as 1981[13]. Until recently, the dosages required to achieve chemopreventive effects have been outweighed by the well documented adverse cardiovascular side effects[13]. A recent study by Nan et al. however, has suggested that a patient's individual genotype may confer either an increased risk, no risk or protective risk of CRC with NSAID use. It is perhaps therefore feasible in the future that targeted use of NSAIDs may well benefit some patients in reducing their CRC risk[14].

Adenoma formation in the hereditary colorectal cancer syndromes (FAP, HNPCC, Peutz-Jeghers syndrome, juvenile polyposis) is defined by germ-line mutations predisposing to polyp formation[9,11,15]. *APC*, the tumour suppressor gene involved in FAP appears to be a multi-functional gene, regulating several intracellular processes. The key 'hit' however, seems to be the loss of the ability to regulate intra-cellular β-catenin levels[15]. This loss results in a number of downstream effects, disrupting cell adhesion, migration and signal transduction, amongst others but ultimately allowing progression to malignant transformation[15]. HNPCC is characterised by mutations in mismatch repair genes responsible for repairing mistakes made during DNA replication. Loss of this repair mechanism allows rapid destabilisation of the

genome and therefore development of malignancy[16]. Rate of transformation of polyps is significantly faster in HNPCC than in FAP, as would be expected by its underlying pathophysiological mechanism.

Crohn's Disease and Ulcerative Colitis are underpinned by inflammation and proliferation of the colonic epithelium during episodes of active disease that predispose the individual to colorectal cancer. Although colorectal cancer secondary to inflammatory bowel disease accounts for only 1-2% of all colorectal cancers, the incidence and prevalence of colorectal cancer in the inflammatory bowel disease patient population is still significantly higher than in the general population[17]. As such, the mean age of developing colorectal cancer is lower than in sporadic cases, with the magnitude of risk related to age at diagnosis and extent of disease, with pancolitis carrying the greatest risk. Thus, the risk of developing colorectal cancer in a patient with inflammatory bowel disease is approximately 0.5-1% per year, 8-10 years after diagnosis[17].

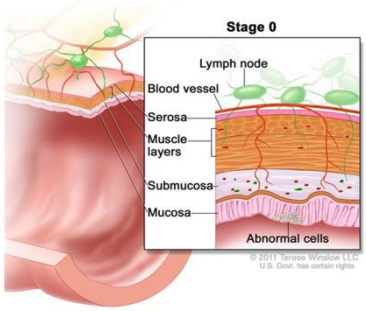
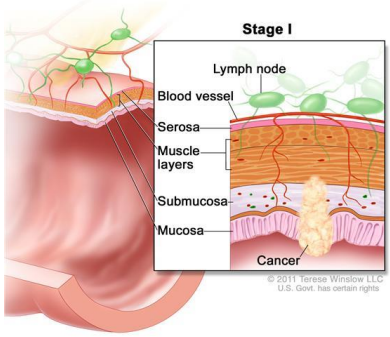
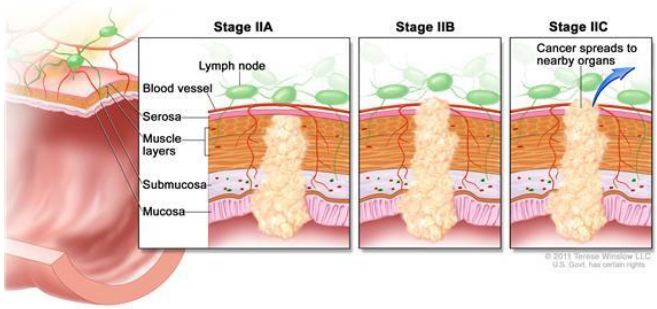
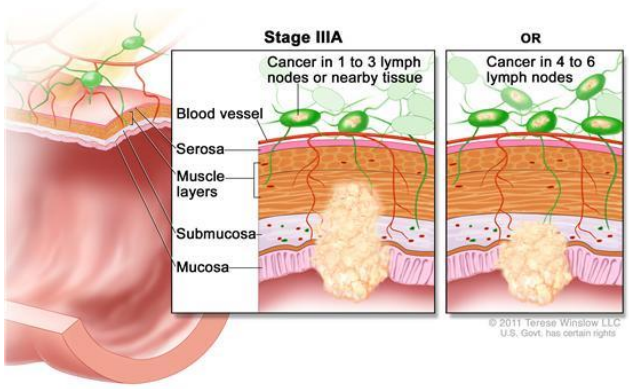
African Americans and Ashkenazi Jews have been found to be at higher risk of developing colorectal cancer than other populations[11]. The movement of the Ashkenazi Jews across Europe, where they settled and married within tight communities, may have allowed founder-mutation effects to occur thus explaining the increased incidence in this group[11]. African Americans suffer from an increased risk of colorectal cancer for as yet unclear reasons but are thought to be related to past exposure to underlying risk factors, access to diagnostics, timely intervention and exposure to the Western lifestyle [11,18].

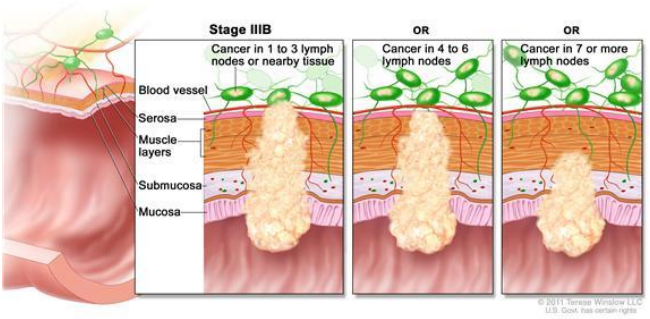
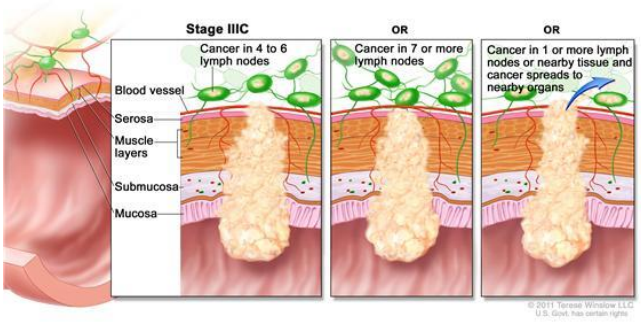
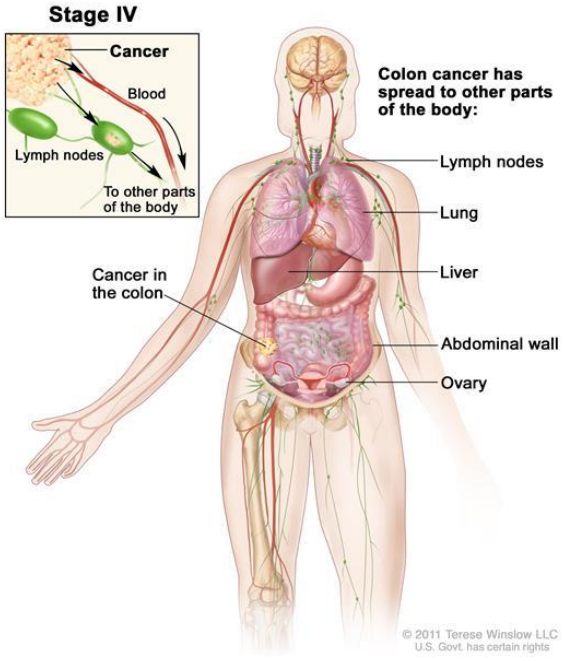
Diet has long been recognised as a modifiable risk factor for cancer within industrialised nations[12]. Type 2 diabetes has been found to be independently associated with the development of colorectal cancer, even after adjustment for conditions associated with the development of both colorectal cancer and type 2 diabetes such as obesity[19]. Diet has been considered to be a possible risk factor for colorectal cancer since the 1960's when Burkitt proposed the hypothesis that low fibre diets and subsequent slow colonic transit may be implicated in the development of colorectal malignancy[8]. Data from the on-going EPIC trial (European Prospective Investigation into Cancer and Nutrition) study has now been released, which provides strong evidence for the role of fibre in prevention of colorectal cancer, suggesting that in populations with a low dietary fibre intake, doubling intake could result in a 40% reduction in rates of colorectal cancer. Processed or red meat consumed in large

quantities (160g or two portions/ day) was associated with a 35% increase in colorectal cancer, whilst consumption of fish was found to be protective[20]. Energy intake, body mass index and degree of physical activity have been shown to be related to colorectal cancer risk (with lower levels of intake and higher levels of activity giving a lower risk), although the underlying mechanisms remain unclear[21].

Colorectal cancer is divided into stages using either the Tumour, Nodes, Metastasis system (from the American Joint Committee on Cancer) or the system devised by the British pathologist Cuthbert Dukes, the Dukes criteria (note Dukes 'D', representing metastatic disease was added later to the original classification)[22,23]. The classification system proposed by Astler and Coller in 1954 and now modified to the Modified Astler Coller (MAC) system, is much less frequently used[24]. Each system is based around depth of penetration of the tumour into the layers of the bowel, invasion into surrounding structures (including lymph nodes and blood vessels) and spread to distant sites.

5.1.5. Figure 4: Staging of Colorectal Cancer*

Stage	TNM	Dukes'	MAC	Depiction
0	Tis, N0, M0	–	–	
I	T1, N0, M0	A	A	
	T2, N0, M0	A	B1	
IIA	T3, N0, M0	B	B2	
IIB	T4a, N0, M0	B	B2	
IIC	T4b, N0, M0	B	B3	
IIIA	T1–T2, N1/N1c, M0	C	C1	
	T1, N2a, M0	C	C1	

Stage	TNM	Dukes'	MAC	Depiction
IIIB	T3–T4a, N1/N1c, M0	C	C2	
	T2–T3, N2a, M0	C	C1/C2	
	T1–T2, N2b, M0	C	C1	
IIIC	T4a, N2a, M0	C	C2	
	T3–T4a, N2b, M0	C	C2	
	T4b, N1–N2, M0	C	C3	
IVA	Any T, Any N, M1a	D	-	
IVB	Any T, Any N, M1b			

*Adapted from the National Cancer Institute website (http://www.cancer.gov/cancertopics/pdq/treatment/colon/HealthProfessional/Page3#Section_331)[25]

5.2. Management of Colorectal Cancer

Patients with colorectal cancer usually present first to their primary care physician, and most often with a change in bowel habit, change in appetite/ unintentional weight loss, blood in their stools or unexplained anaemia[26]. Within the UK, approximately 20% of patients with colorectal cancer will present as an emergency, usually with either obstruction or perforation of their bowel[27].

Throughout the United Kingdom, the National Institute for Health and Care Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN) and the Association of Coloproctology of Great Britain and Ireland (ACPGBI) have each produced guidelines for the diagnosis and management of colorectal cancer[3,28,29]. Each group recommends colonoscopy and biopsy for the diagnosis of CRC, although each accepts that CT colonography may be used as an alternative in the elderly or in difficult to reach right sided tumours. Each patient should receive a pre-operative CT scan of their chest and abdomen to assess the degree of tumour invasion and for the presence of metastases. Positron Emission Tomography (PET) scanning may also be used to assess for the presence of metastases not visible on conventional imaging although this is not standard practice, except when dealing with potentially curative re-resections. Emergency patients with perforated tumours who are peritonitic are excluded from this requirement, where emergency surgical intervention is lifesaving. Those with rectal cancer should expect to receive pre-operative MRI scanning of their pelvis in order to stage the tumour, assess whether a clear resection margin is possible and the risk of recurrence. Endoanal ultrasonography is recommended by NICE for the assessment of those undergoing local/ transanal excision of early stage disease[3].

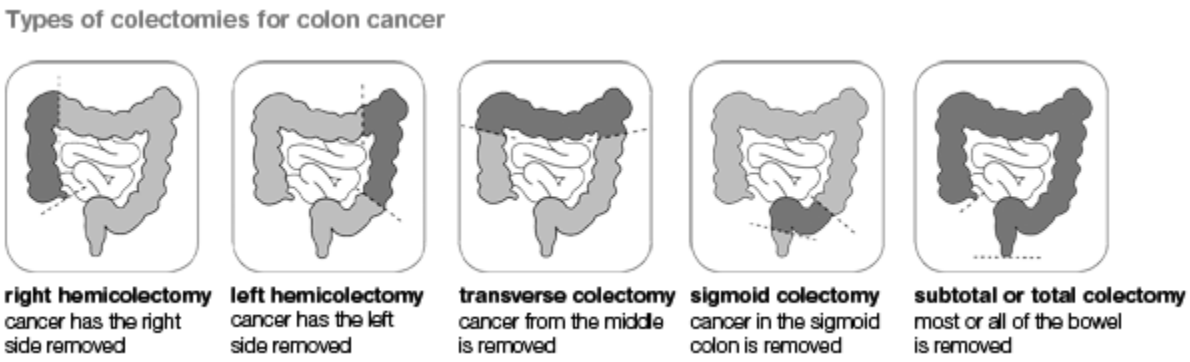
5.2.1. Surgery for Colorectal Cancer

Complete surgical excision of the tumour (R0 resection) forms the mainstay of treatment for CRC and is usually considered a basic requirement for successful treatment. Whilst early stage disease may be treated endoscopically, the majority of patients require surgical excision of the affected segment of bowel.

The bowel and its mesentery are excised segmentally depending on the location of the tumour, with the ‘radicality’ of surgical excision being dependent on the blood supply to the

affected segment, the extent of any lymphatic invasion and/or spread to distant structures (see Figures 5 and 6).

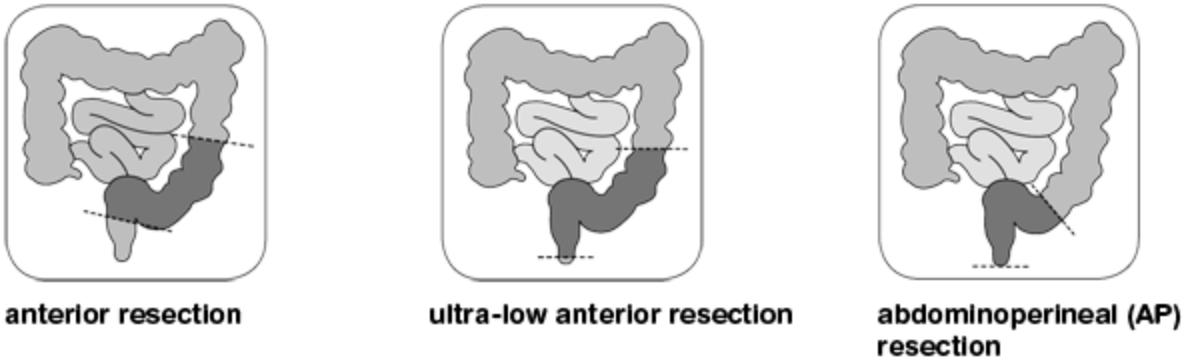
5.2.1.1. Figure 5: Colectomies for Colon Cancer*



The practice of rectal surgery has changed markedly over the last 3 decades. In the mid-1980's the requirement for 5cm distal excision of rectal cancers began to be challenged, with the realisation that distal mural spread of the tumour is seldom greater than 2cm[30]. Thus necessity for patients to lose their anal sphincters (through abdominoperineal excision) to achieve adequate oncological clearance, alongside advancements in stapling technology which allow safe distal rectal or colo-anal anastomoses to be performed, resulted in anterior resection becoming the standard procedure for rectal cancer[31,32].

The 1990's saw the abandonment of conventional blunt dissection of the rectum with the introduction of Total Mesorectal Excision (TME). Heald et al. and Enker et al. demonstrated that through complete removal of lymphovascular tissue and a free circumferential margin surrounding the tumour (through sharp perimesorectal dissection) substantially lower rates of disease recurrence could be achieved[33–35].

5.2.1.2. Figure 6: Rectal Resections for Rectal Cancer*



*Figures 5 & 6 taken from South Australia Cancer Council Website[36] (http://www.cancersa.org.au/information/a-z-index/surgery-for-bowel-cancer#Surgery%20for%20rectal%20and%20anal%20cancers)

5.2.2. Adjuvant Therapies

Despite the best efforts of surgery with curative intent, the risk of disease recurrence in colorectal cancer following surgical excision remains high (up to 50% at 2 years in those with high grade rectal cancer[37]). Neoadjuvant therapies (chemo or radiotherapy), in the pre-operative period, aim to downstage the disease, increasing the likelihood of achieving clear resection margins, limiting the chance of recurrence. For those with high-grade disease (and therefore high chance of micro-metastatic spread), post-operative chemotherapy may be given.

Adjuvant therapy in colon cancer centres is based around the administration of chemotherapy, as use of radiotherapy would cause unacceptable morbidity due to damage to other structures. No single, unifying guideline exists for use of chemotherapy in colon cancer but current NICE guidelines suggest use of capecitabine as monotherapy or oxaliplatin in combination with 5-fluorouracil and folinic acid for those with high-risk stage II or stage III colon cancer. Cetuximab along with folinic acid, fluorouracil and oxaliplatin is recommended as first line therapy in those with advanced (stage IV) disease[3]. Recommendations regarding second line agents vary, but in general are based around the use of capecitabine along with irinotecan[3].

Radiotherapy in rectal cancer may be used either to help achieve locoregional control (short course preoperative radiotherapy, SCRT) or may be used in tandem with chemotherapy (long course chemo radiotherapy, LCRT) where the TME envelope is threatened or the patient has advanced stage disease[38] It is recommended that use of radiotherapy in rectal cancer should be decided following multi-disciplinary team discussion and by the risk of disease recurrence as determined by magnetic resonance imaging (MRI) scanning of the pelvis[39].

5.2.2.1. Figure 7: Risk of Local Recurrence as Predicted by MRI

Risk of local recurrence for rectal cancer as predicted by MRI[3]	
Low	• cT1 or cT2 or cT3a **and** • no lymph node involvement
Moderate	• any CT3b or greater, in which the potential surgical margin is not threatened • any suspicious lymph node not threatening the surgical margin • the presence of extramural vascular invasion
High	• a threatened (< 1mm) or breached resection margin **or** • low tumours encroaching onto the inter-sphincteric plane or with levator involvement

Short course preoperative radiotherapy is usually given as 25Gy in 5 daily fractions over 1 week, with surgery the following week. Long course chemo-radiotherapy (LCRT) is usually given as 45-50GY in 25 daily fractions over 5 weeks alongside 5-FU based chemotherapy, followed by surgery 4-8 weeks after completion of radiotherapy (Figure 8).

5.2.2.2. Figure 8: NICE Guidelines for use of Preoperative Radiotherapy in Rectal Cancer

Recommendation for Preoperative Radiotherapy[3]	
Risk of Recurrence	
Low	Do not offer short-course preoperative radiotherapy (SCRT) or chemo-radiotherapy to patients with low-risk operable rectal cancer, unless as part of a clinical trial
Moderate	Consider SCRT then immediate surgery for patients with moderate-risk operable rectal cancer. Consider preoperative chemo-radiotherapy with an interval to allow tumour response and shrinkage before surgery for patients with tumours that are borderline between moderate and high risk
High	Offer preoperative chemo-radiotherapy with an interval before surgery to allow tumour response and shrinkage (rather than SCRT), to patients with high-risk operable rectal cancer.

5.2.3. Current English Colorectal Cancer Survival

For those diagnosed with cancer in the UK today, prospects of survival have changed beyond all recognition over the last 40 years; 50% would have been alive at 1 year in the 1970's , compared with 50% at 10 years in 2011[1]. Survival from colorectal cancer is no different, in 1971-2, a man diagnosed with CRC would have had a 47% chance of surviving one year (45% for women), compared with 77% in 2010-11 (73.9% for women).[40].

Survival for those diagnosed with colorectal cancer is currently highest in the age group 60-69, with lower survival figures seen in younger patients and a progressive decline in survival occurring from age 70 onwards[41]. Not surprisingly, survival varies by stage of disease at diagnosis. Almost all those with Stage I disease survive at least a year (98% of men, 100% of women) as compared to 40% of men with Stage IV disease and 33% of women. By 5 years from diagnosis, 95% of those with Stage I disease will still be alive, but only 7% of those with Stage IV disease[41].

5.2.4. Purpose of the Study

Whilst there is clear evidence that colorectal cancer outcomes in England (and Wales) have improved over time, outcomes trail behind those of equivalent income level European countries[42]. A major contributing factor is the stubbornly high rate of emergency presentation amongst English patients, with high levels of elderly patients presenting as emergencies with advanced disease[43]. Population level data provides researchers with a unique opportunity to observe chronological sequences, links between clinical and geographic details and to assess the impact of changing clinical management practices on national level outcomes.

Thus, this study attempts to understand why English colorectal cancer outcomes continue to be persistently poor in comparison to Europe. It aims to assess and to highlight the differing short-term outcomes of elective and emergency CRC patients between 1998 and 2010 treated within the English NHS and to suggest ways in which these cheerless comparisons may be improved.

5.3. Literature Review

5.3.1. Identification of Literature

Literature for this review was identified through use of Ovid Medline (1996 to Week 1 January 2018) and Embase (1996 to Week 1 March 2018) using Medical Subject Headings (MeSH), and supplemented through Google Scholar ('exact phrase') and review of the references of relevant publications.

5.3.2. Variation in Cancer Incidence and Outcomes

In 2012, there were an estimated 14.1million new cases of cancer diagnosed worldwide. 53% of these cases occurred in men and 47% in women, with lung cancer being the most common, followed by female breast, bowel and prostate cancer [44]. Over the last 40 years, the global incidence of cancer has remained relatively static, although stomach cancer has declined (most likely as a result of the discovery of *H.Pylori* as a risk factor) and lung cancer (secondary to tobacco smoking) increased as relative proportions of the total[44]. If population growth continues at its projected rate, alongside the projected incidence of major cancers, it is estimated that there will be 23.6million new cases of cancer diagnosed worldwide by 2030[44].

The global cancer incidence varies significantly depending upon a country's economic development (2012 estimates, Australia/ New Zealand: 318 per 100,000, Western Africa: 19 per 100,000), with economically developing countries having markedly higher rates of cancer due to infectious causes (e.g. liver, stomach, cervix) and economically developed countries being disproportionately affected by cancers associated with the Western lifestyle (lung and bowel)[44,45]. Overall however, incidence rates tend to be higher in developed countries (as cancer, as a general rule, is a disease of old age, with high numbers of younger people dying in less developed countries of non-cancer related causes).[44]

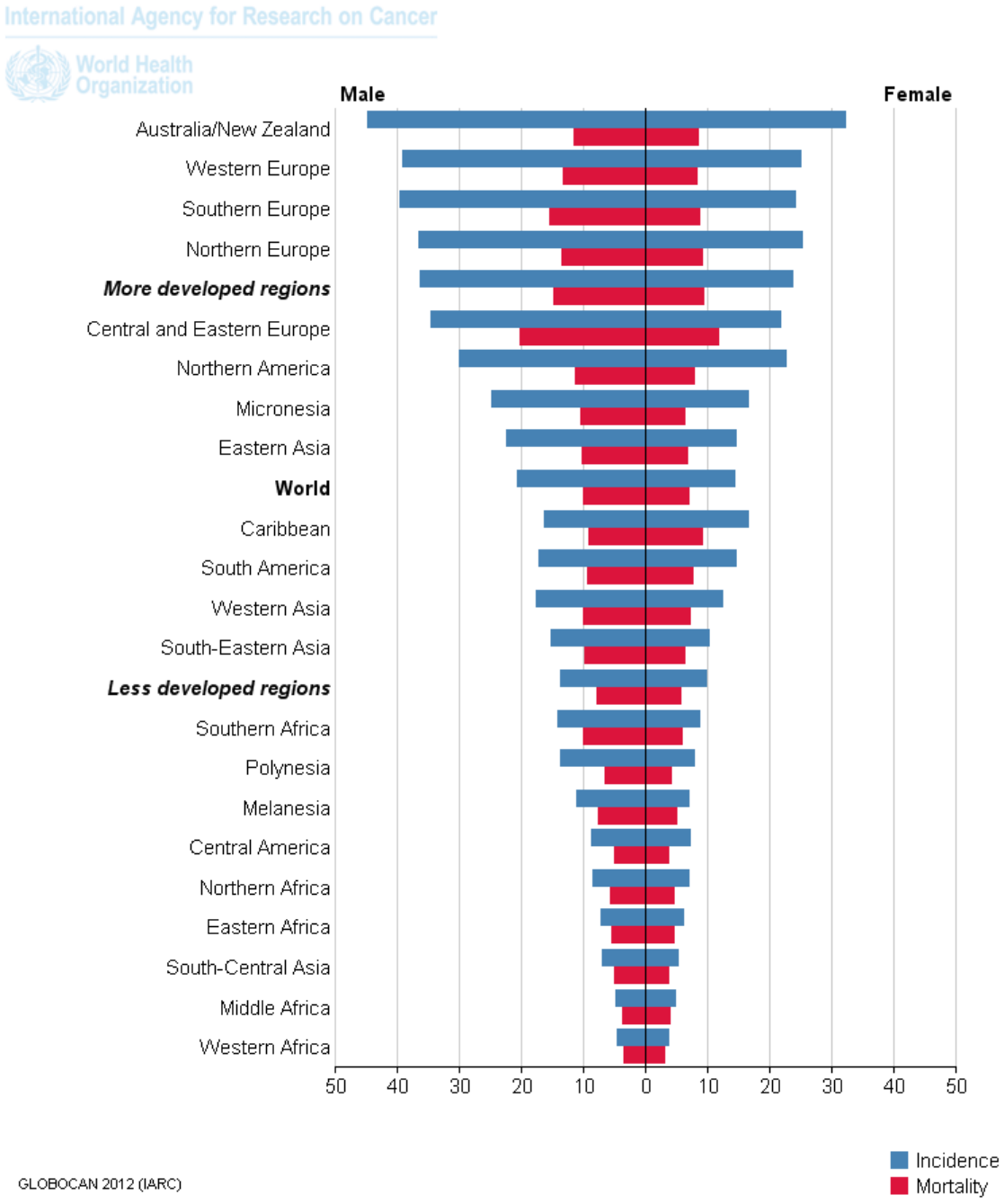
Global cancer mortality exhibits significant variation with an estimated 8.2 million cancer deaths occurring in 2012[44]. Recent years have seen striking improvements in cancer mortality, especially within developing or economically transitioning countries, but wide disparities still remain[46]. More developed regions of the world report age standardised rates of mortality for all cancers in men of 108.5 per 100,000. In comparison, less developed regions report mortality rates of 98.4 per 100,000[47]. What remains striking however, is that within industrialised

nations, whilst rates of cancer mortality have improved at a similar rate, disparities in outcomes have remained static, despite the improvement in overall mortality[47].

5.3.3. Worldwide Variation in Colorectal Cancer Outcomes

Colorectal cancer is estimated to make up approximately 9.7% of the world's yearly cancer burden, with marked geographic differences in both incidence and survival[44]. The highest recorded incidence is in Australia and the lowest in Western Africa (although accurate figures for this region are hard to verify)[47] Worldwide, colorectal cancer is the cause of 694,000 deaths each year, with mortality being highest in Central and Eastern Europe (20.3 deaths per 100,000 men, 11.7 deaths per 100,000 women respectively) and lowest in Western Africa (3.5 per 100,000 for men,3.0 per 100,000 for women). Within developed regions of the world, incidence and mortality rates from colorectal cancer have largely been falling over recent years (thanks mainly to better awareness and earlier treatment), whilst rates of both incidence and mortality in countries with more limited health infrastructures continues to increase[47].

5.3.3.1. Figure 9: Estimated Worldwide Incidence and Mortality from Colorectal Cancer 2012[47]



Accurate statistics for the incidence of and survival from all forms of cancer, not just colorectal are a fundamental requirement to understanding why, and how variation in cancer survival occurs. Prior to the 1960's, international comparison of cancer related outcomes was impossible, as few cancer registries had been in existence long enough to provide reliable data[48]. In 1964, an attempt was made to compare the cancer survival rates of northern

European countries with those of the state of Connecticut. Survival was shown to be, in most cases, significantly better for American than European patients and whilst development of national cancer registries continued, no further efforts to compare international survival rates or to understand international variations in survival were made until the publication of the EUROCARE project in 1995[49,50].

The EUROCARE project (s) are co-operative, cancer registry based studies which aim to compare cancer prevalence, care, survival and time trends across various European countries. Each project compares the outcomes of patients diagnosed within a set time period and illustrates how European outcomes vary and how trends in cancer epidemiology are developing. EUROCARE data was first used to evaluate colorectal cancer outcomes by Sant et al. to compare survival for colon cancer patients between 1978-85 in 10 European countries. Mean European 5 year cumulative survival was found to be 40%, but significant inter-country variability was seen with Switzerland, Finland and the Netherlands achieving results that were significantly above the European mean. Most of the remaining countries (France, Germany, Italy, Denmark and most areas of England) achieved survival figures whose confidence intervals sat astride the European mean, however, Cracow in Poland (22%) and one area of England (Mersey) (29%), achieved figures that were significantly below the mean. This inter-country variability was felt by Sant et al. to be most likely due to differences in healthcare provision, quality of care and stage of disease at presentation.[51]

The expanded EUROCARE-2 project included 3 473 659 patients from all cancer sites, diagnosed between 1978 and 1989 in 17 countries, from 45 different registries[52]. In relation to colorectal cancer, Switzerland, Austria and the Netherlands were all noted to have high levels of 5-year relative survival (>45%), whilst survival in Slovenia and Poland was low (38%) and intermediate in the UK (41%)[53]. Rates of surgical resection were seen to vary widely from >85% in Switzerland, the Netherlands and France to less than 60% in Estonia and Poland, with most of the differences in survival being seen in the first 6 months after diagnosis. Survival at 5-years was seen to be much more homogeneous[53].

EUROCARE-2 raised numerous questions as to what may underlie the differences in survival. Was it rates of surgical resection that improved survival or was it in fact that patients were being diagnosed earlier in differing European countries (and therefore appearing to survive for a longer period)? An attempt to address these questions (and to build upon the data

presented in EUROCARE-2) was undertaken through a high resolution study of colorectal cancer outcomes by Gatta et al. Gatta et al. reviewed the outcomes of 2720 patients diagnosed in 11 European cancer registries between 1988 and 1991 (although it remains unclear from the paper exactly how these patients were selected)[54]. Information on stage at diagnosis (TNM) and other determinants of stage (results of CT or ultrasound scanning of the liver, number of lymph nodes harvested at resection) alongside information on the surgical resection performed was used to compare outcomes at 3 years following diagnosis. Rates of surgical resection varied enormously, from 93% in Côte d'Or to 53% in Cracow, as did rates of elective surgery (87% Côte d'Or, 56% Cracow). Similar variability was seen in 3-year relative survival, with survival ranging from 59% in Modena to 25% in Cracow. The UK registry with the worst survival reported a 5-year relative survival figure of 38% (Thames)[54]. The relative risk of death at 3 years showed much less variability once stage at diagnosis was taken into account, although the Cracow and Thames regions still performed poorly, even after these adjustments. Gatta et al. concluded therefore that there was wide variation in diagnostic and surgical practice throughout Europe but that the variations in outcome were, in actual fact, largely due to stage at diagnosis[54].

More recent updates of the EUROCARE project (EUROCARE 3-5), have again demonstrated clear evidence of variation in European cancer outcomes and that whilst cancer outcomes were, in general improving throughout Europe, the inter-country differences in survival was failing to close[55,56]. The authors of the EUROCARE-4 study also noted that the UK and Denmark, whilst having similar levels of total national expenditure on health to other high income level countries, achieved a lower all cancer survival rate, suggesting that the UK and Denmark may not have been allocating healthcare resources efficiently[56].

The most recent EUROCARE study, EUROCARE-5, now reports the results of over 10 million patents, diagnosed from 1995 to 2007 and followed up to 2008. 5-year relative survival, again, improved for almost all cancers over the study period, with marked improvements in survival from prostate cancer, non-Hodgkin lymphoma and rectal cancer[57]. For colorectal cancer, diagnosed between 2000-2007, the 5-year age standardised European mean mortality for colon cancer was 57.0% and 55.8% for rectal cancer, with high performing countries such as Iceland achieving 62.0% for colon and 73.2% for rectal cancer. In comparison, UK survival figures were 51.8% (colon cancer) and 53.7% (rectal cancer)[57]. Only former Eastern Bloc countries such as Bulgaria, Latvia and Lithuania achieved poorer outcomes[57].

Throughout the series of EUROCARE publications, the authors have consistently argued that it is stage at diagnosis that underlies the disparity in European colorectal cancer outcomes. Whilst they acknowledge the role of cancer biology, wide variations in diagnostic and surgical practices and the impact of socioeconomic and lifestyle factors, it is stage at diagnosis that is given as the primary reason for the differences[57]. How differences in disease characteristics (i.e. stage at diagnosis) affects survival in French and English CRC patients was explored by Dejardin et al., who compared the outcomes of 3 population based cancer registries in France to one in England. French patients were more likely to receive a resection with curative intent within six months of diagnosis at all stages of disease, with the difference in likelihood of resection increasing in line with the stage of disease[58]. A larger proportion of English patients were also noted to have died within a year of diagnosis (compared with the French patients) and that if an English patient survived for at least a year, their long term survival was similar to that of their French counterpart[58]. Thus, Dejardin et al. implied that it may not only be stage at diagnosis that underlies differences in survival, particularly for English patients, it may well also be initial management and likelihood of receiving a resection with curative intent[58].

How colorectal cancer outcomes between English and other European patients differ was explored by Engholm et al. and Morris et al. Engholm et al. analysed 5-year relative survival data from patients diagnosed between 1994 and 2000 from 11 UK registries and 4 from Nordic countries (Denmark, Finland, Norway and Sweden). A 30% higher risk of death was found amongst UK and Danish patients in the first 6 months after diagnosis, compared with Finnish, Norwegian or Swedish patients[59]. The excess deaths were attributed to differences in early patient management, diagnostic processes and co-morbidity amongst UK and Danish patients[59]. Morris et al. compared outcomes of patients diagnosed and managed with CRC in England, Norway and Sweden between 1996 and 2004, measuring 5-year relative survival and excess deaths stratified by age and period of follow-up. 5-year relative survival of English patients (51.1%) was significantly lower than that of either Norwegian (57.9%) or Swedish patients (59.9%), with the greatest excess of deaths occurring in older patients within the first 3 months of diagnosis[60]. Morris et al. therefore concluded that England seemed to have a higher percentage of older patients presenting with more rapidly fatal (i.e. more advanced stage and more aggressive) disease than her Nordic counterparts[60].

The generally poorer outcomes of English patients, compared with their European neighbours, would therefore seem to be due to a mix of stage at diagnosis, initial management/ likelihood of receiving a major resection and England having a high percentage of patents who present late with aggressive disease[57–60]. How age, stage of diagnosis, co-morbidity and initial management affects excess deaths in Danish patients was the subject of a study by Iversen

et al[61]. Iversen et al. compared the outcomes of patients aged over 75 with younger patients who were diagnosed and treated for colorectal cancer between 1977- 1999 in Denmark. Short and long term survival improved for both groups, whilst improvements in survival were greatest amongst the elderly, due to increasing use of radical resection within this group[61]. By the time of the most recent period analysis (1997-1999), there were only minor differences in the relative survival of both younger, middle aged and older patients[61]. There are marked similarities between the English and Danish healthcare systems and the demographics of their populations. Whilst there is good evidence that England has high numbers of patients presenting with advanced disease, Iversen et al. provide evidence that the initial management of colorectal cancer patients may also have a significant impact upon their survival[60,61].

Which factors may be associated with an early death (< 1 year following diagnosis) in English colorectal cancer patients was explored by Downing et al. through the use of a retrospective cohort study. Downing examined all patients diagnosed and treated for CRC between 2006 and 2008 within the English NHS; of which 11.5% of colon cancer patients died within 1 month of diagnosis and 5.4% of rectal cancer patients. The proportion of patients who died before 1 month significantly decreased over the study period, potentially implying that recent changes made to the management of CRC patients within the English NHS are having an effect on likelihood of (at least initial) survival. Those most likely to die early within Downing's study however, were the elderly, those from deprived socioeconomic backgrounds, those with advanced disease at presentation, those with multiple co-morbidities and those who received no form of radical treatment (i.e. surgery or palliative chemotherapy)[62].

A further study by Morris et al., examined the 30-day post-operative mortality in all those who underwent major resection for colorectal cancer diagnosed between 1998 and 2006 in the English NHS; the findings of which mirrored those of Downing et al. This study again found that those most likely to die early after surgery were the elderly, those with multiple co-morbidities, advanced stage of disease, a deprived socioeconomic background but also added the degree of operative urgency (those with greater urgency doing less well)[63]. Significant variation in rates of post-operative mortality dependent upon region was also seen, suggesting that there is much variation in surgical practice throughout England and hence the potential outcomes that are achieveable[63].

The impact of initial post-operative management on outcomes was highlighted by a Dutch study, which assessed the contribution of hospital volume and patient characteristics to 30-day postoperative mortality (Osler et al.)[64]. 11, 287 patients (both elective and emergency) from 43 surgical departments between 2001 and 2004 were included within the study. Rates of 30-day postoperative mortality varied from 3.1% to 44.1% after emergency colon cancer surgery, with emergency patients 5 times more likely to die (odds ratio 4.6) in the worst performing hospitals compared with the best[64]. For those who had elective colon or rectal cancer surgery, differences in mortality were small and insignificant between all hospitals.

Emergency admission and/or operation, clearly therefore, have a significant negative impact on survival in colorectal cancer. How rates of emergency presentation differ throughout Europe are difficult to accurately verify but have recently been reported to vary from 12% in Greece up to 25% in Norway[65]. English rates have been quoted as being 'stubbornly high' at ~20%[43]. English colorectal cancer patients therefore would appear to have a high rate of emergency presentation, often with advanced disease, with more co-morbidity and at an older age in comparison to other, similar income level countries. This does not adequately explain England's poor survival record for CRC patients however; England and Norway have similar levels of emergency presentation but wide differences in outcome. English patients often appear to present late, in an unplanned manner and are subject to significant variation in their initial management. Understanding why English patients present in this fashion, and what may be done to improve early diagnosis and early post-operative management, has the potential to significantly improve English CRC outcomes.

Differences in colorectal cancer outcomes do not just exist between English and European patients of course; there is also marked variability in outcome in colorectal cancer outcomes between England and other first world nations, such as America and Australia. Whilst the EUROCARE studies were pivotal in highlighting differences in European cancer outcomes, Gatta et al. made use of data from EUROCARE-2 and the American Surveillance, Epidemiology and End Result (SEER) programs to compare the outcomes of 738,076 European patients and 282, 398 American patients diagnosed with one of 12 cancers between 1985 and1989. Outcomes for European patients were significantly worse for most cancers compared with for those of American patients and colorectal cancer was no different. 5-year relative survival rates for colon cancer were 60% in American patients versus 47% in European patients and for rectal cancer, 5-year survival was 57% in American patients and 43% in European patients. The authors suggested that the most likely reason underlying this

difference was the increased chance of American patients being diagnosed early, at a less advanced stage and therefore with a greater chance of long-term survival[48].

An attempt to assess differences worldwide cancer outcomes was undertaken by Coleman et al. in the CONCORD study. CONCORD began as an extension of the EUROCARE-3 project but also developed the work of Gatta et al. to assess the cancer related outcomes of 1.9 million patients (aged 15–99 years), diagnosed during 1990-94 and followed up until 1999, with either breast (women), colorectal or prostate cancer, from 101 cancer registries, across 31 countries and 5 continents.[66] Again, wide differences in international cancer survival were seen, and although those differences were present for almost all European countries, in relation to colorectal cancer, United Kingdom patients fared particularly badly. American patients achieved age-standardised, 5-year relative survival figures from CRC of 58.6% for men and 60.0% for women. In comparison, the European average was 45.3% in men and 48.1% in women. High achieving European countries such as Sweden managed 52.8% for men and 56.2% for women, but the UK only achieved 42.3% for men and 44.7% for women. Only former Eastern bloc countries such as the Czech Republic fared worse (33.8% (men) and 38.3% (women))[66].

The survival of colorectal cancer patients in the CONCORD study, was looked at in detail by Allemani et al, who noted rates of Dukes' A and B tumours were similar between the United States (US) and Europe, whilst Dukes' C was more frequent in the US and Dukes' D more frequent in Europe[67]. Resection with curative intent was found to be significantly more likely in the US (85% patients) compared with Europe (75% patients). Use of adjuvant chemo and/ or radiotherapy was also much higher in the US than in Europe, with 28% of Dukes' B colon cancer patients receiving chemotherapy in the US compared with 20% in Europe. For Dukes' C patients, 56% received chemotherapy in the US, in contrast to 47% in Europe. Those with rectal cancer demonstrated a similar disparity with 47% of Dukes' A-C patients receiving radiotherapy in the US compared with 37% of European patients. As a consequence, survival in American CRC patients was noted to be between 12-14% higher than in comparable European patients with this difference in survival being attributed to earlier stage at diagnosis, more extensive use of surgery and neoadjuvant therapies in American patients.[67]

Differences in colorectal cancer outcomes do not occur only between American and English patients however. Yu et al. examined the survival of all patients diagnosed with either breast

(female), lung or colorectal cancer diagnosed between 1992 and 2000 and registered with either the Northern and Yorkshire Cancer Registry and Information Service (NYCRIS) or the New South Wales Central Cancer Registry (NSWCCR). For all cancers studied, English (i.e. NYCRIS) patients reported a 47-58% higher risk of excess death compared with those of New South Wales (i.e. NSWCCR), whilst 5-year age-standardised relative survival rates for CRC cancer patients were 50.3% in English patients and 60.1% in Australian patients respectively[68].

Yu et al.'s work is especially important in establishing that a real difference exists in cancer related outcomes, and colorectal cancer in particular, between England and other first world nations. One of the frequent criticisms levied at international comparisons of outcome data are the differences in cancer registration methods used and the completeness of available data. Such differences present numerous potentially confounding (and therefore explanatory) variables, but the strength of Yu et al.'s work is that English and Australian cancer registration and mortality systems are directly comparable. Both registries (i.e. NYCRIS/ NSWCCR) are well established, containing high quality data, with high levels of completeness and rates of survival that are similar to those reported at a national level[6869,70]. Thus Yu et al.'s work provides compelling evidence that the differences in outcomes are real and that UK cancer outcomes are genuinely inferior to those of Australia.

The results of the International Cancer Benchmarking Project (ICBP) provide further evidence that UK cancer outcomes are inferior to those of Australia and other first world nations. The ICBP was setup to look specifically at international disparities in cancer survival. It assessed the survival of 2.4million adults diagnosed with primary lung, colorectal, breast (women) or ovarian cancer in 12 jurisdictions in 6 countries (Australia, Canada, Denmark, Norway, Sweden and the UK) between 1995-2007, with follow-up to 31st December 2007[66]. Survival improved for all cancers over the study period but was persistently higher for those treated in Australia, Canada and Sweden, intermediate in Norway and lower for those in Denmark and the UK (in this study, UK refers to England, Wales and Northern Ireland)[66].

In relation to colorectal cancer, 732,005 patients were treated over the course of the ICBP. In that time survival increased at a similar pace within each country, but wide deficits in were seen between the UK and Denmark when compared to Australia, Canada and Sweden. For the most recent period (2005-2007), age standardised, 1 year relative survival in the best

performing nation (Australia) was 84.7%. The UK in comparison achieved 74.7% and Denmark 77.7%. By 5 years, the differences in relative survival were 66.4% (Australia) and 55.8% (Denmark) and 53.6% (UK)[66]. Data quality, classification and other confounding variables were not felt to be likely explanations for the differences seen in survival, as the patterns in cancer related outcomes were consistent with later diagnosis and differences in management of patients, especially for those patients managed in the UK or Denmark[66].

Stage at diagnosis has been suggested by several authors as a key explanation behind the differences in international colorectal cancer survival[54,67]. The impact stage at diagnosis has on the outcome of colorectal cancer patients was investigated in detail by Maringe et al., who analysed 313,852 patients from Australia, Canada, Denmark, Norway, Sweden and the UK, treated for colorectal cancer between 2000 and 2007. Again, 1 and 3 year survival was persistently worse in the UK and Denmark, with the UK achieving a 1 year survival rate from colon cancer of 67% against 80% for Australia (and 71% in Denmark)[71]. Rectal cancer outcomes were similarly disparate, with UK survival at 1 year being 75% against 84% in Australia (Denmark 79%)[71]. Differences in stage at diagnosis were felt by the authors to partly explain the differences in outcome, especially for Denmark, where an adverse stage distribution contributed to comparatively low survival. Nevertheless, survival differences existed between nations for each stage of disease, suggesting that access to the best available treatment may have a greater role to play in outcome than stage at diagnosis and also that there may be unequal access to treatment, especially within the UK[71].

It would appear therefore, that there is substantial evidence that there is not only significant variation in reported colorectal cancer outcomes within first-world countries, but also that English/ UK colorectal cancer outcomes fall someway behind those of other, similar income level countries. The disparity in reported colorectal cancer outcomes has been the subject of fierce debate within the academic literature and remains on-going to this day.

5.3.4. Disparity amongst reported colorectal cancer outcomes

The EUROCARE studies, ICBP and CONCORD studies (amongst others) appear to provide sound evidence that the disparity within reported European colorectal cancer outcomes is real and that European outcomes fall behind those reported by America and Australia[57,67,71]. Not all

authors are convinced of the validity of these international outcome comparisons however, especially in relation to English/ UK outcomes.

Poor English/ UK cancer related outcomes are frequently attributed to stage at diagnosis, especially as variations in survival are greatest for the first 3-12 months after diagnosis. After this time period, survival is much more homogenous between UK and European/ other first world CRC outcomes.[65]. Autier and Boniol use this argument as the basis for a letter published in the Lancet, reasoning that there are numerous other factors not associated with a country's performance in treating cancer which may affect survival[72]. Autier and Boniol note that the UK has been criticised for poor administrative systems in relation to cancer registration (for example registration of date of recurrence rather than date of diagnosis) and a comparatively poor level of complete case ascertainment. They quote the case ascertainment of breast and colorectal cancer cases in the UK in comparison to Finland as evidence (Thames Cancer Registry case ascertainment 1990-2001: breast cancer 85%, colorectal cancer 87.8%; Finnish case ascertainment 1990-2001: breast cancer 98.5%, colorectal cancer 98.8%), concluding that to fully understand country specific survival data, it must be looked at in the context of country specific incidence and mortality data[72].

Beral and Peto writing in the British Medical Journal then go on to argue that it is the lack of compulsory registration of cancer (as opposed to death, which is compulsory) within the UK, that is the underlying cause of the disparity in survival[73]. Within the UK, death certificates are an important tool for the identification of patients who had cancer. These cases are almost always excluded from survival analyses for obvious reasons but in order to limit exclusions, intensive searching of the medical notes for mention of cancer is undertaken. If the first mention found of a cancer is that of recurrence (but which is then subsequently recorded as the date of diagnosis), falsely short survival times are derived. Beral and Peto also argue unregistered survivors are frequently not included in UK cancer survival statistics (in one catchment areas, up to 23% of cancer survivors were unregistered), again leading to misleading survival figures[73].

In order to test the assumption that 1 year differences in survival were not linked to health system performance, but wholly to measurement artefact, McPherson and Brown fitted a crude model to the data presented by Coleman et al. for breast and colorectal cancer reported in the ICBP[74]. They then extrapolated this survival to 5 years and compared the observed (i.e.

Coleman et al.) with the adjusted results. UK 5-year relative survival figures for CRC were 53.6% (observed) and 59.3% (adjusted). Danish figures were 55.8% (observed) and 58.6% (adjusted), whilst Swedish figures were 62.6% (observed) and 59.2% (adjusted). Using their model, UK survival figures from colorectal cancer were significantly better than previously reported. Whilst McPherson and Brown acknowledge their model is crude and has only been applied to a limited range of data, they argue that artefactual bias may be contributing substantially to the UK's poor reported outcomes and that until these factors are considered, current estimates of UK survival following colorectal cancer (amongst others) may well be wrong[74].

Despite the arguments put forward by Autier and Boniol, Beral and Peto and McPhearson, the work of authors such as Yu et al. and Maringe et al., alongside projects such as the ICBP, makes it difficult not to conclude that English (UK) colorectal cancer outcomes fall behind those of Europe, America and Australia. Yu et al. presented data from two very closely matched datasets, both in size, completeness and how the data was collected. Maringe et al. show that stage at diagnosis only partly explains differences in outcome but also that the differences in outcome remained, not matter what the stage of disease. Maringe et al.'s results are further reinforced by those of the ICBP, where again, differences in survival were consistent at each stage of disease. It is likely therefore that poor English colorectal cancer outcomes are real and that whilst English outcomes are certainly influenced by a high number of patients presenting with advanced disease, other factors are likely to be contributing.

5.4. Emergency Colorectal Cancer

Stage at diagnosis of any cancer, not just colorectal, has an obvious impact on likely survival, yet stage at diagnosis in colorectal cancer is not the only predictor of poor outcome. Patients who present with colorectal cancer in an emergency fashion have been shown to undergo longer operations, have longer admissions with more re-admissions and a higher rate of perioperative mortality than those who present in an elective fashion[63,75,76]. Thus emergency presentation with colorectal cancer is a stage-independent predictor of negative outcome and identifying factors which may predict emergency admission, offers one potential route to improving English colorectal cancer outcomes[76].

5.4.1. Patient factors which may contribute to Emergency Presentation

Emergency presentation of colorectal cancer has been recognised as a persistent problem with English (and UK) colorectal cancer patients since the 1990's.[65,77–79] The vagaries of colorectal cancer symptoms, the reluctance of patients to discuss bowel habit and the fear of a potentially life-limiting diagnosis, contrive to make patients reluctant to present and the diagnosis of colorectal cancer clinically challenging[80,81].

Attempts to elicit factors in a patient's history or presentation that may point to an early diagnosis of colorectal cancer (and in particular those most likely to present as emergencies) have been the subject of numerous studies[82–85]. Traditional 'red 'flag' symptoms of CRC include weight loss, change in bowel habit, decreased appetite, rectal bleeding and relevant family history. Nevertheless, a full time GP is likely to see only 1 new case of CRC each year, against a multitude of abdominal pain, changes in weight and appetite and rectal bleeding[86]. Therefore, although a common disease, CRC remains an uncommon diagnosis in primary care.

Attempting to define those most likely to present as an emergency was the subject of a review by Wallace et al. 97 907 patients, presenting to primary care with CRC between 2007 and 2011 were reviewed. This study demonstrated that women, the socioeconomically deprived, those of non-white ethnic descent, those with dementia, and those with cardiac, neurological or liver disease were the most likely to present as an emergency[87]. These findings were confirmed by the study of Rabeneck et al. who again noted that it was women

and the socioeconomically deprived who were most likely to present to primary care with CRC; suggesting that one of the reasons women may present more frequently as an emergency was a sense of embarrassment about undergoing large bowel endoscopy performed by a male doctor[88].

Whilst the 'red flag' symptoms for CRC are well recognised by healthcare workers, Cleary et al. in a case control study of primary care patients, attempted to identify clinical features associated with emergency CRC presentation[89]. They noted that those most likely to present as emergencies were those who had abdominal pain, weight loss and/ or diarrhoea, but also that the majority of patients who subsequently presented with emergency CRC (63%) had reported symptoms of their disease at least 30 days beforehand. Cleary et al. therefore concluded that at least some cases of emergency presentation of CRC should be preventable[89].

Stapley et al. assessed the mortality of CRC in relation to symptom presentation and symptom duration in primary care, noting that rectal bleeding was associated with a less advanced stage at admission, but that a mild anaemia found on phlebotomy was associated with a more advanced stage (and therefore higher mortality)[90]. No relationship was found however, between length of symptom duration and stage at presentation or mortality[90]. Gunnarsson et al., in a review of patients presenting to one Swedish district general hospital between 1996 and 2005, even found that emergency admission with CRC was more likely in the summer (July and August) than at other times of the year; they were unable however to offer a satisfactory answer as to why this might be[91].

Risk factors for emergency admission in English patients were assessed in a review by McPhail et al. that encompassed all colorectal cancer cases diagnosed in England between 2006 and 2008[65]. They found that older age and advanced stage of disease were predictive for emergency admission, as were but to a lesser extent, co-morbidity, lower socioeconomic grouping and female sex. Emergency presentation was independently associated with short-term mortality, even after taking account of confounding variables[65]. The enormous effect of age on emergency presentation was elegantly displayed by a further study by Elliss-Brookes et al. looking at Routes to Diagnosis for Cancer. Whilst this study included all types of cancer, it notes that for those aged ≥85years, 43% of cancer diagnoses were made on emergency admission.

5.4.1.1. Figure 10: Cancer Diagnoses by Route and Age in England 2006-2008[92]

	Screen-detected (%)	TWW (%)	GP referral (%)	Other outpatient (%)	Inpatient elective (%)	Emergency presentation (%)	DCO (%)	Unknown (%)	*n*
All cancers	5	26	21	10	6	24	1	8	739 667
Under 50 years	2	29	24	10	6	15	0	13	81 072
Aged 50–59 years	12	26	21	9	6	15	0	10	102 487
Aged 60–69 years	10	26	22	10	6	18	0	8	181 958
Aged 70–79 years	2	28	23	10	6	25	1	6	207 389
Aged 80–84 years	0	25	20	9	5	34	1	6	87 940
Aged 85+ years	0	20	16	7	4	43	3	7	78 821

*TWW: Two Week Wait, DCO: Death Certificate Only

Duration of symptoms has been put forward by some authors as a possible explanatory variable for the high numbers of English colorectal cancer patients presenting as emergencies with aggressive, advanced stage disease. It has been suggested that there may be sub-groups of disease, such as those with slow-growing tumours, who have a long duration of symptoms and yet a relatively early stage at diagnosis. Those with aggressive disease may have a shorter symptom duration and subsequently more advanced disease at diagnosis[85,90,93,94]. Symptom duration being associated with poor survival has been reported for over 30 years. Mulachy et al. reviewed the outcomes of 777 consecutive CRC patients presenting to their institution (St. Bartholomew's, London) to assess the impact of symptom duration on survival, independent of other clinical and pathological factors. Long term survival was found to increase consistently with length of symptom duration in univariate analysis, whilst the addition of stage, bowel obstruction, age, sex and tumour site in multivariate analysis had no effect on survival[85]. A similar finding was noted by Jullumstrø et al. in an analysis of all 1263 patients presenting to Levanger hospital between 1980 and 2004 and

2892 patients presenting in Norway in 2004, finding that increasing symptom duration was associated with less advanced disease at presentation and better survival in colon cancer patients, although no such association was found for rectal cancer patients[84].

Factors most clearly associated with emergency admission in colorectal cancer, would therefore appear to be older age, advanced stage of disease, female sex and lower socioeconomic grouping. Emergency presentation with colorectal cancer may also be influenced by the time from first symptoms to presentation at medical services and by time from physician assessment to diagnosis and treatment (i.e. diagnostic delay). Traditionally, it has been difficult to assess the impact that factors such as diagnostic delay may have on the outcomes of cancer patients, especially at a population level (as the necessary infrastructure has not been in place). Recent advances with large, population level databases, such as the National Cancer Data Repository (NCDR), are powerful tools that allow researchers to track patient outcomes from presentation to death and to assess the influence of multiple variables (e.g. diagnostic delay, differing treatments, regional variation, age, sex, socioeconomic status) upon outcomes. The advent of such databases which are ‘searchable’ and ‘linkable’ to other sources of information (e.g. primary care data) opens up further routes of investigation, potentially highlighting key symptoms or attributes which make a diagnosis of colorectal cancer more likely and as such have the potential to profoundly improve outcomes for all cancer patients.

5.4.2. Diagnostic Delay and Emergency Presentation

Predicting emergency presentation in some patients will always be impossible, as there will always be those who present with a short symptom history, due to aggressive, rapidly progressing disease. In others however, diagnostic delay may be a significant factor influencing their presentation. Diagnostic delay has been reported as being a concern in the identification and management of patients with CRC as far back as the 1960's. In 1968, Holliday and Hardcastle reported that only 30% of patients with colon cancer presented within 3 months of the onset of their symptoms and that for those with rectal cancer, 25% had had symptoms for over 12 months prior to presentation.[95] In their study, 42% of patients with colon cancer presented as an emergency, with the authors attributing most of the delay to inadequate patient examination in primary care and to patients not appreciating the importance of bowel symptoms. Of the delay that was attributed to hospital delay, most was ascribed to waiting for investigations and to poor quality barium enemas or sigmoidoscopy. There was a notable absence of commentary on the time taken for surgical intervention however.[95]

The importance of how presentation of cancer affects outcome, and the fact that many patients do not follow a standard route to diagnosis, was recognised by Elliss-Brookes et al., who used linked data records from the National Cancer Data Repository for every patient diagnosed with cancer in England between 2006 and 2008 to create an algorithm allocating a 'routes to diagnosis' category for each individual[92]. Significant variability was noted in the proportion of cancers diagnosed by each route. For those with colorectal cancer, two-week wait and GP referral constituted 27% and 20% of all diagnoses respectively, whilst the proportion of screen detected cancers increased from 0.1% in 2006 to 5% in 2008 (reflecting the roll out of the NHS Bowel Cancer Screening Program). Emergency presentations made up 26% of all presentations but were proportionally much higher in teenagers and young adults (57% of all diagnoses in this age group). Emergency presentation was also, unsurprisingly, associated with a considerably lower one-year survival compared with those who presented by other routes (1 year relative survival for CRC patients: screen detected- 98%, two-week wait 82%, GP referral 82%, emergency presentation- 50%)[92].

How variation in the number of primary care consultations (for potential cancer related symptoms) prior to secondary care referral affects outcomes was the subject of a large study by Lyratzopoulos et al. 41,299 patients with 24 different cancers, who participated in the 2010 National Cancer Experience Survey in England were assessed for the number of general

practitioner consultations prior to hospital referral[96]. Wide variation in the number of primary care consultations before referral was found, with younger patients, women and those from ethnic minorities being significantly more likely to have 3 or more consultations prior to referral, as were those with colon cancer in comparison to rectal cancer (OR 1.60, 95% CI 1·36–1·87). Lyratzopoulos et al. concluded that researchers should focus on better understanding of cancer signs and symptoms in these groups in order to improve outcomes.[96]

Lyratzopoulos et al. failed to account however for rapid repeat consultations to follow up appropriate investigations (and which are therefore not a failure to suspect the diagnosis) and did not record the time interval between consultations for those who attended more than once, and as such their study has been criticised for these reasons.[96] Colorectal cancer by the nature of the disease, tends to have an insidious onset, and symptom recognition may be challenging for both the patient and clinician alike. Studies which have assessed patient/ clinician interaction in primary care, prior to referral to secondary care for investigation, have found the majority of patients to be asymptomatic prior to presentation and therefore to have limited opportunities for reduction in diagnostic delay, except potentially through screening)[85,97,98]. Nevertheless, what the work of Ellis-Brookes, Lyratzopoulos and others clearly demonstrates is that despite recent efforts, there is much variation (and therefore potential delay) in the way patient's access secondary care and that if efforts to reduce unplanned or emergency admission for cancer in general, not just CRC, are to be reduced, this variability must be addressed.

5.4.3. Management of the Emergency Colorectal Cancer Patient

The diagnosis of cancer and any variation in time to diagnosis represents only one component of a treatment pathway. Differences in management are also of crucial importance in determining an individual's outcome. Whilst variation in the outcomes of colorectal cancer treatment worldwide are widely reported, no direct comparison has been undertaken of how the management of emergency colorectal cancer patients in England compares to other countries with similar healthcare systems[51,57,66,67,99,100]. The 2011 paper of Morris et al., provides a 30-day postoperative mortality figure for all English colorectal cancer patients of 6.7% and 14.9% for those undergoing emergency resection, but notes marked variability in treatment outcomes throughout England, even after adjustment for case-mix[63]. The overall figure of 6.7% was significantly higher than that reported in the National Bowel Cancer Audit (NBOCAP) report of that year (4.7%) (although Morris et al. used population level data, whilst the audit data was provided voluntarily) and significantly higher than that reported in Scandinavia, Canada and the USA (2.7% (rectal cancer alone) to 5.7%)[63]. Increased likelihood of death at 30-days was associated with elderly males, increased socioeconomic deprivation, increased co-morbidity, advanced stage of disease at presentation and necessity for urgent operative intervention[63].

An attempt to establish why such variation in outcomes exists in English colorectal cancer outcomes was undertaken by Warwick et al. through and in-depth analysis of patients treated in East Anglia. All cases of colorectal cancer registered with the Eastern Cancer Registry and Information Centre (ECRIC) between 1999 and 2005 were assessed.[101] A similar distribution of demographic variables, stage of disease and treatment factors was found among the hospitals enrolled, but significant differences were obtained in the number of lymph nodes resected and examined, the number of patients who received a major resection and/ or chemotherapy and the proportion of patients with advanced disease who did not receive an operation. The authors concluded that there was a lack of consistency in colorectal cancer management in East Anglia, but that no one single factor could be found to account for this[101].

Other authors have suggested that, rather than variation in the initial management of a patient, it is in fact a clinical team's failure to recognise and treat deterioration in a patient's postoperative condition (hence *failure to rescue*), that is the underlying cause of variation in postoperative outcomes. Henneman et al. evaluated the association between structural hospital characteristics (i.e. volume of patients, teaching status and ICU facilities) and failure to rescue in Dutch colorectal cancer patients[102]. Of the 25, 591 patients, from 92 different

hospitals included within the study, average mortality was 4.3% with 23% of patients suffering a severe complication. Failure to rescue rates varied between 0 and 39%. Hospital type and hospital volume were not found to be independently associated with failure to rescue, but access to intensive care facilities was, with those hospitals with the lowest levels of intensive care support having the highest rates of failure to rescue[102]. England has a particularly low level of intensive care support in comparison to other developed nations. Germany provides 24.6 beds per 100,000 population, the United States 20, France 9.3 and Sweden 8.7. England in comparison has 3.5[103].

Patients undergoing surgery for colorectal cancer frequently require intensive care support, either because of their index operation or to overcome complications. Almoudaris et al. used Hospital Episode Statistics (HES) data to compare rates of failure to rescue in those being treated for colorectal cancer in 150 English NHS Trusts. In a study encompassing 144, 542 patients treated between 2000 and 2008, significant differences were found in the rates of failure to rescue between Trusts. Those in the highest mortality quintile had a 1.7 times greater chance of death if they required re-intervention than those in the lowest mortality quintile[104]. Although Almoudaris et al. were not able to define exactly which complications or interventions were most associated with likelihood of death (due to limitations in coding within HES), their study suggested significant differences in the management of post-operative complications within the English NHS. The work of Henneman et al. and Almoudaris et al., alongside that of Morris et al. and Warwick et al. would suggest that, not only is there a lack of consistency in the management of the English colorectal cancer patients, but also variation in the ability of clinical teams to recognise the deteriorating patient. Combined with a relative lack of intensive care support, there is much scope for improvement in the management of the colorectal cancer patient in secondary care in England.

5.5. Improving Colorectal Cancer Outcomes in England and the United Kingdom

In the mid-1990s the UK government became aware of the rising incidence and prevalence of cancer within the UK, alongside a recognition that there was inequality of access to cancer services, the so called ‘postcode lottery’. Since that time, there has been a sustained effort, both on the part of the UK government/ Department of Health and by the medical profession itself, through various initiatives to improve access to cancer services and overall cancer related outcomes.

The initial response to the recognition of poor UK cancer related outcomes was to commission the chief medical officers of the day, Kenneth Calman (England) and Deidre Hine (Wales) to write a report as to how cancer services may be restructured to meet rising demand and to ensure that each patient received equal access to expert care. The ‘Framework for Commissioning Cancer Services’ report (known almost universally as the Calman-Hine report) was broadly accepted and implemented, and was the first in a series of reports aimed at continually improving UK cancer services and outcomes.

5.5.1. The Calman-Hine Report

The Calman-Hine report of 1995 proposed radical reform of UK cancer services, recommending change from a generalist model (whereby patients were treated by a general surgeon or physician with specialist support) to a fully specialist model[105]. Its recommendation of concentration of surgical cancer services into smaller surgical centres of excellence, working alongside site specialist multidisciplinary teams, was a fundamental departure from how services had previously been provided[106].

Implementation of the suggested model of care was at first sporadic, as the NHS was also undergoing a period of profound organisational change[105]. However by the mid 2000’s, the majority of suggested changes had been implemented with authors reporting increased use of multidisciplinary teams, increased adherence to guidelines and evidence of subsequent improved 5-year survival rates for cancer[107–110].

5.5.2. The NHS Cancer Plan 2000

The NHS Cancer Plan of 2000 was a direct result of the successful implementation and improved outcomes for cancer patients of the Calman-Hine report, but at the same time, recognised the continuing disparity in cancer incidence, prevalence and outcomes amongst different socioeconomic groups and the enduring variability in treatment delivered throughout the country. It aimed, for the first time, to link prevention, diagnosis, treatment, care and research[111]. The Cancer Plan of 2000 also introduced cancer waiting time targets; 2 weeks from GP referral to specialist outpatient review, 31 days from decision to treat to first treatment and 62 days total from GP referral to first treatment[111].

The Cancer Plan of 2000 has received a mixed reception. Whilst some authors (Rachet et al.) examining English cancer outcomes in comparison to Welsh (where a cancer plan was only introduced in 2006) note that 1 year survival for all cancers was initially better in Wales than England, but that this trend was reversed when those diagnosed in 2004-6 were considered[112]. There was little difference between 3-year outcomes, with the authors concluding that the Cancer Plan had had a modest impact upon outcomes. Others have found that cancer waiting times have had no impact on outcomes for certain cancers (Raptis et al.)[113]. In relation to colorectal cancer, the majority of studies conclude that cancer waiting times have had little impact on a patient's journey time or on their survival, although some studies note a higher cancer detection rate, albeit at the expense of many referrals which failed to adhere to the guidelines[112,114–117].

One of the flagship policies within the Cancer Plan was the introduction of the 'two week wait' from point of referral by general practitioner to review in secondary care (from a previous system of urgent/ routine referrals to a named clinician). Opinions as to the effect 'two week wait' have had on cancer detection and treatment times are divided. Some authors report that whilst patients with cancer referred to the two week wait clinic are seen faster than standard referrals, they also tend to have more advanced disease in comparison to direct referrals, who take longer to come to treatment but have less pathologically advanced disease[118,119]. Quicker access to investigation, diagnosis and review may also be assumed to result in an improved patient experience. Yet is recognised that the majority of 'two week wait' referrals do not have cancer, but that in order to meet the target, patients often receive a less individualised service, leading to a lack of doctor/ patient interaction[116]. Thus the patient feels that are merely an item moving along a 'production line' to diagnosis.

The greatest criticism of 'two week wait' however, comes not from erosion of the doctor/ patient relationship but from the recognition that time to referral is most often not the not the major source of delay in a patient accessing cancer services. It is in fact the time preceding referral and after the appointment that are the major sources of delay[120]. Addressing the issue of time preceding referral (i.e. earlier diagnosis) has begun with the introduction of the bowel cancer screening program, but addressing delay in investigation and treatment requires significant investment in cancer services in an era of ever more stretched healthcare budgets.

5.5.3. Improving Outcomes: A Cancer Strategy

Following on from the NHS Cancer Plan 2000, the Cancer Reform Strategy was published in 2007. This again aimed to improve outcomes but also to set the direction of development of NHS cancer services over the following 5 years. In particular, it recognised new opportunities for prevention, early diagnosis and better treatments that had become available through greater scientific understanding of cancer[121]. The Cancer Reform Strategy subsequently led to the publication of the Improving Outcomes: A Strategy for Cancer report in 2011[122]. This set out the coalition government's ambition to improve cancer outcomes (primarily through earlier diagnosis), whilst dealing with the continuing rising incidence and prevalence of cancer, inequality and suboptimal care, the slow diffusion of new technologies and managing the rising costs of cancer care[122].

Whilst it is currently too early to assess the impact of Improving Outcomes: A Strategy for Cancer, the report will have been implemented during a period of unprecedented reform and change within the NHS. Cancer care is becoming ever more expensive, with rising numbers of people both surviving and living with the disease. Delivery of cancer care to an ageing population, in the face of continuing scientific advancement, will remain a persistent challenge for both government ministers and clinicians.

5.5.4. The National Institute for Health and Care Excellence

The National Institute for Clinical Excellence (NICE) was set up in 1999 as a body independent of government to provide guidance as to how to reduce variation in the availability and quality of NHS treatment and care. It was subsequently merged with the Health Development Agency in 2005 to create the National Institute for Health and Clinical Excellence and has a mandate to set quality standards and indicators for NHS care and to

provide guidance on standards of care, the clinical management of patients and the use of novel technologies and medicines. In 2011, NICE published guidelines on the diagnosis and management of colorectal cancer (CG131). This was updated in December 2014 and currently represents the most up-to-date guidance on the management of CRC in the UK[39]. Full discussion of the guidelines is beyond the scope of this literature review, but is available at https://www.nice.org.uk/guidance/cg131.

5.5.5. Screening for Colorectal Cancer

Colorectal cancer, with its long pre-malignant course and ~5% lifetime risk makes it a suitable candidate for screening. The most widespread screening method in use throughout Europe is Faecal Occult Blood Testing (FOBT), although a pilot study for screening with flexible sigmoidoscopy has been rolled out in 6 areas of the United Kingdom since March 2013[8,123,124]. FOBT relies on the tendency of adenomas and malignant lesions within the colorectum to bleed and the peroxidase activity of haem to be detected on guaiac impregnated card.[8] The Minnesota Colon Cancer Study showed a reduction in mortality from colorectal cancer by 33% with annual FOBT screening, whilst the English Bowel Cancer Screening Pilot study evaluated 480,250 individuals for colorectal cancer using FOBT with a 56.8% uptake and a positive test rate of 1.9%. 1.62 cancers were detected per 1000 individuals screened with a positive predictive value of 10.9% for malignancy and 35.0% for adenomas.[8]

As a result of the English Bowel Cancer Screening Pilot study, the NHS Bowel Cancer Screening Programme was introduced in 2006 with full roll out achieved in 2009. Currently all individuals over the age of 55 are invited to participate in a one off bowel scope screening test if offered in their area, or all individuals over the age of 60 (nationally) are offered FOBT testing. Recent estimates suggest that by October 2008, 2.1 million invitations to participate will have been sent out, with a predicted response rate of 49.6% in men and 54.4% in women[125]. Of the 1.08 million tests returned so far, 2.5% men and 1.5% of women had an abnormal test result. Very much in line with the trials and pilot studies, malignancy was discovered in 11.6% men and 7.8% of women with a positive FOBT. High risk adenomas were found in 43% and 29% respectively with 71% of tumours identified being classified as 'early'.[125]

In relation to emergency admissions, increasing evidence is being published that screening has had a marked effect on the number of emergency presentations, the requirement for

emergency operation, 30 day mortality and rates of stoma formation[126,127]. Scholefield et al. reviewed the outcome of 150,000 individuals who were offered FOBT screening in Nottingham beginning in 1981. Of those invited, 60% responded and of the 1962 who had a colorectal cancer over the study period, 23.9% presented as an emergency. Those who engaged with screening had a significantly lower rate of emergency presentation, 30-day post-operative mortality and stoma formation. Conversely, those who had declined screening (i.e. non-responders) had a significantly higher rate of emergency admission and stoma formation.[127]

The findings of a study by Goodyear et al. comparing rates of emergency admission and outcomes before and after the introduction of a colorectal cancer screening programme in North Warwickshire re-iterated the findings of Scholefield et al. Goodyear et al. found that when rates of emergency admission were compared in 1999 (the year before screening was introduced) with those at the end of the study period (2004), rates of emergency admission had halved from 29.4% to 15.8%.[83] A similar decrease was seen in the number of emergency procedures performed and their mortality. The absolute number of advanced (Dukes' C or above) tumours presenting as an emergency halved over the study period, although as a proportion of emergency admissions, numbers of advanced tumours remained static[127].

Both the studies by Goodyear et al. and Scholefield et al. provide compelling evidence that a well-executed screening programme can have a marked effect on both the numbers of emergency presentations and their outcomes. Other endeavours to prompt early diagnosis include the National Awareness and Early Diagnosis Initiative (NAEDI). NAEDI was formally launched in 2008 and is a partnership between public (Department of Health, National Cancer Action Team, Cancer Research UK) and third sector organisations to support activities and research which lead to the earlier diagnosis of cancer. Despite this, the most recent National Bowel Cancer Audit Project report states that for colorectal cancer, emergency admissions remain a significant problem at 'around 20%' of all cases diagnosed in England.[27] These efforts are laudable and steps have clearly have been taken to attempt to reduce the UK's high emergency admission and early mortality rate, however it is likely that their effects will take several years to 'filter through.'

5.5.6. Audit of Colorectal Cancer Outcomes: The National Bowel Cancer Audit Program

Recognition of the increased mortality from CRC in comparison to other developed nations and that national standards of care were not being uniformly met prompted the development of the National Bowel Cancer Audit Program (NBOCAP). The first NBOCAP report was produced in 2006 and it represents the most up-to-date 'snapshot' of colorectal cancer care throughout England and Wales available[128]. NBOCAP is run jointly by the NHS Digital and the Association of Coloproctology of Great Britain and Ireland (ACPGBI) and aims to improve the quality of care and survival of those with colorectal cancer[43].

The most up-to-date report is the 2017 report, publishing data regarding those treated for colorectal cancer in England and Wales between 2015 and 2016. Case ascertainment for this period was 95% (of the 30 710 patients diagnosed with CRC). Mortality for all those undergoing surgical resection has fallen consistently since the audit began and now stands at 3.2% (at 90 days). Emergency admission remains stubbornly high at 21% of admissions, with emergency or urgent major surgery being associated with a mortality of 10.3% at 90 days. 1 in 4 colorectal cancer patients will not undergo a procedure with curative intent, although this comprises a complex group of the old and frail, those with early stage disease (who may only require endoscopic excision of a polyp cancer) and those with advanced disease[43].

Wide variations in length of stay, use of laparoscopic surgery, those chosen for surgical resection and 2-year survival are seen across Strategic Clinical Networks (the organisations tasked with providing and commissioning, amongst other things, cancer services across the English NHS). 2-year survival for the 78,609 patients treated for CRC between 1st April 2008 and 31st March 2011 was 67%, with 80% surviving for 2 years if undergoing surgical resection, but only 43% surviving 2 years if no resection was undertaken[43]. Information regarding use of neoadjuvant therapy was too incomplete to be meaningful[43]. Identifying reasons underlying variability in who is selected for surgery, use of neoadjuvant therapies and rates of survival are the challenges that the NBOCAP audit team now face.

5.5.7. Routine Datasets and 'Big Data'

The term 'big data' is a relatively new one, coined to cover the collection and analysis routine data at a population level relating to anything from health, to the sales of goods, to changes in

demographic trends. The collection and use of routine data in cancer however is not new, and has been taking place in most advanced healthcare systems for many years. Over recent years, a ‘step change’ in relation to the collection and use of routinely collected datasets has taken place, facilitated mainly by developments in technology.

The publication of the Calman-Hine report, with the subsequent restructuring of cancer services and the development of cancer networks in the mid-1990s, created an opportunity within the NHS for routine data on cancer to be collected and brought together in a systematic manner for the first time. With the advent of accurate, searchable and analysable population level data relating to cancer, the realisation occurred that ‘big data’ represented a new and previously untapped source of information, whereby at risk individuals may be identified and the outcomes of treatments or changes in management assessed at a population level.

Currently, responsibility for the collation of routine cancer data within the English NHS lies with the National Cancer Registration and Analysis Service (NCRAS), itself a part of Public Health England (PHE). NCRAS was preceded by the National Cancer Intelligence Network (NCIN), which was formed in 2008 with the aim of offering an efficient and effective method of cancer related data collection, acting as a national repository for cancer datasets, informing and supporting audit and research in the English NHS and exploiting and driving improvements in cancer care. NCIN was subsequently merged with the cancer registration service in 2016, creating NCRAS[129].

As part of the then NCIN, the Northern and Yorkshire Cancer Registration and Intelligence Service (NYCRIS, now itself amalgamated into PHE) was fundamental in the creation of the National Cancer Data Repository (NCDR). The NCDR acts as a national cancer database which links data from cancer registries with that of the Hospital Episode Statistics (HES) data, to create an extensively cleaned database which may be used for the analysis of surgical procedures, mortality and workload in relation to cancer patients in England and Wales. Like all ‘big data’ databases, the NCDR suffers from limitations (data quality, inconsistency and instability, challenges regarding validation of data and it’s analysis). Nevertheless, the NCDR at the time of its inception was regarded as a model database for cancer, allowing for the exploitation of comprehensive, population level datasets for the improvement of cancer services and outcomes. It is from the NCDR that the data underpinning this thesis was drawn.

5.6. Summary

The weight of evidence suggesting that colorectal cancer outcomes in England are behind those of similar income level European countries and substantially behind those of America and Australia is overwhelming[57,60,67,71]. England appears to have high numbers of patients presenting as emergencies with rapidly fatal disease, but also wide variations in patient management and outcome, particularly in the early stages of treatment[58,62,63,101,104]. To improve English colorectal cancer outcomes, patients must be identified earlier, prevented from presenting as an emergency, be (if possible) made fit enough to undergo major surgery and, should they deteriorate through the course of their treatment, have that deterioration recognised and acted upon before it is too late to 'rescue' them. Cancer plans and increased availability of critical care beds will partially assist in this aim, but the key to improved outcomes will remain earlier diagnosis and more consistent treatment.

'Big data' in the form of the NCDR and other large datasets allows researchers to assess the impact interventions have on cancer care and to compare our standards of care with others, but also to identify those patients who are most likely to benefit from any particular intervention. This project aims to reflect on, quantify and compare recent colorectal cancer care in England and to highlight where efforts may best be spent in order to bring about the greatest possible improvement in colorectal cancer related outcomes.

6. Aims and Objectives

6.1. Aims

Whilst there is no doubt that outcomes for all patients with colorectal cancer (within the developed world at least) have improved considerably over the last 40 years, outcomes for English colorectal cancer patients are consistently reported as less favourable than those of Europe, the United States and Oceania.

Reasons why English colorectal cancer outcomes remain poor are uncertain, with seemingly high numbers of emergency patients with aggressive disease. These outcomes however, are often based on data from before the introduction of major structural changes to the English NHS and its reorganisation of cancer services. Further, England enjoys comparatively accurate and complete datasets in relation to other countries. Questions arise therefore as to whether English outcomes are truly as poor as described and to the extent of any improvement of those outcomes over recent years.

This body of work therefore, aims to evaluate through use of population and local level data, whether outcomes for English colorectal cancer patients have improved and to document the changing face of English colorectal cancer. It hypothesises that through exploring the differing outcomes for elective and emergency colorectal cancer patients within the English NHS, previous international comparisons of poor outcomes may not be a true reflection of English colorectal cancer care.

6.2. Objectives

1. To demonstrate how population level databases may be used to inform colorectal cancer practice.

2. To observe differences in the demographics of English elective and emergency colorectal cancer patients, demonstrating how the outcome for each method of admission varies.

3. To investigate the short-term outcomes of elective and emergency surgery in English colorectal cancer patients.

4. To demonstrate how English colorectal cancer outcomes (both elective and emergency) have changed over the study period and how the introduction of the NHS Bowel Cancer Screening Program and novel technologies such as laparoscopic surgery have affected outcomes.

5. To investigate the effect on outcomes of colorectal cancer patients of Self-Expanding Metal Stents (SEMS) when used as a ‘bridge to surgery’ and to compare those outcomes to those of patients who received a defunctioning stoma as their ‘bridge to surgery’.

7. Study Design, Study Period, Data Sources and Patient Identification

7.1. Study Design

This project comprises a retrospective, observational, cohort study of English colorectal cancer patients diagnosed and treated within the English NHS between 1998 and 2010; this being the most up to date data available at the time this project was undertaken.

The data analysis and statistical package Stata (Version 13.1, 4905 Lakeway Drive College Station, Texas 77845-4512, USA) is used throughout to create statistical models to assess the outcomes of care.

7.2. Study Period

The research work for this thesis was undertaken between August 2012 and July 2014. All patients diagnosed and registered with colorectal cancer between 1st January 1998 and 31st December 2010 within the English NHS were included in the study. 1998-2010 was chosen as the most up to date data set available for which complete outcome and follow-up information was available at that time.

7.3. Ethical Approval

Section 251 and National Information Governance Board requirements for this study are satisfied by the East of Scotland Research Ethics Service approval (no. 08/SO501/66) given to Professor Eva Morris (Principal Research Fellow, Cancer Epidemiology Group, Division of Epidemiology & Biostatistics, Leeds Institute of Cancer and Pathology) for the data linkage and analysis of datasets for research into colorectal cancer. This permission allows for the analysis of population level datasets to be carried out under Professor Morris' supervision, as was the case here.

7.4. Data Sources, Data Cleaning and Patient Identification

Data for this project were drawn from the National Cancer Data Repository (NCDR). The NCDR is an amalgamation of Cancer Registry, Hospital Episode Statistics Data (HES), National Bowel Cancer Audit Program data and death data drawn from the Office for National Statistics (ONS). Linkage of these data creates a complete dataset that covers the entirety of

a patient's treatment pathway from diagnosis to death. The NCDR provides a comprehensive dataset on all individuals diagnosed with a malignant neoplasm in England between 1990 and 2010 and is part of Public Health England (PHE).

Cancer Registry data provide basic demographic, diagnostic (including pathological staging), treatment and death data on all individuals diagnosed with cancer within the United Kingdom. HES data provide detailed records of demographic, geographic, diagnostic, clinical and administrative data for all admissions, outpatient appointments and A&E attendances at NHS hospitals within England back to the financial year 1989-90. National Bowel Cancer Audit Project (NBOCAP) data provide demographic, diagnostic and staging data, case mix data of individual Trusts, hospitals and surgeons, details regarding grade of operating surgeon and operative urgency and clinical outcomes. ONS death data cover the date, place and cause of all deaths within England and Wales and supplement the data provided by Cancer Registries and HES.

Thus the author was provided with a 'cut' of data from the NCDR in order to undertake this study. Data processing and analysis was undertaken as set out below. Support and guidance in relation to data processing and analysis was provided by Professor Morris and her team, but was performed independently by the author.

Pooled cancer registry data from the NCDR were de-duplicated under World Health Organisation/ International Association of Cancer Registries rules (as tumours may be identified by more than one registry). This dataset was then linked to an extract of HES (using all or a combination of NHS number, date of birth and postcode at diagnosis) that included any individual who presented to an NHS hospital with a diagnostic code for cancer between April 1997 and March 2010.

This 'cut' of data was then loaded into Stata™ and command syntax written to clean, validate and risk adjust the data in the following manner. As anomalies became apparent within the data, fresh 'cuts' of data were requested and the command syntax re-written, until such time as a 'clean' dataset was achieved.

Information on all individuals over the age of 15 years (the cut-off age between paediatric and adult services) who had a diagnosis of colorectal cancer (ICD10[130] C18-C20) were identified and those patients <15 years of age or who did not have a diagnosis of colorectal cancer were excluded from the dataset. Information on age, sex, Dukes' stage at diagnosis and, where relevant, date of death was extracted from the cancer repository data.

Management information and outcome data for each individual were extracted from HES with a primary procedure being sought for every individual identified in both the cancer registry and HES datasets (the linked dataset). Major resections (as defined by appropriate OPCS Classification of Intervention and Procedures codes (version 4) for major colorectal resection) were identified for all linked patients up to a month prior to, and up to 12 months after, diagnosis. For those undergoing two or more colorectal resections in different episodes of care the first procedure was taken as their major resection. For those undergoing two or more resections in the same episode of care the most radical procedure was used. If no major resection could be found the dataset was searched again in the order of minor resection, bypass and formation of stoma. If no operative procedure was identified then episodes of care which included placement of a stent were searched for. If an individual linked to HES but no information on intervention could be found these individuals were allocated to a 'No surgical treatment within the NHS' category. If an individual did not link to HES (as they were managed entirely in the independent sector or died before receiving any treatment), they were allocated to a separate category and subsequently excluded from the dataset.

Laparoscopic procedures were identified as those major resections with accompanying OPCS-4 codes indicating a minimal access approach to the abdominal cavity (Y75), other specified approach to abdominal cavity (Y508) or endoscopic resection of lesion of peritoneum (T421, T428 or T429). Converted laparoscopic operations were identified as those major resections with an accompanying OPCS-4 code indicating a failed minimal access approach (Y714). If information on the approach to surgery was not present for an individual in the HES data within the NCDR, but was available in the NBOCAP dataset, then these data were used instead.

Each patient identified was assessed for their age (at diagnosis), site of disease, Dukes' stage of disease, Charlson co-morbidity score, score in relation to indices of deprivation, their index

admission and length of stay and, if they underwent a procedure, their post-procedural mortality.

Site was assessed by ICD-10 classification as set out in Table 1 below:

7.4.1. Table 1: ICD-10 Code and Tumour Site

ICD-10 Code	Tumour Site
C18	Caecum
C18.1	Appendix
C18.2	Ascending Colon
C18.3	Hepatic Flexure
C18.4	Transverse Colon
C18.5	Splenic Flexure
C18.6	Descending Colon
C18.7	Sigmoid Colon
C18.8	Colon- overlapping
C18.9	Colon- unspecified
C19	Rectosigmoid Junction
C20	Rectum

Codes C18-C18.9 were amalgamated and classified as ‘colon’ cancer, code C19 as cancer of the rectosigmoid junction and code C20 as ‘rectal’ cancer.

Cancer Registry data contain multiple different fields of staging (e.g. clinical, pathological and integrated TNM, Dukes’) (described as ‘string’ data in Stata™). To allocate each tumour, and therefore patient, a stage at diagnosis, command syntax was written for Stata™ that removed invalid entries within TNM fields before converting them to equivalent Dukes’ stages. Dukes stage was chosen as the primary descriptor of a patient’s disease stage as it neatly encompasses a tumours local spread, nodal and metastatic status. If multiple Dukes’ stages were recorded, the highest stage was retained. If no pathological stage was recorded, then clinical stage was used. If there was any evidence of nodal or metastatic disease the stage was upgraded to Dukes’ C or D as appropriate. If no staging information at all was available within the NCDR, but was available within NBOCAP data, then the NBOCAP stage was used.

A Charlson co-morbidity score was calculated for each individual based on diagnostic codes (excluding cancer) for any hospital admission in the year preceding diagnosis. The cancer component of the Charlson index was derived from the cancer registry data within the NCDR. Patients were grouped into Charlson score categories of 0, 1, 2 and ≥3; higher scores indicating greater co-morbid disease.

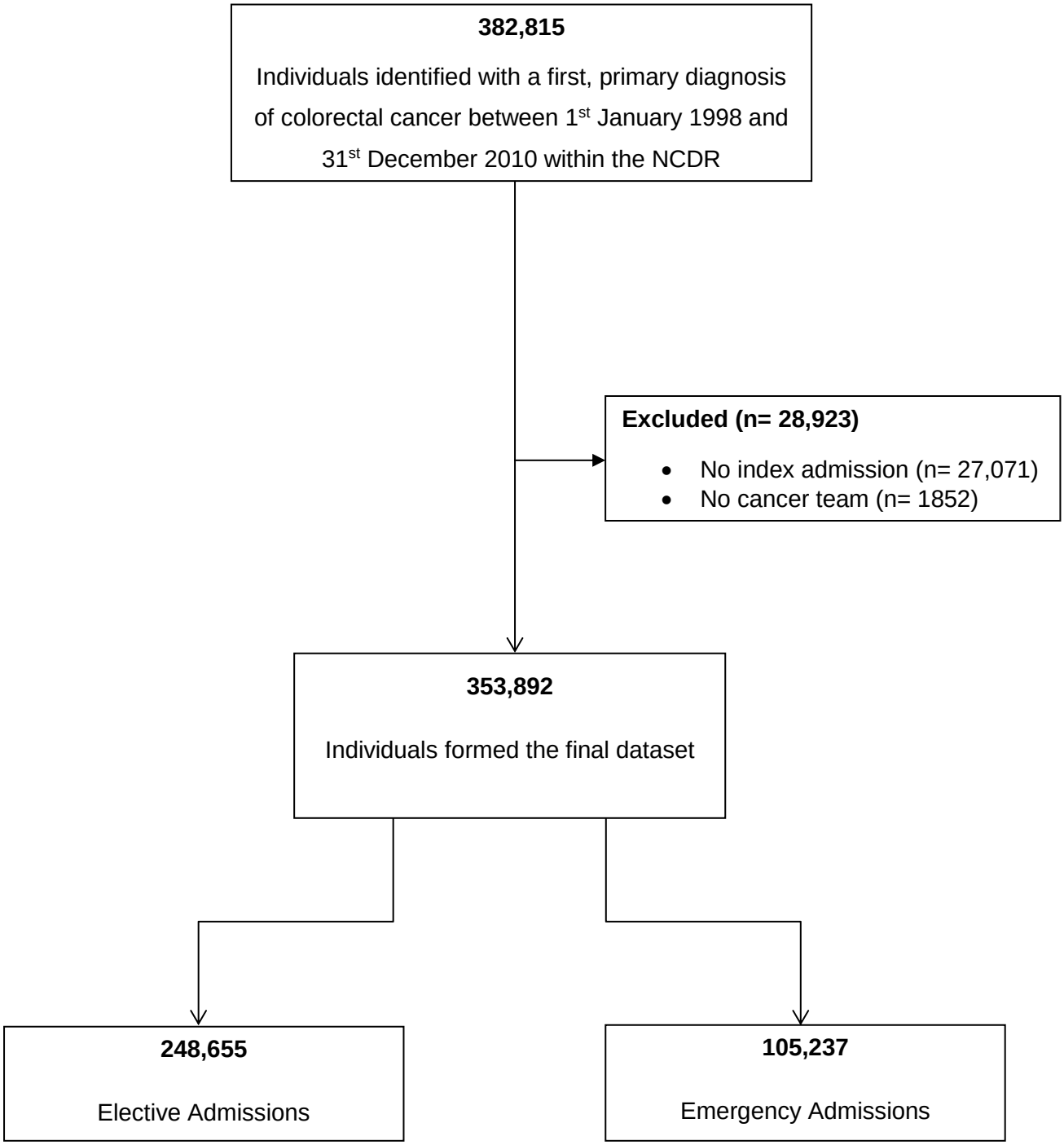
Admission method was defined as elective if the patient was admitted from a waiting list or had a booked or planned admission date. Emergency admission was defined as admission through the emergency department, transfer from any other acute specialty (following an emergency admission to that specialty), via the GP following request for immediate admission or any other unplanned admission. Throughout this work, 'emergency' or 'elective' refers to a patient's admission status and not their CEPOD status on an operating list.

Post-procedural mortality was defined as the 30-day mortality from the date of primary procedure. For completeness, 90-day post-procedural mortality was also calculated. Survival time was calculated from date of diagnosis to date of death or when censored (30th June 2010). For those individuals whose primary procedure preceded the date of diagnosis, the primary procedure was taken as the date of diagnosis.

7.5. Exclusions from the Dataset

Any patient who did not match did not have an index admission method, did not match to a cancer team or did not match to HES was excluded from analysis. It was impossible to decipher the reasons underlying why these patients did not link and therefore accurate dates of admission, diagnosis and treatment were not available for these individuals. Those individuals identified as having duplicate records within the dataset had their duplicate record removed.

7.5.1. Diagram of study patient inclusion and exclusion



8. Demographics of Elective and Emergency Colorectal Cancer Patients

8.1. Demography of Elective and Emergency Colorectal Cancer Patients

Colorectal cancer in England/ the United Kingdom has a marked North/South divide, with a higher incidence of disease recorded in Scotland, Northern Ireland and the North of England, whilst the picture in the remainder is much less clear, with isolated areas of high incidence and prevalence within the east and south west[2].

Socioeconomic deprivation throughout the United Kingdom (like all countries) is mixed, but it is generally accepted that again, a North/ South divide exists (with greater socioeconomic deprivation in the North)[131]. Socioeconomic deprivation in relation to cancer has been shown to be predictive, not only of delay in diagnosis, but also of poor outcome after treatment[132–135]. Emergency presentation is recognised as being associated with a significantly worse prognosis compared to elective presentation and is associated, along with socioeconomic deprivation, with increasing age, female sex and number of co-morbid conditions[88,136–138].

Both the United Kingdom and Denmark are recognised as having inferior outcomes in relation to colorectal cancer compared to equivalent income level countries[100]. Both countries have broadly similar population demographics, alongside broadly similar expenditure on healthcare. Recent years have seen a significant improvement in Danish colorectal cancer outcomes, which has been attributed to a focus on expeditious diagnosis and a reduction in treatment delay (and therefore reduced numbers of emergency presentation)[139].

Attempting to reduce the numbers of those who present as an emergency with colorectal cancer has also been a key part of recent efforts to improve colorectal cancer outcomes in England/ the United Kingdom, particularly through the recent introduction of the NHS Bowel Cancer Screening Program (NHSBCSP)[111,124]. Given the link between socioeconomic deprivation, co-morbidity etc. and the likelihood of unplanned admission, establishing demographic factors which may place an individual at higher risk of emergency presentation, how risk of emergency presentation varies throughout England and how programs such as the

NHSBCSP affect likelihood of emergency presentation are essential in evaluating current interventions and in understanding where and to whom further efforts should be targeted.

Thus, this chapter aims to display crude demographic data for patients diagnosed with colorectal cancer within the English NHS between 1998 and 2010, how presentation of patients with emergency colorectal cancer varies throughout England by volume of work (of NHS Trusts) and how numbers of emergency admissions have been influenced since the introduction of the NHSBCSP. Logistic regression will be used to demonstrate those variables most associated with emergency admission and to demonstrate the likelihood of admission by NHS Trust.

Logistic regression is the statistical process used to analyse a dataset in order to take account of the effect of independent variables (e.g. age, sex, co-morbidity) on a dichotomous (i.e. binary) dependent variable (e.g. emergency/ elective admission). In doing so, logistic regression accounts for the impact of explanatory variables on an outcome of interest and obtains the odds ratio for that outcome (i.e. the likelihood of that outcome occurring, given the presence of the independent variables). Once a dataset has been analysed by logistic regression, it may be considered ‘risk adjusted’.

The advantage of logistic regression is that it does not require either the dependent or independent variables to be normally distributed, nor to have equal variance, thus avoiding confounding effects. Logistic regression was chosen for data analysis for this dataset as it provides clear evidence of the effect of multiple independent variables on the outcome of interest (e.g. effect of being male, elderly with multiple co-morbidities on likelihood of emergency admission with colorectal cancer).

Logistic regression does suffer from limitations however. Whilst excellent for the analysis of categorical outcomes, it is not appropriate for the analysis of continuous outcomes (e.g. length of stay). It is also very dependent on the identification of all relevant variables (e.g. given that colorectal cancer is, usually, a disease of the elderly, age of patient is a key variable; to not include age would much reduce the validity of any results). Those variables must also be independent of each other. If the variables are linked (e.g. if all patients chosen for analysis are known to carry a certain genetic mutation for aggressive disease) then logistic regression

overstates the significance of observations and can be vulnerable to overconfidence in its predictions.

Efforts were made to ensure that the dataset used for this project was 'cleaned' thoroughly and key variables for inclusion were identified by review of the literature prior to analysis. It was anticipated that use of key variables, with similar methods of analysis would also allow for easier comparison between results, with (again) a reduced chance of confounding errors.

8.2. Methodology and Statistical Modelling

Patients diagnosed with colorectal cancer between 1st January 1998 and 31st December 2010 were identified from the NCDR database. Each patient identified was assessed for their age (at diagnosis), year of diagnosis, site of disease, Dukes' stage of disease, Charlson co-morbidity score, level of socioeconomic deprivation (IMD income category) and their index admission status (i.e. elective or emergency). Ethnicity was not included as there were numerous patients with missing or duplicate data, such that any conclusions drawn would have been unreliable.

Univariate analysis was used to produce unadjusted odds ratios for each variable relating to likelihood of emergency admission (i.e. the effect that variable alone had on the prospect of emergency admission). Multiple logistic regression analysis (i.e. the effect a variable has on the outcome of interest, taking into consideration multiple other variables, all of which also influence the outcome of interest) was used to investigate associations between each independent variable and risk of emergency admission; this was performed using the *xtmelogit* function within Stata™ Version 13.1. Variables adjusted for in this case included likelihood of emergency admission sex, age, site of disease, Dukes' stage at diagnosis, IMD income category, Charlson co-morbidity score and year of diagnosis. Two hospitals Trusts (The Christie and Royal Marsden) were excluded from both the univariate and logistic regression analyses (although were included in the presentation of the crude data), as each Trust provides supra-specialist services in relation to colorectal cancer treatment, and therefore has very few emergency admissions. Inclusion of these Trusts would have falsely skewed any results. Statistical significance was set at $p \leq 0.05$.

Funnel plots were drawn using the Stata command *funnelcompar* to compare rates of emergency admission by NHS Trust and rate of emergency admission against volume of work. A funnel plot is a diagrammatic representation of the size of effect of the outcome of interest measured against each study's (or in this case institution's) size or precision[140]. A funnel plot provides clear visual evidence of expected variation in outcome whilst also displaying divergent performance. Like all statistical methods, it suffers from disadvantages, mainly in that choice of outcome and metric of interest can markedly affect the appearance of the plot. Nevertheless, with carefully selected data, funnel plots represent an excellent method for the detection of outlying performance in a simple, graphical manner.

Funnel plots were drawn for both unadjusted and risk adjusted rates of emergency admission (against volume of work). Risk adjusted rates included adjustment for age, sex, site of disease, Dukes' stage, Charlson co-morbidity score and IMD category.

8.3. Results

8.3.1. Crude Demographic Data

382,815 individuals were identified within the NCDR as having a first, primary diagnosis of colorectal cancer between 1st January 1998 and 31st December 2010. Of these 28,993 either had no index admission or failed to match to HES and so were excluded, leaving a total of 353,892 cases which formed the final dataset. Within this final data set 105,237 were emergency admissions (29.7%).

Presentation of the crude demographic data is set out in Table 2. The overall proportion of patient admitted as an emergency fell over the study period from 32.6% admissions in 1998 to 25.3% in 2010, with more women than men presenting as emergencies (26.8% of men, 33.3% of women).

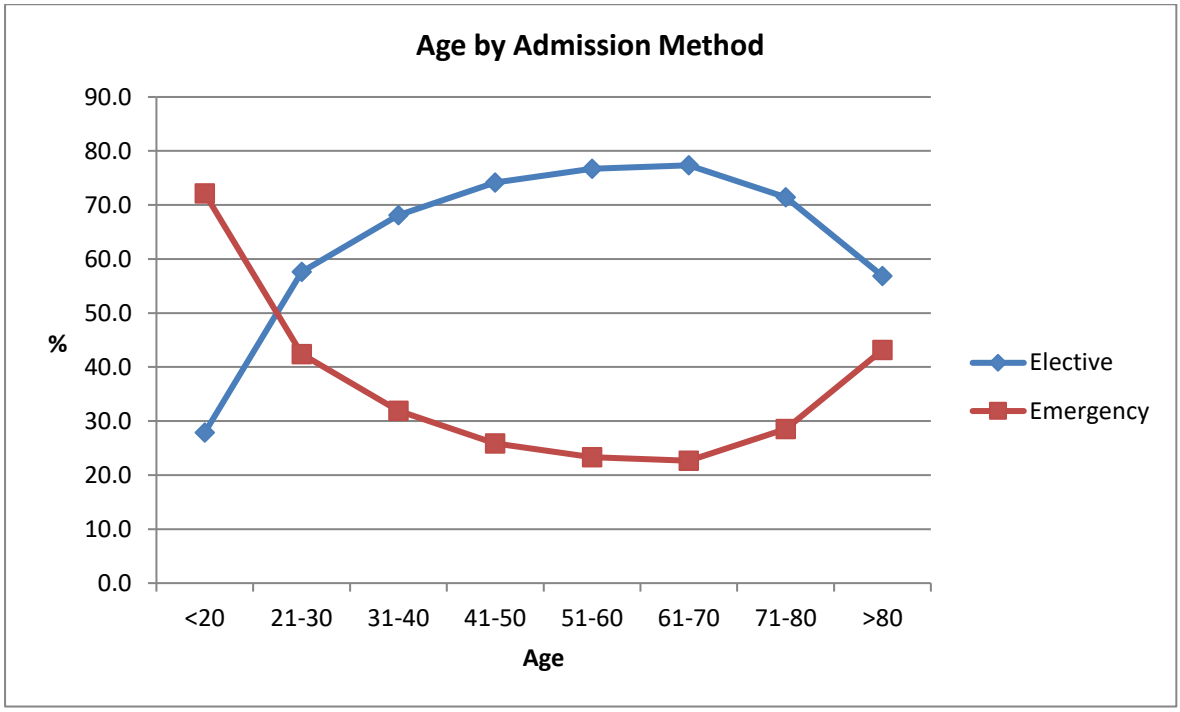
8.3.1.1. Table 2: Crude Patient Characteristics 1998-2010

Crude Patient Characteristics

		Elective Admissions		Emergency Admissions		Total
		n	%	n	%	n
Sex	Male	142,288	**73.2**	52,205	**26.8**	194,493
	Female	106,367	**66.7**	53,032	**33.3**	159,399
Age	≤60	47565	**75.1**	15,788	**24.9**	63,353
	61-70	69586	**77.3**	20,381	**22.7**	89,967
	71-80	85518	**71.5**	34,157	**28.5**	119,675
	>80	45986	**56.8**	34,911	**43.2**	80,897
Site	Colon	140,354	**62.8**	83,136	**37.2**	223,490
	Rectosigmoid	21,455	**76.1**	6,724	**23.9**	28,179
	Rectum	86,846	**85.0**	15,377	**15.0**	102,223
Dukes' Stage	A	31,973	**94.0**	2,055	**6.0**	34,028
	B	66,521	**76.1**	20,944	**23.9**	87,465
	C	63,841	**72.8**	23,902	**27.2**	87,743
	D	29,338	**55.8**	23,238	**44.2**	52,576
	Unknown	56,982	**61.9**	35,098	**38.1**	92,080
Charlson Co-Morbidity Score	0	199,855	**74.1**	69,964	**25.9**	269,819
	1	32,176	**60.4**	21,087	**39.6**	53,263
	2	10,855	**56.6**	8,337	**43.4**	19,192
	≥3	5,769	**49.7**	5,849	**50.3**	11,618
IMD Income Category	Most Affluent (1)	51,479	**74.1**	17,984	**25.9**	69,463
	2	55,415	**72.4**	21,129	**27.6**	76,544
	3	53,396	**70.5**	22,366	**29.5**	75,762
	4	48,365	**68.4**	22,372	**31.6**	70,737
	Least Affluent (5)	40,000	**65.2**	21,386	**34.8**	61,386
Year of diagnosis	1998	16,167	**67.4**	7,832	**32.6**	23,999
	1999	16,653	**67.7**	7,946	**32.3**	24,599
	2000	17,004	**67.8**	8,068	**32.2**	25,072
	2001	16,392	**67.0**	8,078	**33.0**	24,470
	2002	16,553	**67.1**	8,132	**32.9**	24,685
	2003	17,863	**68.7**	8,129	**31.3**	25,992
	2004	18,540	**68.3**	8,623	**31.7**	27,163
	2005	19,436	**69.9**	8,389	**30.1**	27,825
	2006	20,533	**71.9**	8,030	**28.1**	28,563
	2007	21,254	**73.0**	7,866	**27.0**	29,120
	2008	22,240	**73.2**	8,138	**26.8**	30,378
	2009	22,791	**73.7**	8,150	**26.3**	30,941
	2010	23,229	**74.7**	7,856	**25.3**	31,085

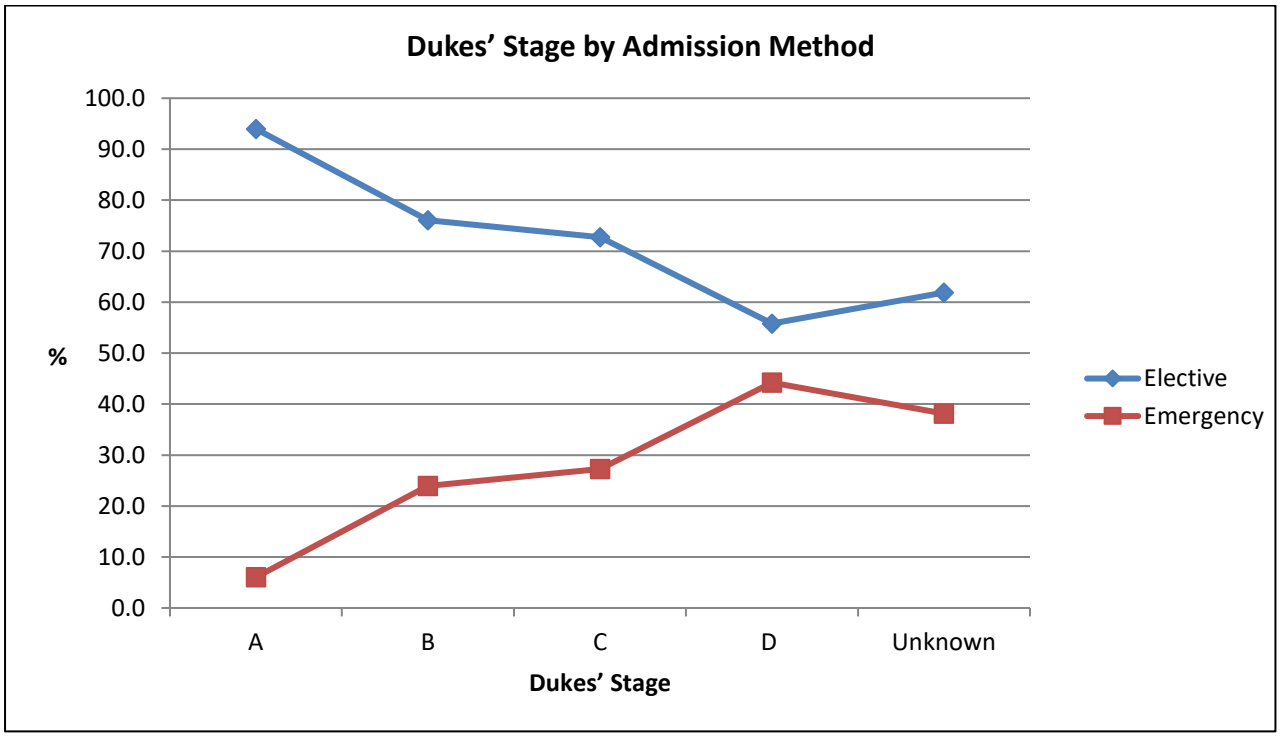
Age was associated with a higher proportion of emergency presentations at the upper and lower ends of the age spectrum, with those aged ≤20 years and >80 years both having markedly higher percentages of patients presenting as an emergency. From age 21 years onwards, elective admission steadily rose (and emergency admission fell), before 70 years of age, after which emergency admission rose and elective admission fell (Figure 11).

8.3.1.2. Figure 11: Age by Admission Method



The highest proportion of elective admissions by site of disease was in rectal cancer patients (85.0%), whilst those with colon cancer made up the greatest proportion of those presenting as an emergency (37.2%). Few patients presented as an emergency with Dukes' A disease (6.0%), whilst those with Dukes' D disease were roughly equally split between elective (55.8%) and emergency presentation (44.2%) (Figure 12).

8.3.1.3. Figure 12: Dukes' Stage by Admission Method



A higher proportion of those with a greater numbers of co-morbidities presented as an emergency (Charlson score ≥3, emergency admission 50.3%) compared to those with fewer co-morbidities (Charlson score 0, emergency admission 25.9%). Greater socioeconomic deprivation was also associated with a greater likelihood of emergency admission (25.9% of those in IMD income category 1 admitted as an emergency vs. 34.8% of those in category 5). The proportion of patients admitted as an emergency fell over the study period from 32.6% of total admissions in 1998 to 25.3% in 2010.

8.4. Impact of Screening on Emergency Admission

The majority of patients included in this study developed and were treated for their cancer before the NHSBCSP began in 2006. Table 3 however, clearly displays the impact that the NHSBCSP had on emergency presentation.

8.4.1. Table 3: Screening Status by Admission Method

Screening Status by Admission Method

	Elective		Emergency		Total
	n	%	n	%	n
Precedes BCSP start	148,921	**68.3**	69,263	**31.7**	218,184
Screen-detected	7,346	**98.0**	150	**2.0**	7,496
Interval Diagnosis	3,456	**79.2**	905	**20.8**	4,361
Non-participant	6,361	**75.4**	2,070	**24.6**	8,431
Never invited (<60)	15,905	**76.4**	4,918	**23.6**	20,823
Never invited (60-74)	27,845	**77.5**	8,090	**22.5**	35,935
Never invited (>74)	38,821	**66.2**	19,841	**33.8**	58,662
Total	248,655		105,237		353,892

Those who were invited to participate in the NHSBCSP and were found to have CRC had a very low rate of emergency admission (2%) compared with those who were invited but did not participate (24.6%). Further, the proportion of Dukes' A tumours in those who participated in screening was significantly greater compared with those who did not (Dukes' A 27.7% tumours screen detected, 10.3% non-participant, Chi^2 p= <0.001). The reverse was true for those with Dukes' D tumours (Dukes' D 6.3% tumours screen detected, 21.2% non-participant, Chi^2 p= <0.001).

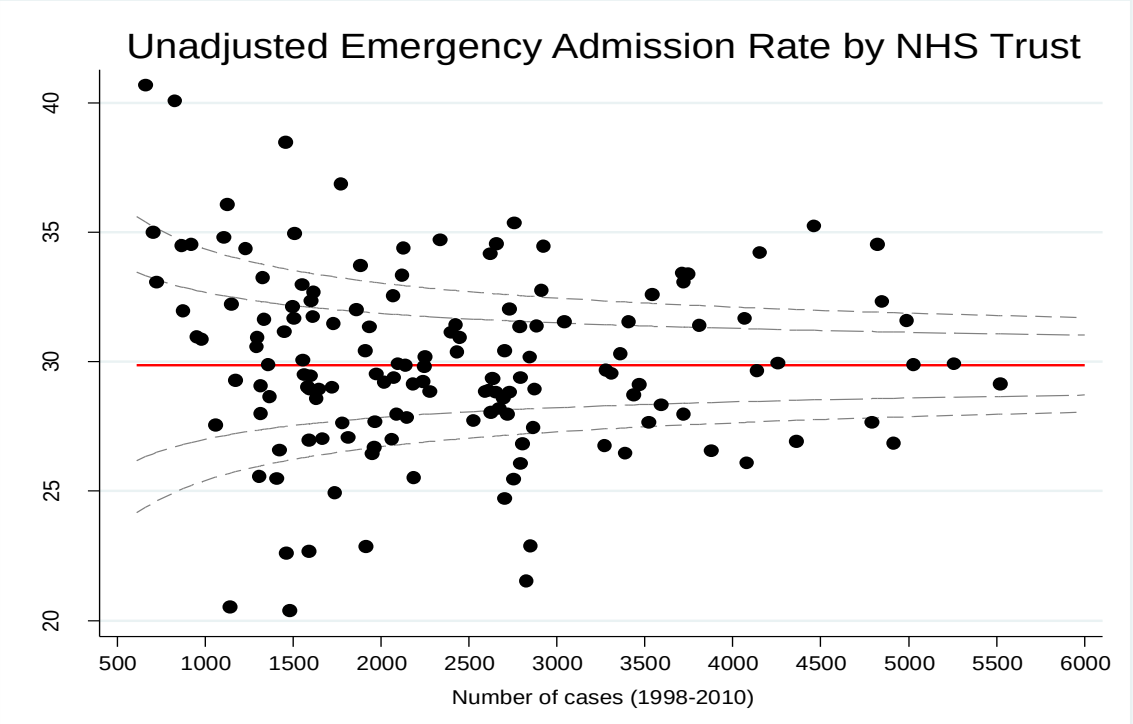
8.5. Volume of Work and Rate of Emergency Admission by NHS Trust

After exclusion of the two Trusts who undertake supra-specialist work, 147 NHS hospital Trusts were included for analysis (352,337 individuals; 247,197 (70.2%) elective admissions and 105,140 (29.8%) emergency admissions). The Trust with the greatest volume of work admitted 5,523 patients over the study period; of these 3,914 (70.9%) were elective admissions and 1,609 (29.1%) were emergency admissions. The median number of admissions for all Trusts was 2,192 (IQR 1,298). The median number of elective admissions was 1546 (IQR 959) and emergency admissions 654 (IQR 435).

In terms of crude data, the Trust with the highest proportion of elective admissions admitted 79.6% (1,196 patients) electively. In comparison, the Trust with the lowest proportion of elective admissions and therefore the highest number of emergency admissions, admitted 59.3% (391 patients) electively and 40.7% (268 patients) as an emergency (total 659 patients). This Trust was also the Trust with the lowest volume of work undertaken over the study period.

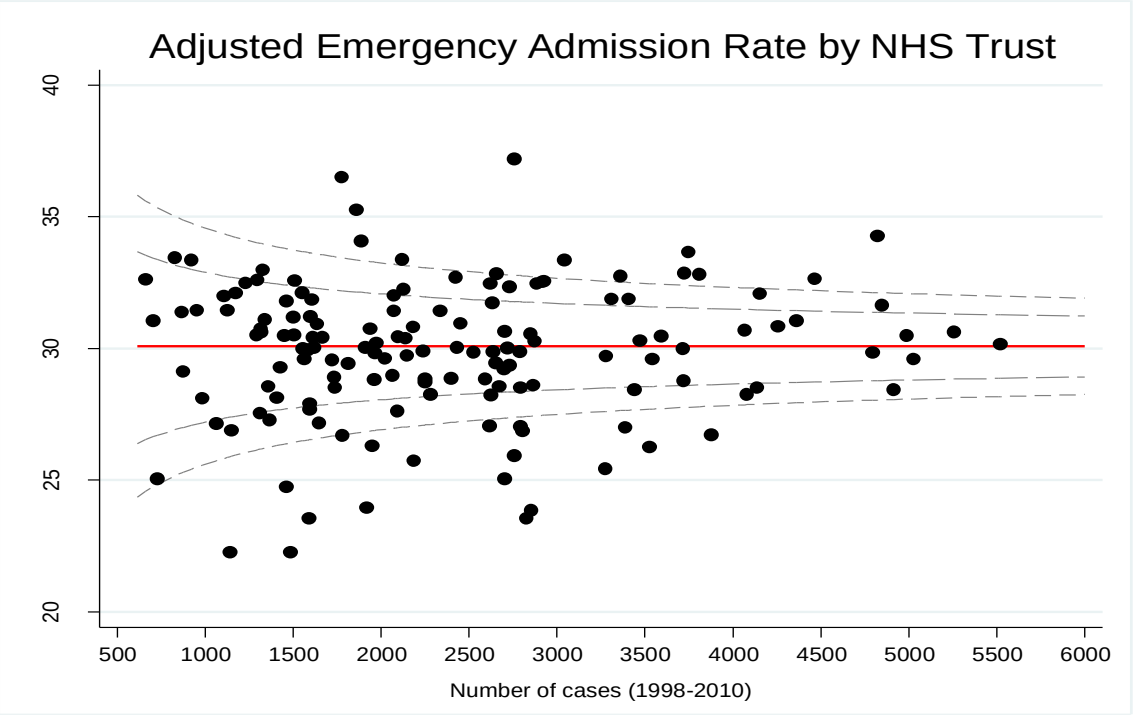
Rates of unadjusted and adjusted emergency admissions (by sex, age, stage of disease, site of disease, socioeconomic deprivation, co-morbidity and year of diagnosis) are presented in Figures 13 and 14 below.

8.5.1 Figure 13: Unadjusted Rate of Emergency Admission by NHS Trust*



*Red lines indicate overall emergency admission rate; dashed lines indicate the 95% and 99.8% control limits.

8.5.2. Figure 14: Risk Adjusted Rate of Emergency Admission by NHS Trust*



After risk adjustment, the Trust with the highest proportion of emergency admissions admitted 37.5% of patients as an emergency; this was not the same Trust as had the highest rate of emergency admissions within the crude data. The Trust with the lowest rate of admissions admitted 22.2% patients as an emergency; again this was not the same Trust as had the lowest percentage of emergency admissions within the crude data. There did not appear to be a relationship between the volume of work undertaken by an individual hospital Trust and its rate of emergency admissions.

8.6. Risk of Admission as an Emergency

Odds ratios (both unadjusted and adjusted) for emergency admission reflected the patterns seen in the crude data (see table 3). Overall, likelihood of emergency admission decreased with time (OR 0.95 (95% CI 0.95-0.96)) over the study period, whilst disease at a site other than within the colon was associated with a significantly decreased chance of emergency admission (rectosigmoid OR: 0.53 (95% CI 0.52-0.55), rectum OR: 0.31 (95% CI 0.30-0.31)). Sex and socioeconomic background were associated with comparatively small rises in likelihood of emergency admission (women OR 1.21 (95% CI 1.19-1.23), IMD Income Category 5 OR 1.43 (95% CI 1.39-1.47)). Advancing stage of disease was associated with increasing likelihood of emergency admission, with a marked increase for those with Dukes' D disease (OR 11.06 (95% CI 10.53-11.62)).

8.6.1. Table 4: Risk of Admission as an Emergency

Odds Ratio for Risk of Admission as an Emergency									
		Unadjusted				Adjusted			
		OR	p	95% CI		**OR**	p	95% CI	
Sex	Male	**1**				**1**			
	Female	1.36	<0.01	1.34	1.38	1.21	<0.01	1.19	1.23
Age	≤60	**1**				**1**			
	61-70	0.88	<0.01	0.86	0.90	0.84	<0.01	0.82	0.86
	71-80	1.20	<0.01	1.18	1.23	1.03	0.01	1.01	1.06
	>80	2.29	<0.01	2.24	2.35	1.80	<0.01	1.76	1.85
Site	Colon	**1**				**1**			
	Rectosigmoid	0.53	<0.01	0.51	0.54	0.53	<0.01	0.52	0.55
	Rectum	0.30	<0.01	0.29	0.30	0.31	<0.01	0.30	0.31
Dukes' Stage	A	**1**				**1**			
	B	4.87	<0.01	4.65	5.11	3.74	<0.01	3.56	3.92
	C	5.81	<0.01	5.54	6.09	5.02	<0.01	4.78	5.27
	D	12.34	<0.01	11.76	12.95	11.05	<0.01	10.52	11.61
	Unknown	9.72	<0.01	9.28	10.19	8.01	<0.01	7.63	8.40
Charlson Co-Morbidity Score	0	**1**				**1**			
	1	1.90	<0.01	1.86	1.94	1.67	<0.01	1.64	1.71
	2	1.32	<0.01	1.28	1.35	1.93	<0.01	1.86	1.99
	≥3	2.31	<0.01	2.24	2.39	2.51	<0.01	2.41	2.61
IMD Income Category	Most Affluent (1)	**1**				**1**			
	2	1.09	<0.01	1.06	1.11	1.06	<0.01	1.03	1.08
	3	1.20	<0.01	1.17	1.22	1.13	<0.01	1.10	1.16
	4	1.31	<0.01	1.28	1.34	1.23	<0.01	1.20	1.26
	Least Affluent (5)	1.52	<0.01	1.48	1.56	1.43	<0.01	1.39	1.47
Year of diagnosis	1998	**1**				0.95	<0.01	0.95	0.96
	1999	0.98	0.42	0.95	1.02				
	2000	0.98	0.30	0.94	1.02				
	2001	1.02	0.40	0.98	1.06				
	2002	1.01	0.55	0.97	1.05				
	2003	0.94	0.00	0.90	0.97				
	2004	0.96	0.03	0.92	0.99				
	2005	0.89	<0.01	0.86	0.92				
	2006	0.81	<0.01	0.78	0.84				
	2007	0.76	<0.01	0.73	0.79				
	2008	0.75	<0.01	0.73	0.78				
	2009	0.74	<0.01	0.71	0.76				
	2010	0.70	<0.01	0.67	0.72				

8.7. Discussion

Over the course of the study period, the number of admissions for colorectal cancer rose almost every year, whilst the proportion of those admitted as an emergency fell (from 32.6% in 1998 to 25.3% in 2010). These data show that colorectal cancer in England overwhelmingly remains a disease of the elderly, with women, those with greater numbers of co-morbidities and those from a more socioeconomically deprived background are more likely to present as an emergency and are also more likely to have advanced disease[87,88,136,141,142]. These risks remain even after adjustment for case mix.

Those who are very young (i.e. <20 years), are also much more likely to be admitted as an emergency, as demonstrated by Figure 1, rather than electively. This is understandable to a certain degree, in that colorectal cancer is a rare condition in this age group outside of certain genetic syndromes. As such, unless a patient has a family history of colorectal cancer, a general practitioner is highly unlikely to consider colorectal cancer in a patient in this age group. Younger patients (i.e. <50 years) however, by nature of their age (and presumed good quality of life with little co-morbidity) have the most to gain from early diagnosis of colorectal malignancy. There is now increasing evidence of a rising incidence of colorectal cancer amongst 'younger' patients (<50 years), with a recent review of the SEER data by Bailey et al. noting rising incidence in those aged 20-49 years of age) and a declining incidence in older age groups. Bailey et al. predict that if current trends continue, a rise in the incidence of colon cancer of 90% and rectal cancer of 124% will be seen in the age group 20-34 years by 2030, with rises of 27.7% (colon) and 46% (rectal) in those aged 35-49[143]. If these trends are repeated in the European (and therefore English) population, then strategies for the prevention and early detection of colorectal cancer in younger patients will need to be developed.

Early detection of colorectal malignancy through screening has a clear beneficial effect on likelihood of emergency admission and stage at diagnosis (Table 5.4.1), with very few emergency admissions and a higher percentage of Dukes' A tumours being identified in those who participated in the screening program, compared with those who declined. Several authors (Goodyear, Scholefield, Mayor) have reported decreased rates of emergency admission with bowel cancer screening with others (Libby et al.) also reporting a decreased length of stay and reduced short-term mortality in screen-detected patients[126,127,144,145]. Further, Libby et al. note that whilst participation in screening is negatively associated with

socioeconomic deprivation, the effect on rates of emergency admission are independent of deprivation[144].

The studies of Libby, Goodyear, Scholefield and Mayor however have tended to report the results from patient populations who have been invited to participate in a screening program (and may therefore be more motivated that the general populace to participate). Whilst screening undoubtedly brings positive results to those who participate, with cancer being diagnosed at an earlier, more treatable stage, the introduction of the NHSBCSP does not appear, when compared against population level data, to have dramatically influenced the rate of emergency admissions. There may well be a lag effect, and it may well be that we are only just beginning to see the positive impact of screening, but currently levels of participation in screening are only around 50% of those invited[146]. The most recent 'Routes to Diagnosis' work, available through the NCIN website, suggests that screen detected colorectal cancer diagnoses have increased from a negligible number in 2006 to ~10% of diagnoses in 2015[147]. The same work also notes that there has been a marked increase in diagnoses through Accident and Emergency departments (with a matching decrease through emergency GP admission) and may represent changing access to medical services by the general public[147]. Efforts must continue therefore, to increase the rate of take up of the NHSBCSP amongst the population at large, and amongst the socioeconomically deprived especially, to bring about its presumed beneficial effects.

The volume of work undertaken by an NHS Trust did not appear to relate to the number of emergency admissions for colorectal cancer a hospital Trust received. Understanding the pattern of emergency admissions is important when trying to improve outcomes in order that resources may be most effectively allocated. There is evidence that the volume of work undertaken by a surgeon and a hospital is associated with improved outcomes[148–150]. Indeed, a key facet of improvements in Danish colorectal cancer outcomes has been the centralisation of colorectal services[151,152]. That volume of work does not appear to relate to the number of emergency admissions in England implies that efforts to improve English colorectal cancer outcomes will need to be applied throughout the health service, rather than being targeted at a few high volume centres to realise the greatest benefits..

Socioeconomic deprivation and increasing co-morbidity have been shown here to have a clear deleterious impact on likelihood of emergency admission. It remains unclear as to why

socioeconomic deprivation may have this effect, particularly as socioeconomic deprivation has been shown not to deter health-seeking behaviour[153]. This may suggest that inequalities in healthcare provision in relation to colorectal cancer exist, preventing the most deprived from accessing care in a timely fashion. Increasing numbers of co-morbidities were demonstrated by Wallace et al. to increase the likelihood of emergency admission and are replicated here. In Wallace's study, they argue that lack of awareness of cancer related symptoms and health-seeking behaviour may underlie the particularly high rates seen in those with dementia[87]. It may also be possible that cancer related symptoms (loss of weight, decrease in appetite) are attributed too often in primary care to other conditions, or that minor changes in bowel habit or rectal bleeding are ignored whilst other, more immediate concerns are addressed.

Strategies to reduce rates of emergency admission for colorectal cancer will likely require a multi-faceted approach. Key will be the identification of those most at risk in primary care, with particular attention paid to the potential rising incidence of colorectal cancer in younger patients and to the elderly who may have other conditions that mask the presence of colorectal cancer. Socioeconomic deprivation should not be a barrier to accessing healthcare in the United Kingdom and this area requires further research to determine where the barriers lie. Screening almost certainly has an important role to play in reducing emergency admissions, but efforts to increase participation and the awareness of colorectal cancer symptoms must continue.

9. Short Term Outcomes of English Colorectal Cancer Treatment

9.1. Introduction

Surgical resection of the tumour, with clear excision margins, remains the main treatment modality for early colorectal cancer, and maintains an important role in more advanced disease. Longer survival in colorectal cancer is due either to earlier diagnosis, better treatment or a combination of the two. A high resolution study using the EUROCARE-II data (Gatta et al.) demonstrated wide variation in five year survival rates for colorectal cancer throughout Europe with rates of >45% in Sweden, Switzerland, France, Italy, Spain and the Netherlands, compared to <35% in Slovenia and Poland[54]. England was intermediate at 41%. This variation in survival however, was confined to the first 6 months after diagnosis, after which survival was much more homogeneous. The wide variation in survival was also mirrored by wide variation in the percentage of patients who underwent surgical resection of their tumour (>85% in Switzerland, the Netherlands and France, <60% in Poland and Estonia). The authors of the EUROCARE-II study concluded that much of the survival differences between countries were likely due to the proportion of advanced cases at diagnosis, but given the wide variation in rates of surgical resection, it is also probable that rates of surgical intervention (and subsequent short term mortality rates) may also have made a significant contribution[54].

Gatta et al.'s study used outcomes for the treatment of those diagnosed and treated for colorectal cancer in Europe between 1985 and 1989. Analyses of the treatment of more recent patients have confirmed however that the previously seen variation in European outcomes persists, with England once again achieving poor results for survival[56,57]. A large audit of two thirds of all cases of colorectal cancer treated in England between 2007 and 2008 also showed that whilst 75% of patients in England underwent some form of surgical intervention, only 60% underwent a major resection. Further, large variation existed in the proportion of patients undergoing major resection by cancer network, suggesting that either there was variability in the patients suitable for major surgical resection, or that patients were being classified as unsuitable for surgery for other reasons[154].

Variation in short term survival following major colorectal cancer resection in England was the subject of a large study by Morris et al. who use the NCDR to review the 30-day mortality of

160,920 individuals treated within the English NHS between 1998 and 2006. Whilst overall mortality fell over the study period, significant variation was seen in mortality rates between NHS hospital Trusts, even after adjustment for case-mix[63].

Thus, it would appear that England has a comparably low rate of surgical resection, with wide variation in short-term outcomes dependent upon hospital Trust. Institutional comparison is difficult, with data that is not risk-adjusted presenting obvious difficulties. The NCDR is a useful dataset for institutional comparison being a population level dataset of routinely collected data. As such, it is not subject to the biases that may occur with datasets that are contributed to voluntarily. The data stored within the NCDR is also of good quality and reasonable completeness, allowing for trends in outcome to be seen. This section aims to build on the work of Morris et al. to assess patient characteristics associated with poor short term outcomes and to present risk-adjusted funnel plots to display variation in institutional performance.

9.2. Methodology and Statistical Modelling

Patients diagnosed with colorectal cancer between 1st January 1998 and 31st December 2010 were identified from the NCDR database. Each patient was assessed for whether they underwent a major surgical resection, minor surgical resection (e.g. endomucosal resection), bypass, stoma formation, stent or no surgical intervention. 30 and 90-day mortality rates were then calculated for each group of patients depending upon their intervention, with the exception of those who did not undergo any form of surgical intervention, for whom no mortality information was available. Each group of patients was assessed for their short-term (30 and 90-day) mortality depending upon their index admission status (elective or emergency), age (at diagnosis), year of diagnosis, site of disease, Dukes' stage, Charlson co-morbidity score and level of socioeconomic deprivation (IMD income category).

For those who underwent major surgical resection, unadjusted and adjusted odds ratios for likelihood of early mortality by admission status were calculated for each variable. Again, two hospitals Trusts were excluded from both the univariate and logistic regression analyses due to their provision of supra-specialist services. Statistical analyses were undertaken in Stata™ Version 13.1 as before, with institutional comparison again being performed using the *funnelcompar* command to compare institutional short-term mortality rates with volume of admissions. Statistical significance was set at $p \leq 0.05$.

9.3. Results

9.3.1. Crude Mortality Figures

275,325 patients were identified who underwent major resection, minor resection, bypass, stoma formation or stent insertion. 78, 567 (28.5%) patients did not undergo any form of surgical intervention (and were excluded). Overall mortality for all patients (whether they underwent resection or not) was 6.9% at 30-days and 10.9% at 90-days. Mortality by mode of admission and resection status is displayed in Table 5.

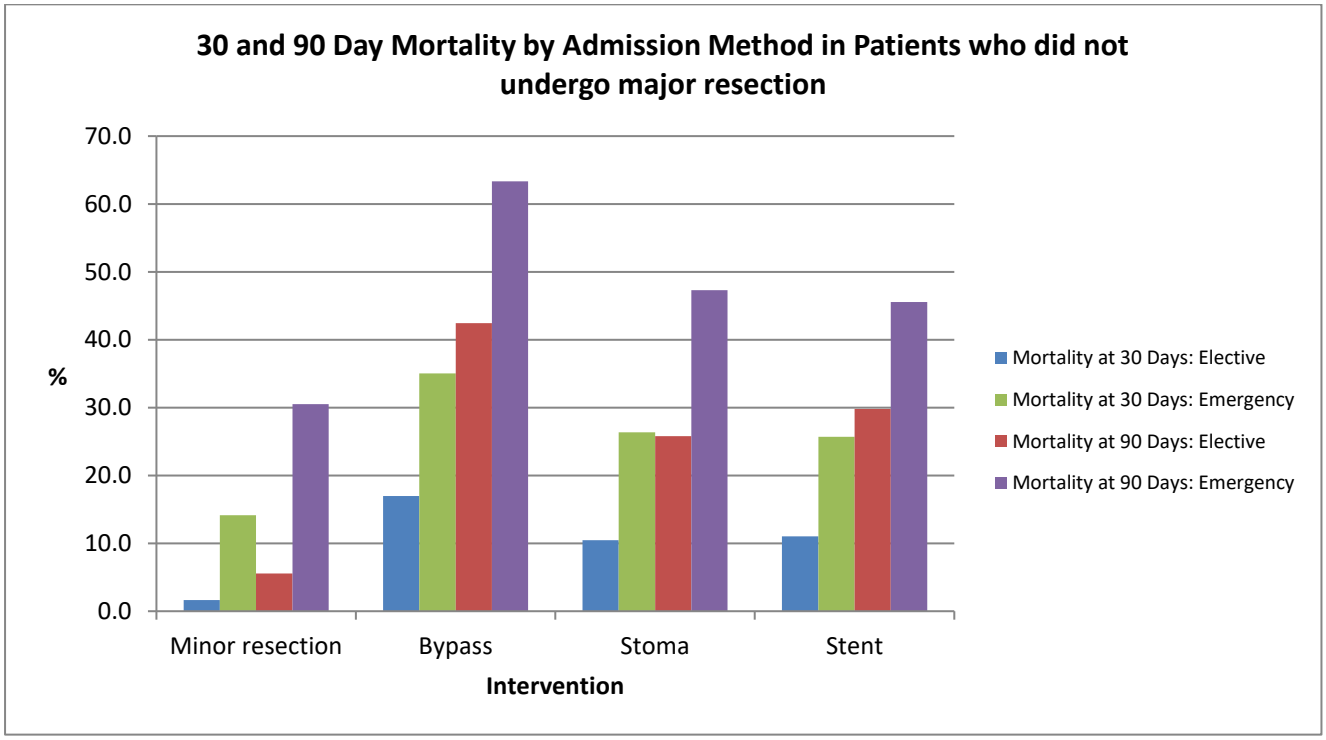
9.3.1.1. Table 5: 30 and 90-day Mortality by Mode of Admission and Resection Status

Resection Status	30-Day Mortality					90-Day Mortality				
	All Patients					All Patients				
	Alive		Dead		Total	Alive		Dead		Total
	n	%	n	%		n	%	n	%	
No Major Resection	28187	88.4	3713	11.6	31900	24164	75.7	7736	24.3	31900
Major Resection	228109	93.7	15316	6.3	243425	221144	90.8	22281	9.2	243425
	Elective Admission					Elective Admission				
	Alive		Dead			Alive		Dead		
	n	%	n	%		n	%	n	%	
No Major Resection	20362	94.9	1103	5.1	21465	18498	86.2	2967	13.8	21465
Major Resection	179211	96.4	6732	3.6	185943	175575	94.4	10368	5.6	185943
	Emergency Admission					Emergency Admission				
	Alive		Dead			Alive		Dead		
	n	%	n	%		n	%	n	%	
No Major Resection	7825	75	2610	25	10435	5666	54.3	4769	45.7	10435
Major Resection	48898	85.1	8584	14.9	57482	45569	79.3	11913	20.7	57482

Mortality in those who underwent minor resection of their tumour at 30-days was 3.1% for all patients, 1.6% in those admitted electively and 14.1% in those admitted as an emergency. 30-day mortality for all those who underwent bypass was 27.8%, stoma formation 18.7% and

stent insertion 18.3%. 90-day mortality was 8.4% for minor resection, 55.0% for bypass, 37.0% for stoma formation and 37.6% for stent insertion. Mortality for those undergoing minor resection only was 1.6% when admitted electively at 30-days compared to 14.1% when admitted as an emergency. A similar trend was seen for all other procedures.

9.3.1.2. Figure 15: 30 and 90 days Mortality in those not undergoing major resection



30-day mortality for all patients who underwent a procedure fell from 8.1% in 1998 to 4.5% in 2010 (90-day mortality: 12.5% 1998, 7.7% 2010) and for those who underwent a major resection from 7.5% in 1998 to 3.9% in 2010 (90-day mortality: 11.0% 1998, 5.9% 2010).

Mortality by patient characteristic showed significantly increased mortality in men at 30 and 90 days in the elective setting (Chi^2 $p<0.0001$) and initially in the emergency setting (Chi^2 $p<0.001$) but this was lost by 90 days (Chi^2 $p=0.65$). There was no difference in mortality by site of disease in the elective setting Chi^2 $p=10.9$) but in the emergency setting, those with rectal cancer did significantly worse (Chi^2 $p<0.0001$) (Table 6).

9.3.1.3. Table 6: Mortality by Patient Characteristic and Admission Status

Mortality by Patient Characteristic and Admission Status

		Elective		Emergency	
		30-Day Mortality	90-Day Mortality	30-Day Mortality	90-Day Mortality
		%	%	%	%
Sex	Male	4.1	6.2	14.9	20.6
	Female	2.9	4.7	13.4	20.8
Age	≤60	0.9	1.8	4.2	7.7
	61-70	2.0	3.5	9.8	14.7
	71-80	4.6	6.8	16.2	22.5
	>80	8.3	11.9	26.1	33.8
Site	Colon	3.7	5.8	14.6	20.4
	Rectosigmoid	3.3	5.3	15.9	21.5
	Rectum	3.5	5.3	18.4	24.6
Dukes' Stage	A	2.8	3.9	10.5	13.8
	B	3.4	4.8	13.1	16.5
	C	3.4	5.4	13.5	19.0
	D	4.1	9.5	14.6	26.1
	Unknown	5.5	7.9	26.1	33.2
Charlson Co-Morbidity Score	0	2.9	4.6	11.2	16.5
	1	5.9	8.3	20.2	26.7
	2	7.6	11.0	26.8	34.7
	≥3	12.5	17.3	37.7	45.3
IMD Income Category	Most Affluent (1)	3.0	4.8	12.9	18.9
	2	3.4	5.2	13.7	19.2
	3	3.7	5.6	15.3	21.1
	4	3.9	6.0	16.2	21.9
	Least Affluent (5)	4.3	6.6	16.4	22.4

9.4. Risk of Death at 30 and 90 days

Odds ratios for risk of death at both 30 and 90 days were similar to the results of the crude data. Women were less likely to die in the elective setting at both 30 and 90 days but there was no difference in risk of death by sex if admitted as an emergency (Tables 7 and 8).

9.4.1. Table 7: Risk of Mortality at 30 days by Admission Status

Adjusted Odds Ratios for Mortality at 30 days

		Elective Admission				Emergency Admission			
		OR	p	95% CI		**OR**	p	95% CI	
Sex	Male	**1**				**1**			
	Female	0.65	<0.01	0.62	0.69	0.97	0.20	0.92	1.02
Age	≤60	**1**				**1**			
	61-70	2.22	<0.01	1.96	2.52	2.38	<0.01	2.12	2.66
	71-80	5.14	<0.01	4.57	5.78	3.99	<0.01	3.59	4.42
	>80	10.50	<0.01	9.31	11.83	7.49	<0.01	6.75	8.31
Site	Colon	**1**				**1**			
	Rectosigmoid	0.99	0.91	0.91	1.09	1.12	0.034	1.01	1.25
	Rectum	1.13	<0.01	1.07	1.19	1.29	<0.01	1.17	1.42
Dukes' Stage	A	**1**				**1**			
	B	1.08	0.072	0.99	1.18	1.36	0.001	1.14	1.63
	C	1.23	<0.01	1.13	1.34	1.56	<0.01	1.31	1.87
	D	1.76	<0.01	1.57	1.98	2.13	<0.01	1.77	2.56
	Unknown	1.96	<0.01	1.78	2.16	3.66	<0.01	3.04	4.40
Charlson Co-Morbidity Score	0	**1**				**1**			
	1	1.87	<0.01	1.75	1.99	1.80	<0.01	1.70	1.91
	2	2.39	<0.01	2.18	2.63	2.49	<0.01	2.29	2.70
	≥3	3.97	<0.01	3.57	4.43	4.25	<0.01	3.86	4.68
IMD Income Category	Most Affluent (1)	**1**				**1**			
	2	1.11	0.009	1.03	1.21	1.03	0.521	0.95	1.12
	3	1.15	0.001	1.06	1.25	1.14	0.001	1.05	1.24
	4	1.21	<0.01	1.12	1.32	1.22	<0.01	1.13	1.32
	Least Affluent (5)	1.34	<0.01	1.23	1.46	1.30	<0.01	1.19	1.41
Year of diagnosis		0.95	<0.01	0.94	0.95	0.98	<0.01	0.97	0.98

9.4.2. Table 8: Risk of Mortality at 90 days by Admission Status

Adjusted Odds Ratios for Mortality at 90 days

		Elective Admission				Emergency Admission			
		OR	p	95% CI		**OR**	p	95% CI	
Sex	Male	**1**				**1**			
	Female	0.70	<0.01	0.67	0.73	0.97	0.164	0.93	1.01
Age	≤60	**1**				**1**			
	61-70	1.95	<0.01	1.79	2.14	2.03	<0.01	1.86	2.22
	71-80	3.93	<0.01	3.61	4.27	3.34	<0.01	3.08	3.63
	>80	7.95	<0.01	7.28	8.67	6.25	<0.01	5.75	6.78
Site	Colon	**1**				**1**			
	Rectosigmoid	1.00	0.91	0.93	1.08	1.07	0.186	0.97	1.17
	Rectum	1.11	<0.01	1.06	1.16	1.25	<0.01	1.15	1.36
Dukes' Stage	A	**1**				**1**			
	B	1.12	0.003	1.04	1.20	1.31	0.001	1.12	1.54
	C	1.43	<0.01	1.33	1.54	1.73	<0.01	1.48	2.03
	D	3.12	<0.01	2.86	3.41	3.35	<0.01	2.85	3.95
	Unknown	2.08	<0.01	1.92	2.26	3.79	<0.01	3.21	4.47
Charlson Co-Morbidity Score	0	**1**				**1**			
	1	1.70	<0.01	1.61	1.79	1.70	<0.01	1.61	1.79
	2	2.28	<0.01	2.11	2.47	2.40	<0.01	2.22	2.59
	≥3	3.75	<0.01	3.41	4.12	3.89	<0.01	3.55	4.27
IMD Income Category	Most Affluent (1)	**1**				**1**			
	2	1.06	0.083	0.99	1.13	0.98	0.554	0.91	1.05
	3	1.12	0.001	1.05	1.19	1.09	0.022	1.01	1.17
	4	1.18	<0.01	1.10	1.26	1.14	<0.01	1.06	1.23
	Least Affluent (5)	1.31	<0.01	1.22	1.41	1.22	<0.01	1.13	1.32
Year of diagnosis		0.94	<0.01	0.94	0.95	0.97	<0.01	0.97	0.98

The elderly, those with advanced disease, those with greater co-morbidity and those from a socioeconomically deprived background were all more likely to die at both 30 and 90 days. Patients with rectal cancer had a higher risk of mortality in both the elective and emergency settings at both 30 and 90 days. Those with cancer of the rectosigmoid junction had a slightly higher risk of death in the emergency setting at 30 days (OR 1.12, p= 0.034, 95%CI 1.01-1.25) compared to those with colon cancer, but otherwise, there was no difference in risk of short-term mortality between those with colon cancer and cancer of the rectosigmoid junction.

9.5. Mortality by Hospital Trust

Crude rates of mortality by hospital Trust ranged from 1.4- 7.2% in the elective setting at 30 days (median 3.6%) to 6.7- 28.5% in the emergency setting (median 15.1%), again at 30 days. 90 days mortality rates ranged from 2.9- 9.6% (elective, median 5.6%) and 10.2- 35.2% (emergency, median 20.9%).

9.5.1. Table 9: Highest and Lowest Crude Rates of Mortality by Hospital Trust

Crude Mortality Figures by Hospital Trust

Trust	30 Day Mortality									
	Elective Admission					Emergency Admission				
	Alive		Dead		Total	Alive		Dead		Total
	n	%	n	%		n	%	n	%	
Lowest Mortality	783	98.6	11	1.4	794	194	93.3	14	6.7	208
Highest Mortality	415	92.8	32	7.2	447	191	71.5	76	28.5	267

Trust	90 Day Mortality									
	Elective Admission					Emergency Admission				
	Alive		Dead		Total	Alive		Dead		Total
	n	%	n	%		n	%	n	%	
Lowest Mortality	705	97.1	21	2.9	726	141	89.8	16	10.2	157
Highest Mortality	320	90.4	34	9.6	354	173	64.8	94	35.2	267

A total of 22 Trusts were above the 95% control limit for mortality at 30 days and 25 at 90 days for those admitted electively (Table 10, Figures 16 and 18), compared with 18 Trusts above the 95% control limit at 30 days and 17 at 90 days for emergency admissions. Trusts below the 95% control limit for both 30 and 90 days are set out in Table 11. Frequently, Trusts either above or below the 95% control limit at 30 days were also above or below the limit at 90 days.

9.5.2. Table 10: Numbers of Trusts above or below 95% and 99.8% Control Limits

Numbers of Trusts above or below Control Limits

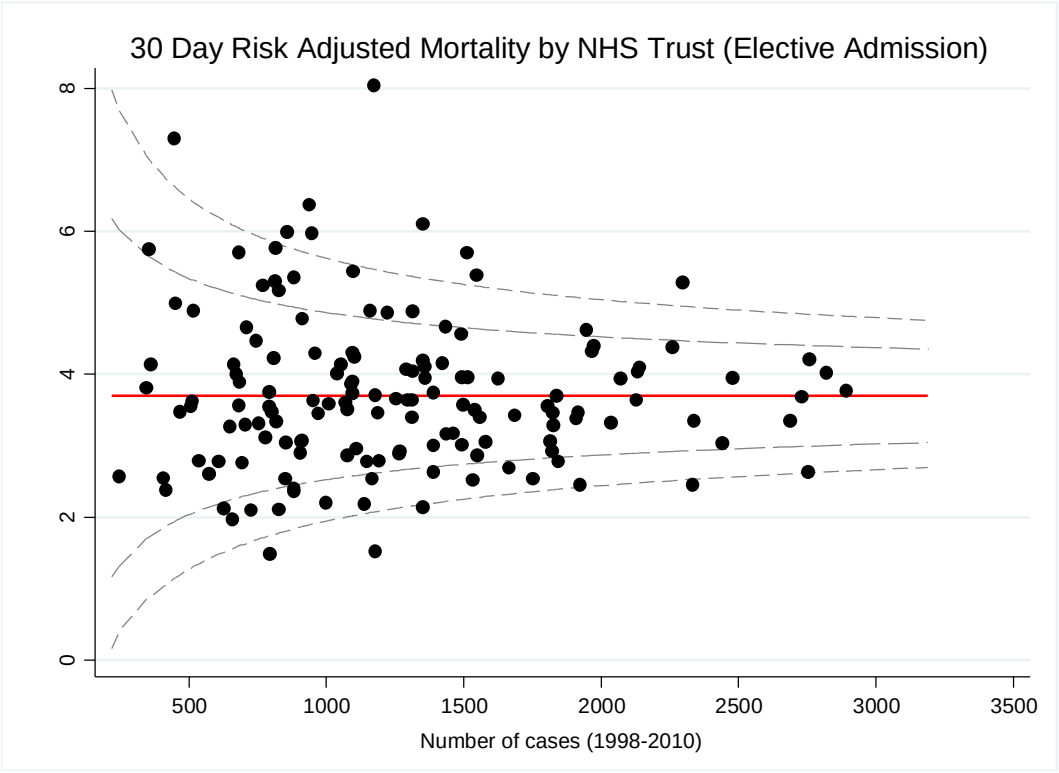
Mortality	Above Control Limit				Below Control Limit			
	Elective Admission		Emergency Admission		Elective Admission		Emergency Admission	
	95%	99.8%	95%	99.8%	95%	99.8%	95%	99.8%
30 Days	13	9	15	3	16	4	15	4
90 Days	17	8	11	6	14	4	8	5

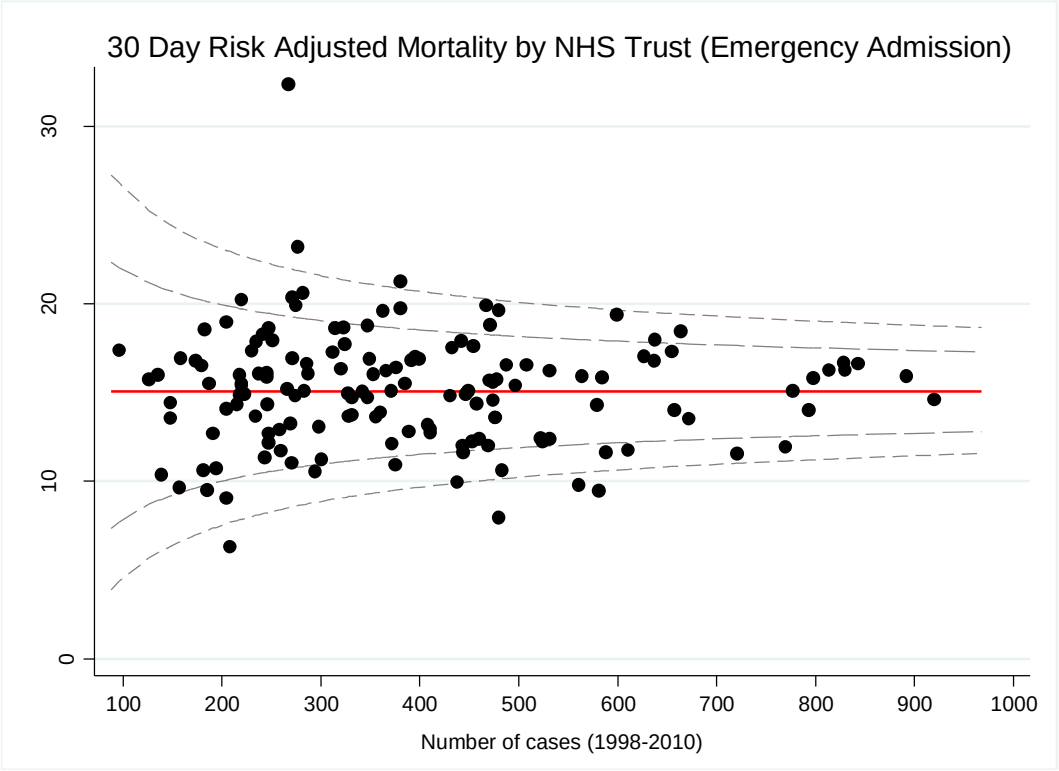
9.5.3. Table 11: Numbers of Trusts above or below 95% Control Limits at both 30 and 90 days

Numbers of Trusts above or below Control Limits at both 30 and 90 days

Control Limit	Elective Admission		Emergency Admission	
	95%	99.8%	95%	99.8%
Above	6	6	5	1
Below	8	3	4	4

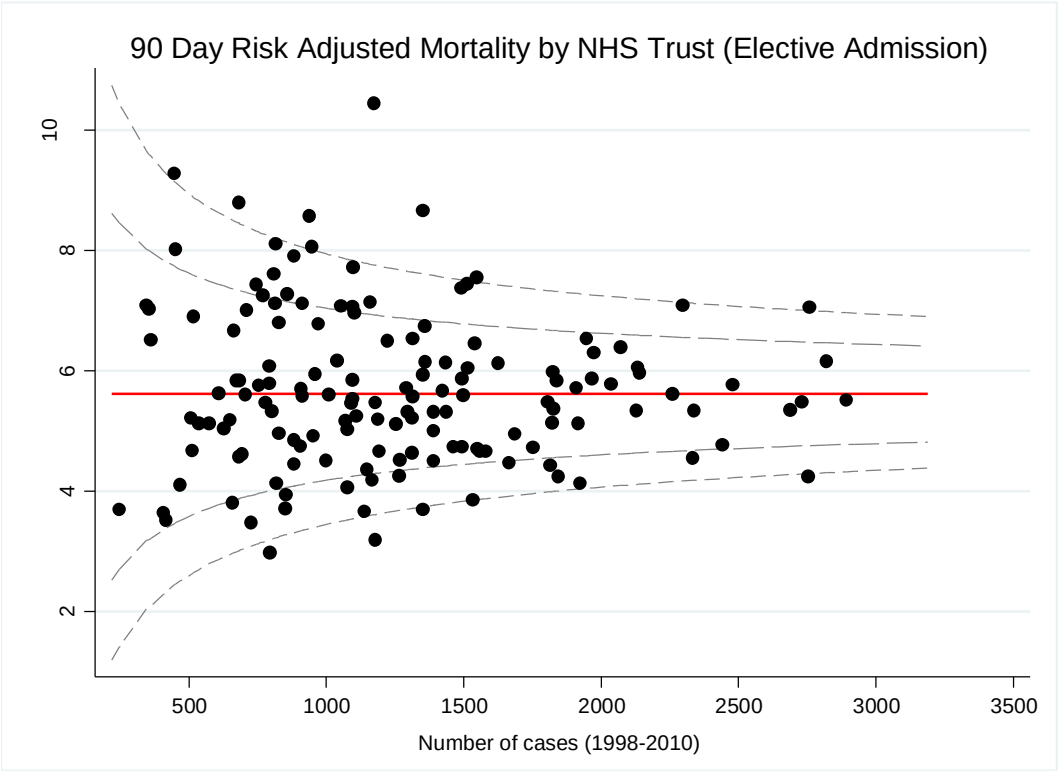
9.5.4. Figures 16 and 17: 30-Day Risk Adjusted Mortality by Hospital Trust and Admission Method*

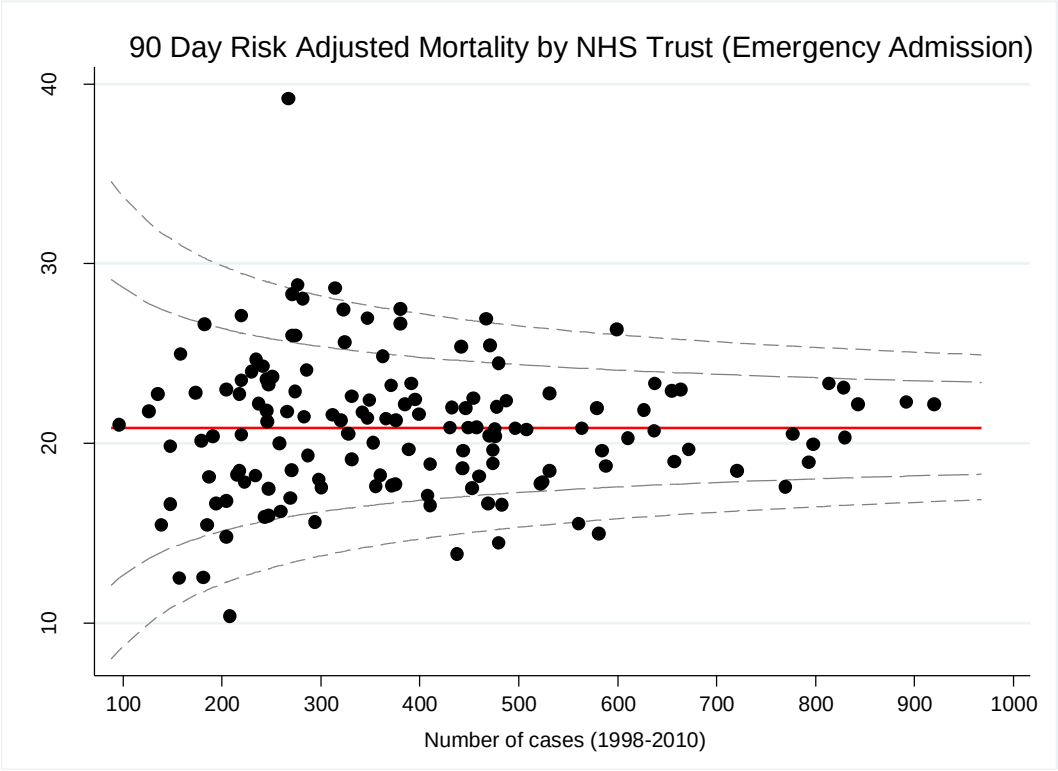




*Red lines indicate overall mortality rate; dashed lines indicate the 95% and 99.8% control limits

9.5.5. Figures 18 and 19: 90 Day Risk Adjusted Mortality by Hospital Trust and Admission Method*





*Red lines indicate mortality admission rate; dashed lines indicate the 95% and 99.8% control limits

Figures 14-17 would appear to show one Trust whose mortality rate was markedly higher for both elective and emergency admissions at 30 and 90 days. This was the same Trust in relation to emergency admissions, but different Trusts for elective admissions.

9.6. Discussion

The overall mortality rate recorded for the duration of the study period of 6.9% at 30 days is broadly in line with other authors[63,129]. The fall in overall mortality from 7.5% in 1998 to 3.9% in 2010, may suggest that recent efforts to reduce mortality from colorectal cancer are beginning to have an impact. What must be borne in mind however, is that although rates for the treatment of colorectal cancer in England have improved over the study period, so have the rates in other countries. As such, the disparity in English colorectal cancer outcomes remains, albeit at a lower level of mortality (e.g. EUROCARE V, 5-year survival from colon cancer, European average 57.0%, England 51.8%). It would appear that England still has a comparatively low rate of patients undergoing major resection (68.8% of all patients) compared with other parts of Europe, although this may be an unfair comparison once those who are unfit for any form of surgical intervention are removed; over 88% of those suitable for intervention received a major resection.

The high mortality rates seen in those who did not undergo major resection are unsurprising (with the exception of the very low mortality rates in those undergoing elective minor resection, who are likely to have had early stage disease, suitable for endoscopic removal or, in recent years innovations such as trans-anal endoscopic microsurgery). What is striking from these data is that those who undergo a bypass procedure seem to fair much worse than those undergoing stoma formation or stent insertion. However these patients are likely to have been those with advanced disease, in which bypass was a procedure of last resort; hence it is unsurprising they had such poor results.

The observations that absolute numbers of deaths and risk of death are highest in the elderly, those with advanced disease and greater co-morbidity is not new, nor is the clear demonstration from these data that emergency presentation is a negative predictor of outcome in almost every case. The persistence of the large disparities in outcome between these groups however suggests that there has only been limited success in improving outcomes for this group of vulnerable patients. Given that it is well recognised that England has a high proportion of elderly patients, with high numbers of co-morbidities presenting as

emergencies, earlier identification of these patients, with clear strategies for their management, should they present in an unplanned manner, would seem a priority.

The rising risk of short-term mortality associated with increased socioeconomic deprivation would suggest that there is inequality of access to treatment throughout England. The previous finding within this study and in many others, that socioeconomic deprivation is a risk factor for emergency presentation reinforces this argument[88,132,133,155].

The large amount of variability in outcomes between hospital Trusts reinforces the findings of the studies by Morris et al and Warwick et al[63,101]. Whilst these figures are not suitable for direct institutional comparison, as no effort has been made to account for missing data and the impact this may have on an individual Trust's performance, these figures demonstrate how outcomes vary across England. Local factors, such as the population a Trust serves will certainly have played a part in the variability of outcomes but this does not adequately explain such broad differences (particularly as those Trusts who performed poorly electively, also tended to perform poorly in the emergency setting). It is likely that high performing Trusts have policies and procedures in place for the management of both elective and emergency colorectal cancer patients where dissemination would be of benefit to many other Trusts.

Examples of such policies or procedures however tend to be restricted to the local level however. Whilst there are national guidelines for the management of the colorectal cancer patient (e.g. NICE/ ACPGBI), there appears to be an opportunity for successful local management strategies to be brought together for others to view before adapting them to local needs. The English NHS expends much effort trying to ensure consistency of quality and outcomes through organisations such as NHS Improvement or the Care Quality Commission but a forum for the easy dissemination of innovative practice is lacking.

Short-term mortality from colorectal cancer appears to be falling throughout England, but it does not appear to be falling at a rate faster than our European neighbours and therefore disparities in outcomes remain. There appears to be persistent wide variation in outcomes, both in the elective and emergency settings and an opportunity for the dissemination of good practice exists. Discrepancy in outcomes will always exist for a multitude of reasons, but until a greater degree of consistency of outcome exists between hospital Trusts, particularly for

those at highest risk, then English colorectal cancer outcomes will fail to improve. Efforts should therefore be focused on earlier diagnosis, especially amongst the elderly and the socioeconomically deprived, with measures put in place to pass on successful management strategies. It is likely that, as large, contemporary databases such as NBOCAP gather more information, this will become progressively easier to achieve.

10. The Changing Face of English Colorectal Cancer 1998-2010

10.1. Introduction

Colorectal cancer in high incidence countries (e.g. Australia, Denmark, Norway), has remained at a steady incidence since a peak in the mid-1980s, but continues to rise rapidly in some traditionally low risk areas such as Japan, Korea and China[45,156,157]. The incidence of CRC in England has recently begun to slowly rise again, in part as a consequence of the ageing English population but also due to a rise in age-specific incidence, especially among men aged between 65 and 84. This rise in age-specific incidence is accompanied by marked variation in regional incidence rates across England, suggesting that lifestyle and environmental factors may also be contributing to this variation[158].

Nevertheless, over the time period covered by this study, alongside changes in colorectal cancer incidence in England, there were notable changes in approach to the management of cancer throughout the United Kingdom and a variety of innovative treatment options specifically for those with colorectal cancer. 1998-2010 covers the period where poor English cancer outcomes were truly recognised and efforts made to improve these (Calman-Hine Report, NHS Cancer Plan, Improving Outcomes: A Cancer Strategy). The introduction of the NHS Bowel Cancer Screening Program (NHSBCSP) occurred and keyhole (laparoscopic surgery) was introduced, as were endoluminal stents (although these will be discussed in a later section).

Thus, the routes that colorectal cancer patients took to achieve admission for their disease will have changed over the study period, patients will have increasingly been treated by colorectal specialists, rather than by generalists with specialist support and laparoscopic surgery will have impacted on patient's lengths of stay.

This chapter therefore aims to demonstrate how, through use of population level data, colorectal cancer admissions changed between 1998-2010, how mortality changed and the impact that innovations such as laparoscopic surgery and the NHSBCSP had on that mortality and how the on-going drive to improve the quality of colorectal services offered to patients impacted on lengths of stay.

10.2. Methodology and Statistical Modelling

Data on all individuals aged 14 and over diagnosed with colorectal cancer (ICD10 C18-20) was extracted from the NCDR for the period January 1st 1998 to December 31st 2010.

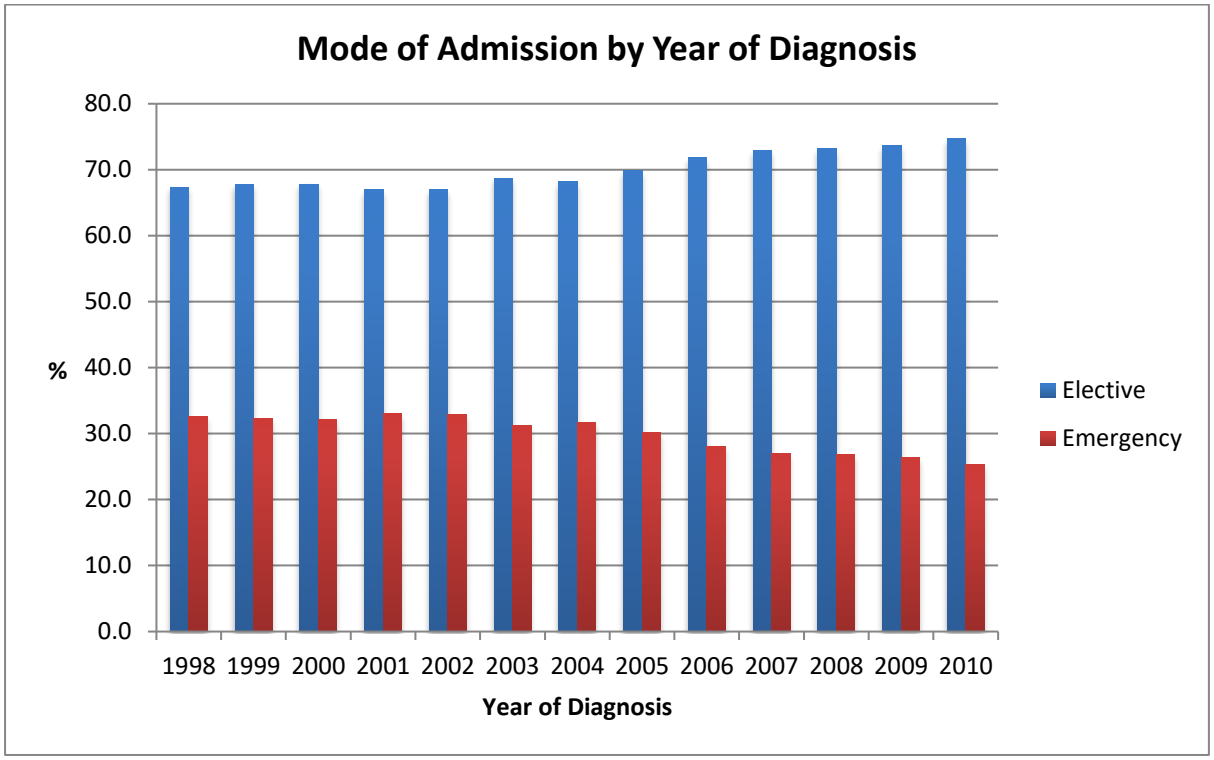
Information on age, sex, patient management and date of death was retrieved. Trends over time were compared by dividing the population into four time periods (1998-2001, 2002-20044, 2005-2007, 2008-10) dependent upon time at. Mode of admission for each individual was noted (elective/ emergency) along with site of disease, Dukes' stage, Charlson co-morbidity score and level of socioeconomic deprivation (IMD income category). Length of stay was recorded, type of procedure (laparoscopic or open) and 30-day and 90-day mortality noted. Where appropriate, logistic regression was used to calculate risk of death, with adjustment being made for sex, age, stage of disease, Charlson co-morbidity score and IMD Income Category. Statistical differences were evaluated using Chi^2. Again all analyses were conducted using Stata Version 13.1 with statistical significance set at $p<0.05$.

10.3. Results

10.3.1. Admission Status

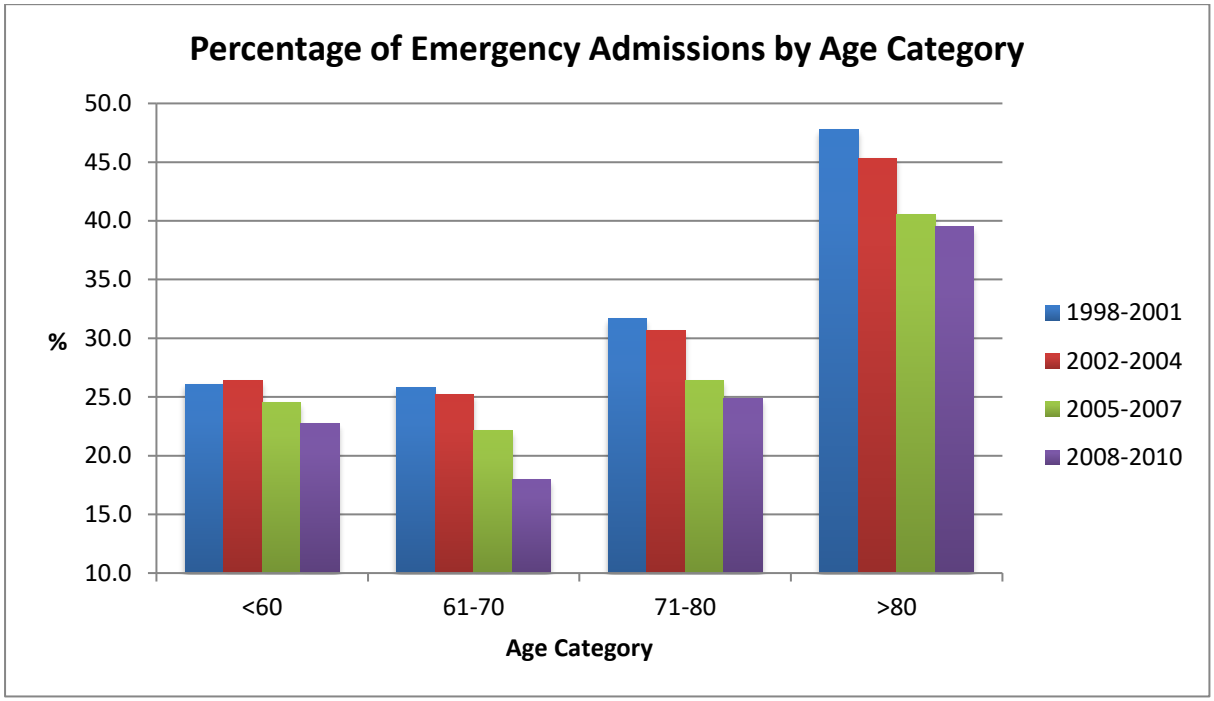
Over the study period, 353 892 patients were admitted with colorectal cancer, of which emergencies made up 32.6% of admissions in 1998. There was a steady, almost year-on-year rise in the number of admissions for CRC from 23,999 in 1999 to 31,085 in 2010. By 2010, the percentage of emergency admissions had decreased to 25.3% (Figure 20). When subdivided by site of disease, colon cancer patients persistently had the greatest proportion of emergency admissions in each time period, followed by those with rectosigmoid cancer, then rectal cancer.

10.3.1.1. Figure 20: Mode of Admission by Year of Diagnosis



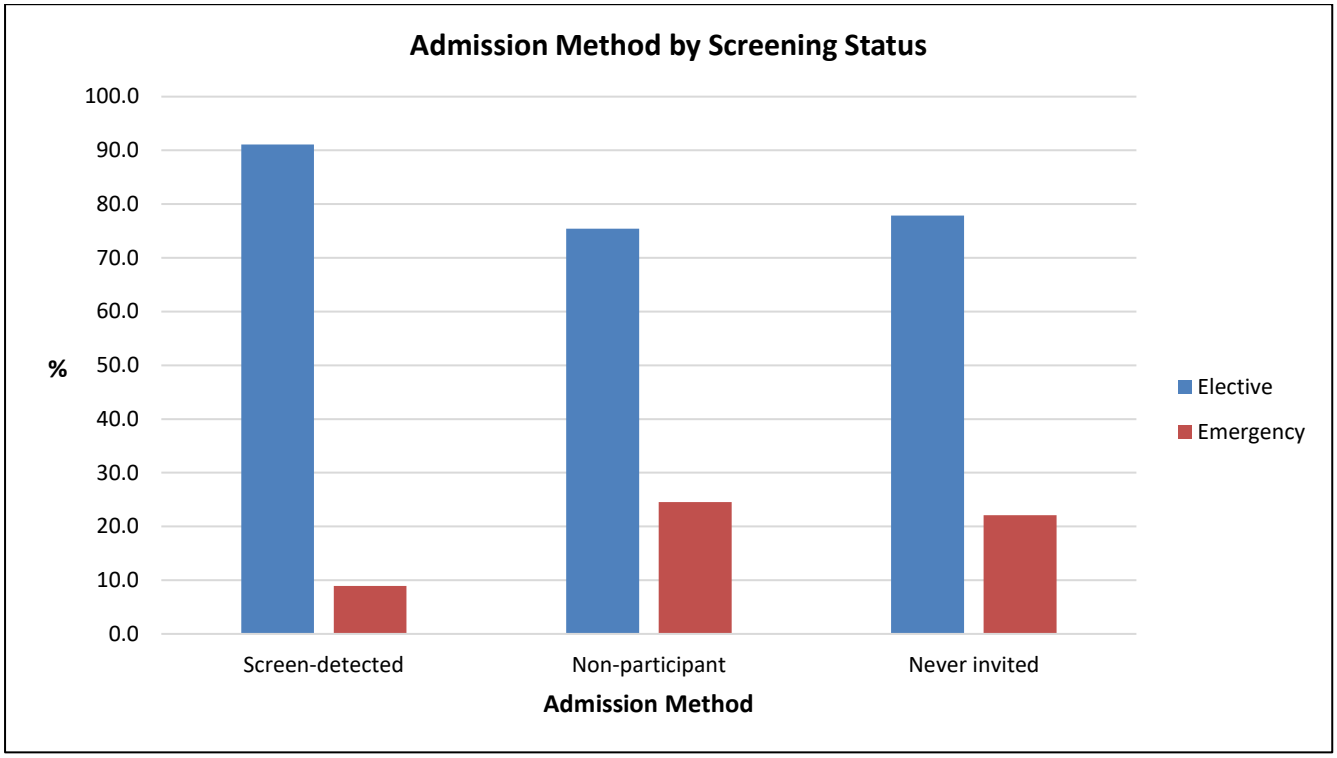
Those aged >80 comprised the greatest proportion of emergency admissions, however this age group also saw the greatest drop in emergency admissions as a percentage of total admissions in this age category over the study period (Figure 21)

10.3.1.2. Figure 21: Percentage of Emergency Admissions by Age Category

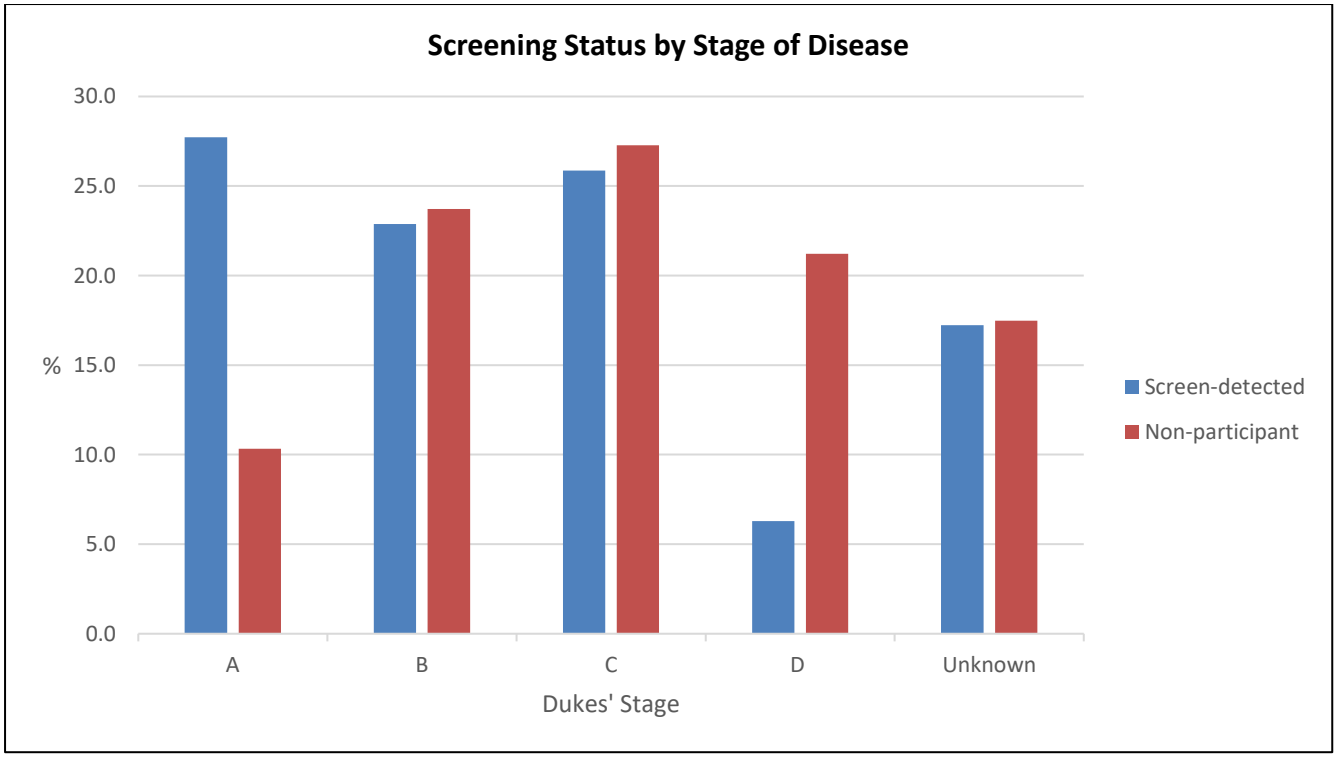


The year 2006 saw the introduction of the NHS Bowel Cancer Screening Program using faecal occult blood testing (FOBT). Those who engaged with the screening program had a markedly better rate of elective admission compared with those who did not (Figure 22). This rate of elective admission continued to be better (compared with those who had not engaged in screening) when those who had engaged but were diagnosed with their cancer in-between tests (i.e. an interval diagnosis) were removed. Those with an interval diagnosis had an elective/ emergency admission rate much closer to those who did not engage in the program at all (Screen diagnosis 98.0% elective admission, 2.0% emergency admission; Interval diagnosis 79.2% elective admission, 20.8% emergency admission). Those who engaged with the screening program also had a much higher rate of early stage disease than those who chose not to participate (Figure 23).

10.3.1.4. Figure 22: Admission Status by Screening Method



10.3.1.5. Figure 23: Screening Status by Stage of Disease



Despite the improvements in emergency admission rates over the study period, the actual percentage of patients who underwent major resection of their cancer decreased over the study period from 72.8% (1998-2001) to 66.6% (2008-2010) (Chi^2 $p<0.001$). The percentage

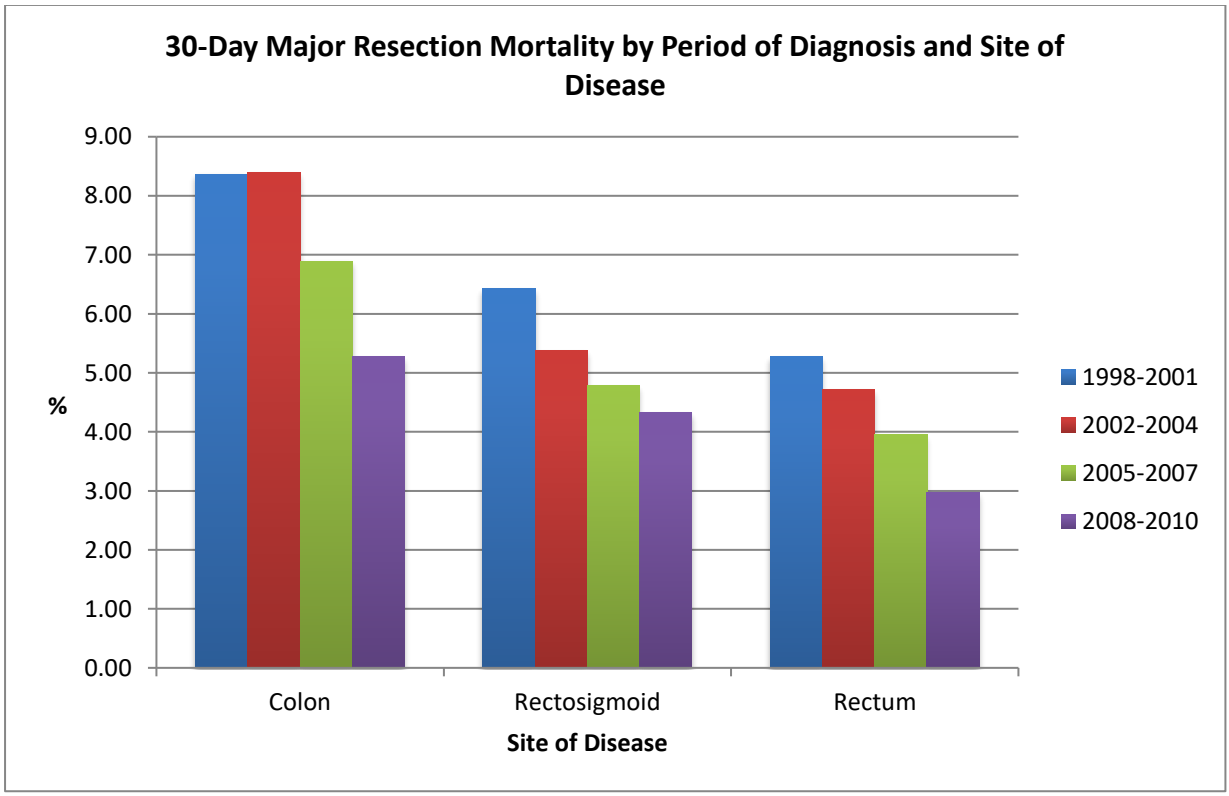
of those who underwent no surgical procedure rose from 19.4% (1998-2001) to 22.6% (2008-2010) (Chi^2 p<0.001).

10.3.2. Mortality at 30 and 90 days

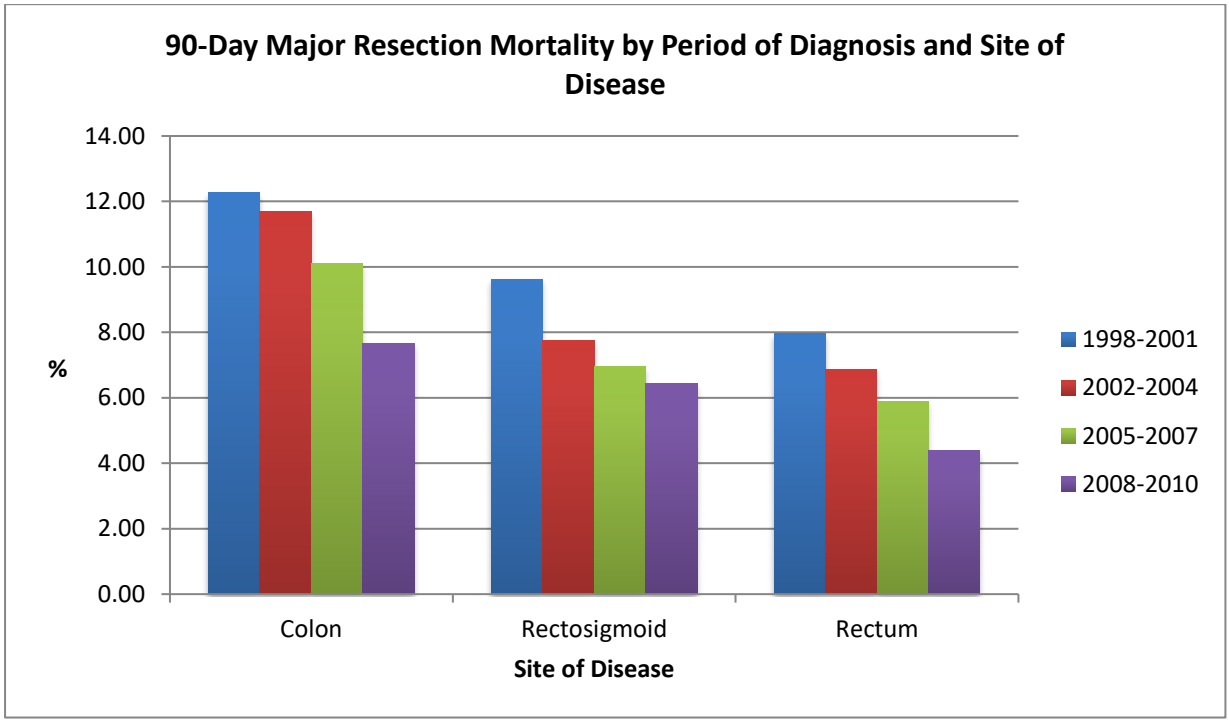
Mortality for all patients undergoing surgical intervention (major resection, minor resection, bypass, stoma or stent) between 1998 and 2010 at 30-days was 6.9% and at 90-days 10.9%. 30-day mortality within the time periods fell from 8.0% (1998-2001) to 5.2% (2008-2010) and 90-day mortality from 12.5% (1998-2001) to 8.5% (2008-2010) (Chi^2 p<0.001).

Mortality at 30-days was greatest in those who underwent major resection for colon cancer and least in those undergoing resection for rectal cancer, this pattern remaining constant throughout the study period. The pattern was replicated in mortality at 90-days (see Figures 24 and 25).

10.3.2.1. Figure 24: 30-Day Mortality by Period of Diagnosis and Site of Disease

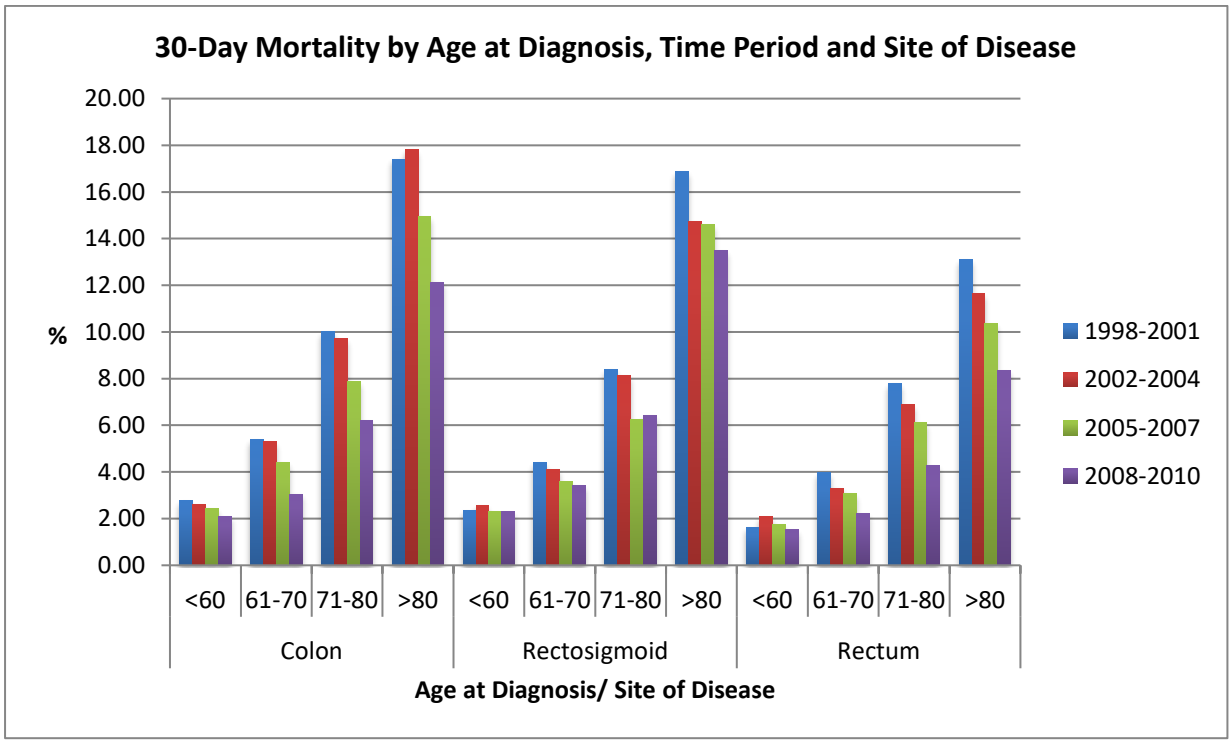


10.3.2.2. Figure 25: 90-Day Mortality by Period of Diagnosis and Site of Disease



Mortality at 30-days rose consistently as age at diagnosis increased, as illustrated by Figure 26 (the same pattern was replicated at 90-days).

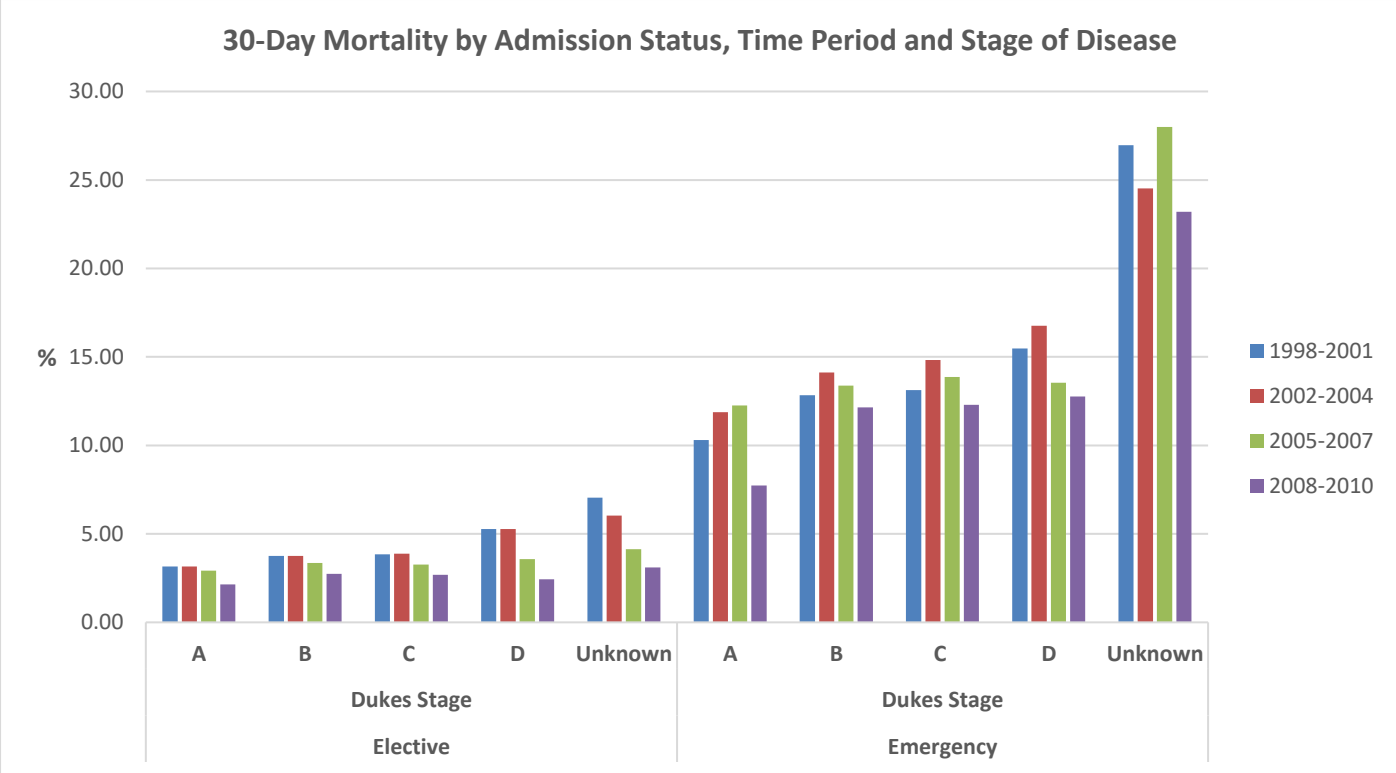
10.3.2.3. Figure 26: 30-Day Mortality by Age at Diagnosis, Time Period and Site of Disease



All patient mortality at 30-days in those who presented electively was 3.8%, whilst at 90-days, it was 6.4% ($p<0.001$ Chi^2); for those who presented as an emergency it was 16.5% and 24.6% ($p<0.001$ Chi^2) respectively.

Mortality for elective patients (at 30-days) decreased from 4.9% in 1998 to 2.4% in 2010 ($p<0.001$ Chi^2); emergency patients decreased from 16.7% to 13.0% ($p<0.001$ Chi^2). At 90-days, the figures were 8.1% (1998) to 4.4% (2010, elective patients, $p<0.001$ Chi^2) and 24.2% (1998) to 20.6% (2010, emergency patients, $p<0.001$ Chi^2). Stage of disease was not associated with a significant difference in mortality at 30-days (between Dukes' stages A-D in the elective setting ($p=0.38$ Chi^2) but was in the emergency setting ($p=0.05$ Chi^2) (Figure 27). A similar pattern of mortality for stage of disease was repeated at 90-days. Factors associated with early mortality were the same as those identified in Chapter 4, namely increasing age, advanced stage of disease and greater co-morbidity.

10.3.2.4. Figure 27: 30-Day Mortality by Admission Status, Time Period and Stage of Disease



10.4. Laparoscopic Surgery

Over the duration of the study period, the introduction of laparoscopic surgery saw 'keyhole' procedures develop from a novel technology to becoming commonplace. This rapid rise in its use is demonstrated in Table 15, where laparoscopic procedures constituted 0.5% major resections in 1998-2001 to 26.4% in 2008-2010 (Table 12; note the ICD code for conversion to open procedure was introduced in 2005 onwards).

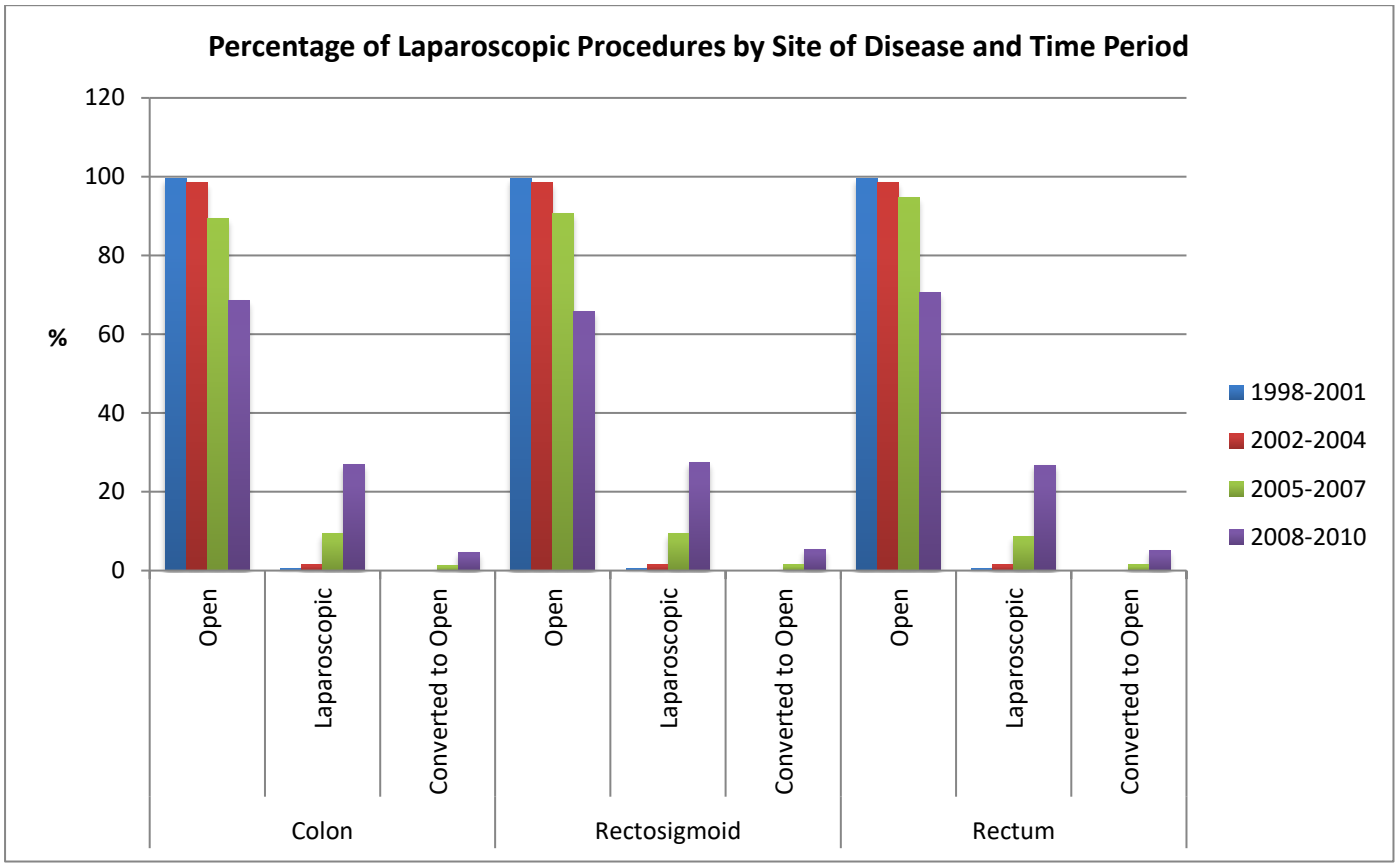
10.4.1. Table 12: Number of Laparoscopic Procedures by Time Period

Numbers of Laparoscopic Procedures by Time Period

Approach	Time Period							
	1998-2001		2002-2004		2005-2007		2008-2010	
	n	%	n	%	n	%	n	%
Open	71,129	**99.5**	52,474	**98.4**	51,187	**89.7**	42,389	**68.9**
Laparoscopic	355	**0.5**	836	**1.6**	5,174	**9.1**	16,233	**26.4**
Converted to Open	0	**0.0**	0	**0.0**	726	**1.3**	2,922	**4.7**
Total	71,484		53,310		57,087		61,544	

No specific site of disease appears to have been favoured for a laparoscopic approach, with approximately equal rates of conversion to open procedure at each site of disease (Figure 28).

10.4.2. Figure 28: Percentage of Laparoscopic Procedures by Time Period and Site of Disease



Unsurprisingly, the majority of laparoscopic procedures were in those admitted electively, but by 2008-2010, a small but significant percentage of procedures were either performed or were attempted laparoscopically in those admitted as an emergency (8.1% of all major resections, 2008-2010).

Mortality was significantly lower in those who underwent a laparoscopic procedure, with adjusted odds ratios for risk of death at 30-days following major resection in elective patients being 0.63 and for emergency patients 0.29 (time period 2008-2010, Table 13). No difference was found in risk of death if a procedure was converted to open. A similar pattern was seen for outcomes at 90-days.

Given the large discrepancy in numbers of laparoscopic procedures carried out within the different time periods and the likelihood of a significant 'learning effect', comparison of length of stay by time period was not carried out. Suffice to say however that those who underwent a laparoscopic procedure consistently remained in hospital for a shorter duration than those undergoing an equivalent open procedure.

10.4.3. Table 13: Crude figures and Odds Ratios for Likelihood of Death at 30-days by Operative Approach (2008-2010)

Crude figures and Odds Ratios for Likelihood of Death at 30-days by Operative Approach

Elective Admission

Operative Approach	Crude Mortality				Odds Ratios							
	Alive	Dead	Alive	Dead	Unadjusted				Adjusted			
	n	%	n	%	OR	p	95% CI		OR	p	95% CI	
Open	30,440	97.0	952	**3.0**	1				**1**			
Laparoscopic	15,214	98.2	280	**1.8**	0.59	<0.001	0.51	0.67	**0.63**	<0.001	0.55	0.72
Converted	2,616	97.1	77	**2.9**	0.94	0.61	0.74	1.19	**0.97**	0.77	0.76	1.23

Emergency Admission

Operative Approach	Crude Mortality				Odds Ratios							
	Alive	Dead	Alive	Dead	Unadjusted				Adjusted			
	n	%	n	%	OR	p	95% CI		OR	p	95% CI	
Open	9507	86.5	1490	**13.5**	1				**1**			
Laparoscopic	706	95.5	33	**4.5**	0.3	<0.001	0.21	0.42	**0.29**	<0.001	0.2	0.42
Converted	212	92.6	17	**7.4**	0.51	<0.001	0.31	0.84	**0.61**	0.06	0.36	1.02

10.5. Length of Stay

Median length of stay for all patients who underwent a surgical procedure throughout the course of the study was 9 days (IQR 8). In those admitted electively it was also 9 days (IQR 7) whilst median length of stay for an emergency admission was 10 days (IQR 12). Length of stay by admission status and primary procedure is demonstrated in Table 14.

10.5.1. Table 14: Length of Stay by Admission Status and Primary Procedure

Post-Procedure Median Length of Stay

Primary Procedure	Median Length of Stay (Days)		
	All Patients	Elective Admission	Emergency Admission
Major resection	10 (8)	9 (7)	10 (11)
Minor resection	0 (1)	0 (1)	4 (11)
Bypass	10 (10)	10 (8)	11 (12)
Stoma	10 (10)	9 (8)	11 (13)
Stent	2 (5)	1 (7)	3 (8)

***Values in parentheses are the inter-quartile range.**

Median length of stay decreased for all patients undergoing a surgical procedure (see Table 15) but most notable was the decrease in length of stay in those who underwent major resection.

10.5.2. Table 15: Length of Stay by Primary Procedure and Time Period

Post-Procedure Length of Stay by Time Period (All Patients)

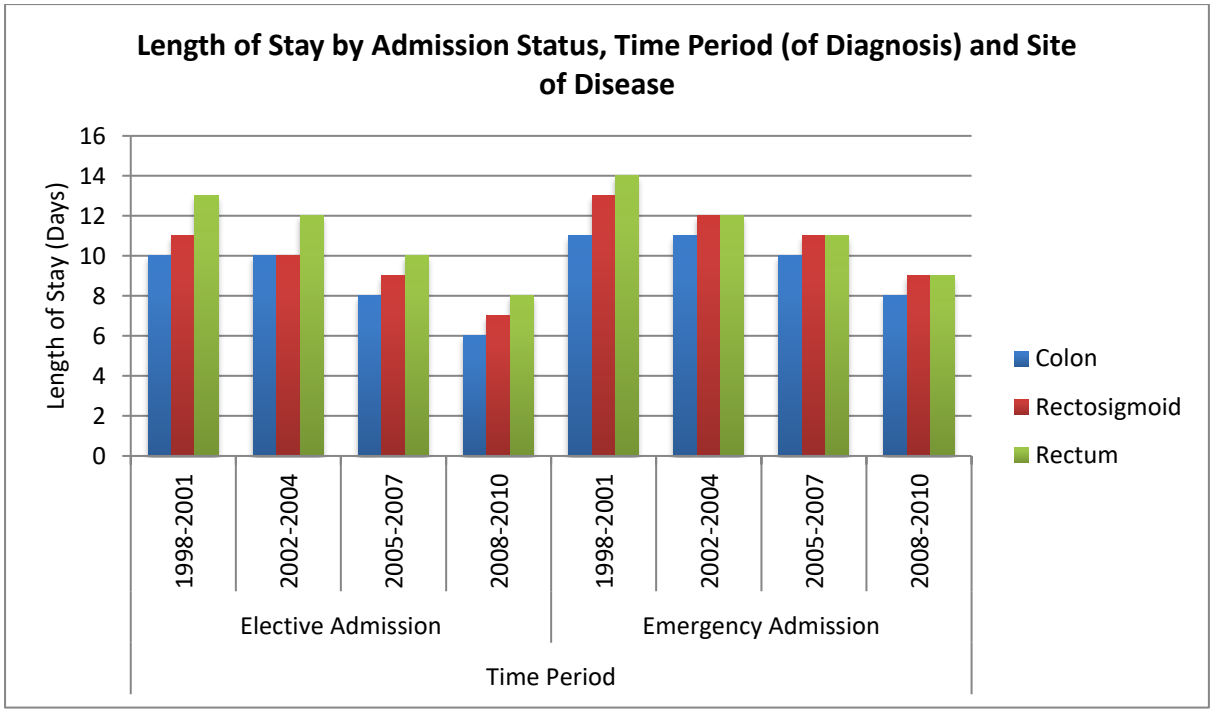
	Time Period			
Primary Procedure	1998-2001	2002-2004	2005-2007	2008-2010
Major resection	11 (7)	10 (8)	9 (7)	7 (8)
Minor resection	1 (3)	0 (2)	0 (1)	0 (0)
Bypass	11 (9)	11 (10)	9.5 (10)	9 (10)
Stoma	12 (10)	11 (10)	9 (10)	8 (9)
Stent	3 (5)	2 (5)	2 (6)	1 (5)

***Values in parentheses are the inter-quartile range.**

Comparison of length of stay by admission status, time period (of diagnosis) and site of disease revealed that those with colon cancer remained in hospital for the shortest period,

followed by those with rectosigmoid cancer, with rectal cancer patients staying the longest (Figure 29).

10.5.3. Figure 29: Length of Stay by Admission Status, Time Period and Site of Disease



Those admitted as an emergency consistently stayed longer than those admitted electively although this was not statistically significant (p=0.93 Chi^2).

10.6. Discussion

This study demonstrated a consistent rise in the number of patients admitted with colorectal cancer (CRC) over its course, with the number of those admitted electively rising whilst the number of those admitted as an emergency fell. This pattern of rising incidence of CRC has been replicated in other nations beyond England/ the United Kingdom, including the United States, Asia and the Oceanic nations, with the highest rise in incidence seen in economically transitioning nations, particularly those of the old Eastern Bloc[159–162]. Further, several of these nations have also seen a comparative rise in the incidence of CRC amongst younger patients, a trend again replicated here[159,161,162]. Reasons underlying these changes in incidence are likely to include an ageing population and better and more successful treatments of other diseases (allowing people who previously would have died of alternative causes e.g. heart disease, to develop CRC). Amongst the young, changes in diet and lifestyle may well be contributory, especially as populations become wealthier with a concomitant rise in the consumption of red meat and processed foods and decrease in levels of physical activity[163,164].

The fall in the number of elderly (>80 years) admitted as an emergency and the fall in the number of emergency admissions in general over the study period may suggest that despite its critics, innovations such as the two-week wait and the 31/62 day cancer targets may be having a positive impact on CRC diagnoses and the route of admission for those found to have CRC[165–169].

The dramatic effect that screening can have on emergency presentation was clearly demonstrated within these results and is again a picture that has been replicated within other countries[170]. Further these results provide an excellent example of how 'Big Data' may demonstrate at a population level (where perhaps at a local level it may be more difficult to ascertain) how interventions affect stage at diagnosis and route of admission. For those with interval cancers (who had almost the same risk of emergency admission as those who had not engaged in the screening program), two explanations are most likely. These patients may have had a missed cancer, either through failure of the FOBT or unfortunate failure of the endoscopist to recognise a small cancer at time of investigation or they may have developed highly aggressive disease, where progression occurs within the screening timeframe.

The trend towards steadily improving 30 and 90-day mortality for those patients who undergo operative intervention is suggestive of better patient selection (and in turn better non-operative treatments for frail patients e.g. endoluminal stents) but also recognition of the increasing importance that peri-operative care is having on patient outcomes. 'Failure to rescue' has been recognised as a concept, with greater emphasis being placed on timely review, investigation (e.g. much greater use of early post-operative imaging) and patient management by senior doctors. Technological advances such as radiological drainage of post-operative collections have now also obviated the need for repeat surgical intervention along with its attendant risks. Much greater importance is now placed on prevention of thromboembolic events, cardiac pre-habilitation and objective physiological testing of a patient's ability to undergo the rigours of major surgical intervention (e.g. CPEX testing), along with greater use of devices such as incentive spirometers to prevent post-operative chest infections.

The introduction of laparoscopic surgery represented a major development within the treatment of colorectal disease and a similar change in surgical technique. Whilst trials such as CLASICC and COLOR showed that there was no difference in oncological outcome,

laparoscopic surgery (like all surgical techniques) was associated with a learning curve[171,172]. It is highly likely that the positive results in terms of post-operative mortality, particularly with earlier results may have been influenced by very careful patient selection, but it is also important to note that at a population level, those undergoing a laparoscopic resection certainly did not do any worse than their 'conventionally' treated peers. Results from a cohort of patients undergoing laparoscopic surgery today are likely to show that they do significantly better than those who undergo an open operation (as laparoscopic surgery is now the accepted norm, with open surgery being reserved for those with disease related or patient factors which prevent a laparoscopic approach).

The fact that by the end of the study period, a small but significant number of patients who were admitted as an emergency were undergoing a laparoscopic procedure, perhaps provides insight into the readiness with which laparoscopic surgery was accepted into the surgical community. Surgery has a long history of innovation but uptake of new techniques or innovative equipment has at times been reluctant[173]. The fact that within a 13-year period, laparoscopic surgery went from introduction to the accepted norm for elective resection with small but increasing numbers being performed in the emergency setting, demonstrates how readily the benefits of laparoscopic surgery were realised and the effort that was made by surgeons to 'upskill' themselves to be able to provide this service.

With the recognised reduction in length of stay associated with laparoscopic surgery (due to less post-operative pain and earlier mobilisation), it is perhaps not surprising that length of stay fell. Nonetheless, the importance of the introduction of enhanced recovery protocols and the use of post-operative analgesic regimens allowing early mobilisation/ prevention of chest infections and encouragement of return of gut function should not be underestimated. These changes all occurred concurrently with the introduction of laparoscopic surgery over the duration of this study and the combined impact of these interventions is well demonstrated by the data provided here. Like with most aspects of life, it is the cumulative effect of marginal gains that result in the greatest impacts.

Overall, therefore, it would appear that the rising incidence of colorectal cancer is being replicated in England as in other developed nations. Reasons underlying this are, as always, multifactorial but the rising incidence in younger patients is of particular concern. Patients are, in general, being identified earlier through increased focus on CRC and interventions such as

screening. Mortality rates are improving as more attention is being paid to peri-operative care (peri-operative care consultants are even being introduced in parts of the NHS) along with other improvements in care (such as laparoscopic surgery) resulting in decreased length of stay and reductions in preventable post-operative complications. These improvements are not happening in isolation in England however, they are occurring across the developed world. As such the English NHS in terms of colorectal cancer care is ‘running furiously to stand still’ in comparison to our European/ Oceanic and American partners. To surpass the standards of care and outcomes achieved in other wealthy nations, still greater improvements to English colorectal cancer care need to occur.

11. Endoluminal Stent Use in English Colorectal Cancer Patients 1998-2010

11.1. Introduction

In 2010 there were 40,695 new cases of colorectal cancer in the UK, with emergency presentation constituting a fifth (21%) of all new diagnoses. [174,175] By 80 years of age, rates of emergency admission increase to 40%, of whom nearly a third of patients (29.5%) are unsuitable for operative intervention[92,175,176]. Acute colonic obstruction has been reported in between 7-30% of all colorectal cancer presentations, particularly in those with lesions distal to the splenic flexure[176]. Traditionally, management has involved the use of one, two or even three stage operative procedures to relieve the obstruction and resect the tumour. Emergency surgery however, by its nature, is high risk and is especially so when operating on patients with malignant large bowel obstruction. Such patients are not optimised for surgery, often have associated co-morbidities and are suffering the acute physiological derangement of colonic obstruction[177].

The use of novel medical devices therefore that may achieve endoluminal decompression and convert the acutely obstructed patient to one who may undergo pre-operative optimisation prior to major resectional surgery is an understandably attractive option. Balloon dilatation and laser re-canalisation have historically been attempted to relieve the obstructed patient, however both are subject to limitations. Balloon dilatation risks perforation and tumour fracture, whilst laser re-canalisation is not widely available and often requires multiple treatments before adequate decompression is achieved, thus limiting its use in the emergency setting[178]. The current guidelines from both The Association of Coloproctology of Great Britain and Ireland and NICE recommend that “in the absence of perforation, peritonitis or closed loop obstruction, endoluminal stent insertion should be considered in the management of malignant colorectal obstruction[3,179].”

Dohmoto first reported the use of an endoluminal stent in the management of acute colonic obstruction in 1991[180]. Under a combination of endoscopic and fluoroscopic guidance, self-expanding stents may be inserted into the colorectum in order to allow proximal decompression from an obstructing lesion. Successful deployment of a stent offers almost immediate decompression allowing either palliation or to act as a bridge to surgery. Technical success rates of up to 92% and clinical success rates of up to 88% have been reported in the published literature[181,182].

Whilst, there has been a steady rise in the use of endoluminal stents since their introduction, this rise has been based on limited randomised controlled evidence; in fact a number of controlled clinical trials have been stopped due to high rates of adverse events.[183,184] Early results from the CREST trial have shown that use of endoluminal stents in the emergency setting have similar outcomes in terms of mortality and length of stay to that of emergency surgery, but result in decreased rates of stoma formation when compared to immediate surgery[185]. Nevertheless, use of endoluminal stents remains controversial and retrospective analysis of large population based datasets may contribute towards the evidence base for their use in obstructing colorectal cancer.

Through use of linked Cancer Registry and HES data in the form of the National Cancer Data Repository (NCDR) a retrospective analysis of the patterns of use and outcomes of endoluminal stents in the management of acute malignant colonic obstruction between 1998 and 2010 within the English NHS has been performed and is the subject of this chapter. This chapters aims to describe how the use of endoluminal stents has influenced the management of acute malignant colonic obstruction and how their outcomes have developed over the study period.

11.2. Methodology and Statistical Modelling

Data were extracted from the NCDR on all individuals with a diagnostic code indicating first primary diagnosis of colorectal cancer between 1998 and 2010. Individuals identified were limited to those with codes for insertion of any endoscopic, image-guided or self-expanding metal stent. These individuals were then further limited to OPCS codes (Version 4.5, 2009) H21.4, H24.3, H24.4, H27.3, H27.4, H31.4 for stents inserted into the colorectum and to stenting within one year of their diagnosis.

Identified individuals were limited to a single episode of stent insertion before de-duplication. Data were extracted on the total number of stents placed within each year, the location of the placement of the stent (derived from the recorded site of the tumour, taken from the cancer registry component of the NCDR) and the 30-day mortality associated with stent placement (defined as time from date of stent insertion to date of death). Other analyses performed included time from admission to stent insertion (as recorded within HES), 30-day mortality in those undergoing operative intervention (defined as set out in the NCIN Major Surgical

Resections report[186]) and overall survival (defined as survival from date of stent insertion to date of death). For purposes of survival analysis, analysis began from the date of stent insertion and the data was censored at 5 years.

Individuals were categorised as ‘Stent Only’ if a stent was their only recorded intervention or if a recorded colorectal operation occurred before stent insertion with no recorded surgery thereafter. ‘Bridge to surgery’ was defined as those who underwent an operation greater than 48 hours after their recorded date of stent insertion. ‘Stent Fail’ was defined as those who underwent stent insertion but had a recorded operative intervention within 48 hours.

In those undergoing surgery, OPCS codes were used to tabulate all procedures performed prior to grouping. ‘Restorative Resection’ was defined as any operation that involved segmental colonic or rectal resection and anastomosis. ‘Hartmann’s/ Stoma’ was defined as any OPCS code that included either formation of an ileostomy or exteriorisation of bowel. ‘Total Colectomy’ was defined as total colectomy (including sub-total colectomy) and panproctocolectomy. Any other procedure was defined as ‘Other’.

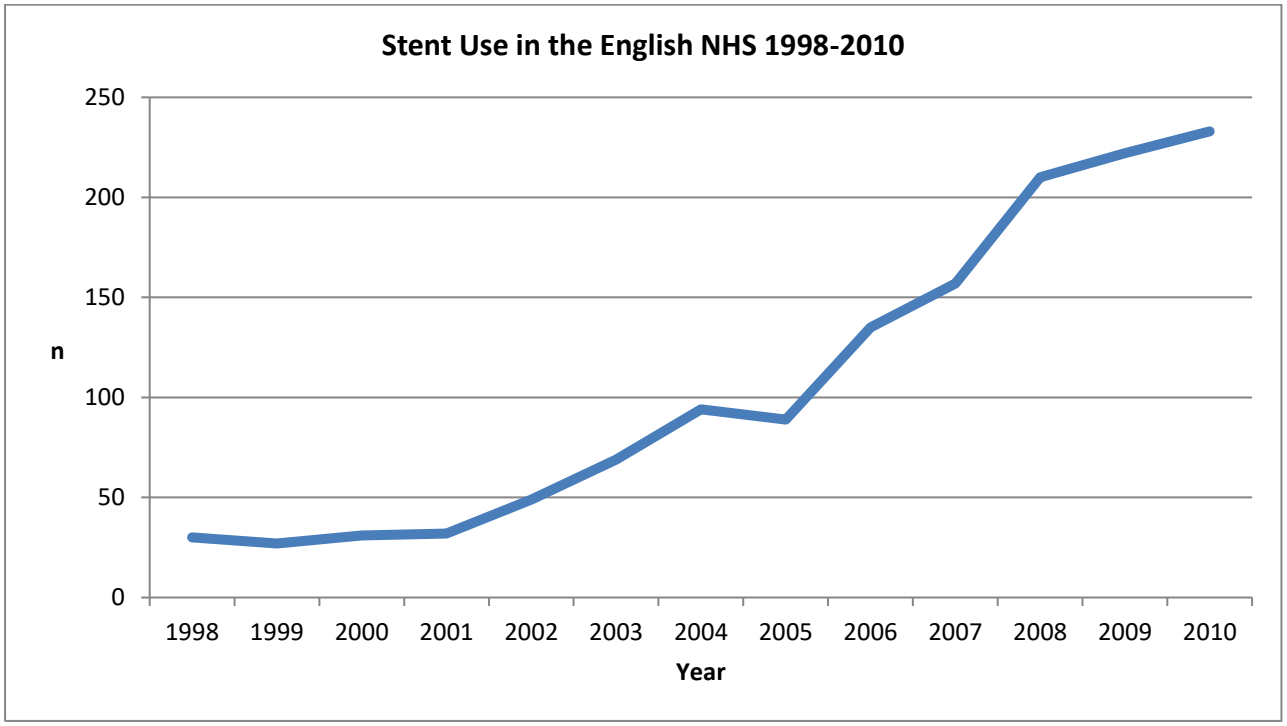
Dukes’ staging was defined by stage at diagnosis as recorded in the NCDR or if staging data was recorded as something other than Dukes’ (e.g. TNM), it was calculated from that. Time from admission to stent was defined by subtracting the date of admission from the date of the stent.

Data were analysed using Stata™ Version 12.1 (StataCorp, 4905 Lakeway Drive,College Station, Texas 77845 USA). Chi Squared was used to compare outcomes across categorical variables. The Chi Square statistic is a commonly used test to assess for relationships between categorical variables. It assumes that there is no relationship between variables and that the outcome of interest is independent. It is however sensitive to sample size (i.e. large sample size will almost certainly give you a statistically significant *p* value). Statistically significant *p* values must therefore be viewed in the context of the sample size, and allowances in their interpretation made accordingly (e.g. with a huge sample size, a *p* value of $p=0.05$ is not particularly significant). Nevertheless, the Chi Square statistic is a commonly used test in most ‘big data’ publications and was again used here to for ease of cross comparison of results.

11.3. Results

Between 1998 and 2010, 1378 patients underwent insertion of an endoluminal stent, with a year on year rise in stent use within the English NHS (Figure 30). In 477 patients the stent was the only recorded (surgical) treatment for that patient's disease, whilst 901 were inserted as a bridge to surgery, of which 785 (86.5%) were inserted electively and 119 (13.2%) as an emergency.

11.3.1. Figure 30: Stent Use in the English NHS 1998-2010



The vast majority of stents inserted as a bridge to surgery were for left sided/ rectal malignancies (798, 88.6%), with the remaining 103 stents inserted for right sided or 'Colon Not Otherwise Specified' malignancy (103, 11.4%). Approximately two thirds were inserted for Dukes' stage C or D disease (37.3% (Dukes' C) and 22.2% (Dukes' D) respectively) and one third for Dukes' stage B disease (29.9%). Sex distribution was again approximately one third/ two thirds; 37.4% bridge to surgery patients were female and 62.6% male (Table 16). Median time from stent insertion to major resection in bridge to surgery patients was 24 days (IQR 12-46 days).

11.3.2. Table 16: Characteristics of Patients who received an Endoluminal Stent prior to Major Resection or underwent Major Resection alone

Characteristics of Patients Undergoing Endoluminal Stent Insertion and Stoma or Bypass Formation Prior to Major Resection or Major Resection Alone

	Stent as Bridge to Surgery		Surgery Only	
	n	%	n	%
Sex				
Male	564	37.4	131,779	55.2
Female	337	37.4	106,882	44.8
Dukes' Stage				
A	12	**1.3**	27973	**11.7**
B	269	**29.9**	80572	**33.8**
C	336	**37.3**	79955	**33.5**
D	200	**22.2**	21083	**8.8**
Unknown	84	**9.3**	29078	**12.2**
Age				
<60	181	**20.1**	41434	**17.4**
60-69	232	**25.7**	63920	**26.8**
70-79	302	**33.5**	84009	**35.2**
>80	186	**20.6**	49298	**20.7**
Charlson				
0	591	**65.6**	174120	**73.0**
1	162	**18.0**	31089	**13.0**
2	94	**10.4**	24338	**10.2**
>/=3	54	**6.0**	9114	**3.8**
IMD				
Least Deprived	189	**21.0**	48474	**20.3**
2	178	**19.8**	52901	**22.2**
3	179	**19.9**	51141	**21.4**
4	196	**21.8**	46735	**19.6**
Most Deprived	159	**17.6**	39410	**16.5**

Patients receiving a stent as a bridge to surgery displayed little difference when compared by age to those who went straight to surgery but had more co-morbidities (Charlson Score ≥3, 6% vs. 3.8%), were more socioeconomically deprived ((Deprivation Quintile 5 17.6% vs. 16.5%) and had more advanced disease (Dukes' C 37.3% vs. 33.5%, Dukes' D 22.2% vs. 8.8%).

30-day mortality was higher amongst those who had a stent as a bridge to surgery compared with those who underwent surgery alone (Table 17).

11.3.3. Table 17: 30-day Post-Operative (Major Resection) Mortality by Stent as Bridge to Surgery against Surgery Alone

All Operations				
Bridge category	Status at 30-days post major resection			
	Alive		Dead	
	n	**%**	n	**%**
Stent as Bridge to Surgery	826	**91.7**	75	**8.3**
Surgery Only	223,478	**93.6**	15,183	**6.4**
Total	224,304		15,258	

*N.B. Those who underwent stoma alone or bypass surgery have been excluded from this table.

Rate of stoma formation following both emergency and elective operation in those who had a stent as a bridge to surgery was higher in those with colon cancer and broadly similar in those with rectal cancer (Table 18).

11.3.4. Table 18: Rates of stoma formation for patients with colon and rectal cancer following endoluminal stent insertion (when used as a bridge to surgery)

Stoma at Major Operation				
Colon- Emergency Operation				
	Stoma		No Stoma	
	n	%	n	%
Stent as Bridge to Surgery	73	70.2	31	29.8
Surgery Only	11198	34.1	21604	65.9
Colon- Elective Operation				
	Stoma		No Stoma	
	n	%	n	%
Stent as Bridge to Surgery	71	66.4	36	33.6
Surgery Only	21554	14.9	122874	85.1
Rectum- Emergency Operation				
	Stoma		No Stoma	
	n	%	n	%
Stent as Bridge to Surgery	12	80.0	3	20.0
Surgery Only	1491	79.1	393	20.9
Rectum- Elective Operation				
	Stoma		No Stoma	
	n	%	n	%
Stent as Bridge to Surgery	71	66.4	36	33.6
Surgery Only	43379	72.8	16168	27.2

In comparison, endoluminal stent use as a bridge to surgery appeared to result in a lower rate of stoma formation (at major resection) than when a stoma or bypass procedure had been undertaken preceding major resection (Table 19).

11.3.5. Table 19: Rate of stoma formation (at major resection) for patients undergoing a bypass procedure or stoma prior to major resection

Stoma at Major Operation				
Colon- Emergency Operation				
	Stoma		No Stoma	
	n	%	n	%
Stoma or Bypass as Bridge to Surgery	20	43.5	26	56.5
Colon- Elective Operation				
	Stoma		No Stoma	
	n	%	n	%
Stoma or Bypass as Bridge to Surgery	555	61.6	346	38.4
Rectum- Emergency Operation				
	Stoma		No Stoma	
	n	%	n	%
Stoma or Bypass as Bridge to Surgery	22	53.7	19	46.3
Rectum- Elective Operation				
	Stoma		No Stoma	
	n	%	n	%
Stoma or Bypass as Bridge to Surgery	1,034	36.3	1,812	63.7

Sixty five (65) stents which were inserted as a bridge to surgery failed over the course of the study period (7.2%), necessitating operative intervention within 48 hours of their insertion (and were therefore included as ‘Emergency’ resections in previous analyses). 33 patients (3.7%) required multiple stent insertions prior to their major resection (but were classified a ‘bridge to surgery’ for the purposes of analysis).

11.4. Discussion

The evolution of endoluminal stents in the management of obstructing colorectal cancer represents not only technical innovation but also the clinician's desire to find new and better ways of managing these complex patients. With this in mind, it is hardly surprising therefore (as shown by our results), that stents have been taken up enthusiastically by clinicians and are regarded by patients as a more attractive alternative to major operative intervention, particularly in the emergency or palliative settings[187].

The majority of the stents placed in this study were for use as a 'bridge to surgery' and whilst this remains a key part of the rationale behind stent use, especially in the context of stubbornly high emergency admission rates (and the potential to 'convert' a patient into a planned operation), modern practice now includes use of many more stents for palliation. It is likely that use of endoluminal stents in modern (i.e. 2018) colorectal cancer practice is very different to that of the period reported here[188]. Nevertheless, when used as a 'bridge to surgery', there is now a wealth of evidence in the medical literature (e.g. the ESCO trial) that stent use is associated with a reduction in stoma formation rate, a body of evidence that contradicts the findings of this study[185,188,189].

Stoma formation rates for patients undergoing major resection following stent placement as a bridge to surgery may have been higher in this study for a variety of reasons. This study covers the mainstream introduction of stents from a research tool to comparative 'everyday' use. Clinicians will have been 'discovering' the role of endoluminal stents in colorectal practice. Patients selected to receive a stent may well have been more likely to have had advanced disease, to have been admitted as an emergency and have more co-morbidities than those selected for immediate surgery (as shown in our results), which by default would make the operating surgeon more wary of performing a primary anastomosis. There remains the question of stent perforation and converting a patient who may have potentially curative disease to one with incurable, metastatic disease. Whilst there is today a greater body of evidence regarding this risk, the results of this study very much cover a period where the answer remained unknown. What is clear from our results is that stent use was associated with a much lower risk of stoma formation at major resection when compared to formation of a defunctioning stoma or bypass procedure. In this context, stent use offers clear advantages; there is no need for the patient to undergo a second general anaesthetic for their major resection and no need for a second major procedure (i.e. major resection following stoma formation/ bypass). That the 30-day mortality rate following major resection was higher in

bridge to surgery patients most likely represents the ‘higher risk’ nature of bridge to surgery patients, rather than any direct effect of the stents themselves.

The risk of tumour perforation (up to 11.5%) and conversion from curable to metastatic disease with endoluminal stent use remains very real and is a question that has not yet been fully answered[190]. Previous studies have been stopped due to high rates of tumour perforation and whilst the ESCO trial showed that bridge to surgery patients had lower stoma formation rates than those who underwent emergency surgery (with equivalent oncological outcomes), this was limited by comparatively small patient numbers and a maximum 3-year follow up period[183,184,189]. The CREST trial found the same, but was again limited by only 1 year of follow up[166]. A recent review of 5-year disease recurrence in patients with and without perforation following stent placement found an adjusted hazard ration of 1.4 (for recurrence) against for those who had had a perforation[191].

Endoluminal stents undoubtedly have a developing role to play in the management of the emergency colorectal cancer patient. Suárez and Jimenez-Pérez in a recent review of long-term outcomes following stent use as a bridge to surgery in obstructed colorectal cancer patients noted that stented patients had a higher lymph node yield at major resection, received earlier adjuvant chemotherapy and were more likely to have undergone a laparoscopic resection[192]. Other authors have noted a significant increase in those achieving primary anastomosis at their major resection[193,194].

Thus in summary, it is clear that endoluminal stents offer certain advantages for carefully selected patients. They are not (like most novel technologies) the panacea they were first thought to be. It is likely that the higher rate of potential recurrent disease/ perforation may make clinicians approach stents with caution in younger patients. On the other hand, the opportunity to optimise a patient for surgery, a greater chance of primary anastomosis and greater likelihood of a laparoscopic procedure may make stents more appealing in the elderly population (where risk of late recurrence is perhaps less of a concern). As stent technology improves and as clinician experience increases, it is likely that endoluminal stents will have an increasing role to play in the management of the emergency colorectal cancer patient. In relation to English colorectal cancer care, refinement of ‘when and how’ endoluminal stents are used may offer particular advantages, especially when dealing with the known subset of patients who present late with aggressive disease, from which England appears to suffer.

Being able to offer these patients a planned operation, with potentially better oncological outcomes (i.e. higher lymph node yield, earlier adjuvant chemotherapy) may be another ‘marginal gain’ we may be able to achieve in improving poor English colorectal cancer outcomes.

12. Overall Discussion

That outcomes for the treatment of colorectal cancer in England and Wales have improved over the last 40 years is clear. One-year net survival from colorectal cancer in England and Wales in 1971-2 was 46.2%; by 2010-11, it had improved to 75.7%[41]. Five-year survival has also undergone a similarly impressive increase - from 25% in 1971-2 to 59% in 2010-11[41]. Yet outcomes still appear to trail behind those reported in Europe, Oceania and the United States. It would certainly seem that England and Wales started from a low baseline; the age standardised incidence rate for men with colorectal cancer in 1985 was 38.8 (per 100,000) in Western Europe whilst in the United States it was 48.2. In comparison, mortality at the same time in Western Europe was 21.4 and in the United States 17.4[195,196].

Colorectal cancer in England is still mainly a disease of the elderly with 43% cases being diagnosed in those aged ≥75 years[197]. Whilst there is a recognised rising incidence of CRC amongst younger patients, the vast majority of patients are still aged over 60[198]. As demonstrated in this study and discussed previously, it is important not to ignore this rising incidence in younger patients, especially as they potentially have the greatest longevity to gain from early diagnosis and treatment. Nevertheless, it is likely the elderly will continue to constitute the bulk of patients with CRC and the United Kingdom, like most developed nations, has a rapidly rising elderly population (in 1976, 14.2% of the population were aged over 65, by 2016 this had reached 18% and is projected to reach 24.7% by 2046)[199]. How increasing age and co-morbidity affects survival in CRC was usefully demonstrated in a study by Gross et. al. Using population based cancer registry data linked to administrative claims data, they were able to demonstrate a reduction in life expectancy from 19.1years (in a man aged 65 diagnosed with Stage 1 CRC with no chronic conditions), to 12.4 years for those with 1 or 2 chronic conditions, to 7.6 years in those with ≥3 conditions). A similar decrease in survival was seen in women and an even greater impact (with increasing numbers of chronic conditions) in those aged ≥81 years[200].

The results of our study showed a clear fall, at a population level, in the number of elderly patients admitted as an emergency over the study period and this may indeed represent some of the national level changes in cancer care beginning to take effect (e.g. two-week wait). Nonetheless, those aged >80 still made up the greatest proportion of emergency admissions and still had the highest mortality from operative intervention at 30 and 90-days, a finding replicated in other, similar studies[63,201].

It would also appear that England has a higher proportion of patients who present with aggressive disease which is rapidly fatal (in comparison to other European countries)[142]. If this pattern were repeated when compared to American and Oceanic patients, this may go some way to explaining some of the differences in outcomes seen between England and these countries, despite the efforts that have been made within the NHS to diagnose CRC earlier (through health promotion, patient education and screening).

It is highly likely that the beneficial effects of screening were not fully illustrated within this study. Bowel cancer screening was only introduced in 2006 (at a population level) and the 'lead time' for its positive impact on rates of emergency admission and stage of diagnosis was far too short to be recorded here. In an exceptionally cruel twist of fate the ex-Health Secretary who helped introduce the NHSBCSP has recently been diagnosed with (Stage III) colorectal cancer[202]. Lord Lansley notes that he only saw his GP following 'nagging' by his wife, but that had screening with flexible sigmoidoscopy been introduced as he intended, it is likely his tumour may have been detected earlier[203]. Population level data, as used here, has a role 'front and centre' in providing the evidence, both from a health and economic perspective, of the efficacy of bowel cancer screening and the information that population level studies can provide should be exploited to the full.

Nevertheless, to attribute the on-going differences in outcome between England and other high-income countries to patient demographics and disease biology alone would be too simplistic. The United Kingdom has an alternative set-up of its primary care services compared to its European neighbours in the role of the General Practitioner (GP) as gatekeeper to secondary care services. In other high-income countries, it is much more common for patients to self-refer to secondary care with their particular ailment (e.g., a patient with rectal bleeding may well make an appointment directly with a gastroenterologist/ colorectal surgeon). As the secondary care physician is primarily interested in the condition for which the patient has attended, they are likely to offer investigation of these symptoms more quickly and perhaps more aggressively than the general practitioner who must consider the patient's holistic needs and other co-morbid conditions[204]. It is not helped by the fact that the primary symptoms of CRC (abdominal pain, fatigue, abdominal mass, rectal bleeding etc.) can be vague and attributed to other conditions; as such it has been estimated that up to a third of patients with CRC experience diagnostic delay[86]. This effect is likely to be amplified in the elderly and in those with multiple co-morbidities. The difficulty in diagnosis, (combined with

the potential for diagnostic delay), the conceivable reluctance of the elderly population to 'bother the doctor/ 'stiff upper lip' and recognised increasing incidence with ageing may go some way to explaining the resilience of poor English colorectal cancer outcomes, especially in light of high numbers of patients presenting late, as an emergency and with aggressive disease. Again, population level data may have a role in providing evidence for the most efficient use of limited NHS resources. For example, population level data may be able to provide new insights into the most efficient use of services such as the 'Two Week Wait' and/or be able to provide evidence for new, more effective referral pathways for primary care, based on symptom analysis and likelihood of detecting disease.

Our study supports other reported data that emergency admission rates, mortality and length of stay fell between 1998- 2010[205]. Emergency admission rates have likely improved through the aforementioned patient education and awareness but also through the introduction of screening and initiatives such as the 2-week wait. The two-week wait initiative was first introduced in 2000 through the NHS Cancer Plan but has remained controversial since its inception. There appears to have been widespread implementation of the mechanisms necessary to meet the requirements of the two-week wait within the English NHS, but poor overall compliance, with a limited impact on rates of emergency admission[168]. It has been noted by several authors that the cancer detection rate with two-week wait referral patients are poor (and decreasing) but that the increasing volume of referrals under the two week rule are impacting on routine referrals, a group who contribute to a significant number of colorectal cancer diagnoses[93,117,120,168]. Indeed, Leung et al, in an analysis of 1100 two-week wait referrals over a 12 month period noted that more cancers were diagnosed by urgent referral, emergency admission, routine referral or screening than through the two-week wait system. They also noted that symptomatic patients tended to have Dukes' B or above disease, whilst those identified through screening were usually Dukes' A; a finding repeated by Chohan et al. who found that whilst two-week wait patients were seen quicker, on diagnosis they tended to have more advanced disease[165,167]. The data provided within this study should support the argument for the case that whilst well intentioned, the two-week wait system is not bringing about the changes in (colorectal at least) cancer diagnosis that was anticipated nor expected. New methods of assessing patients with potential colorectal cancer symptoms must be identified. Population level data provides huge scope for the linking of primary and secondary care data to help produce algorithms to characterise those most at risk and to streamline referral services to secondary care.

Thus ,it would appear that the two-week wait system has had a limited impact on both emergency admission rates and outcomes, but that, as stated above, population level data may have a role in improving this. It would seem that screen detection of early cancer through faecal occult blood testing/ faecal immunochemical testing/ sigmoidoscopy offers a more efficient mechanism for both reduction of emergency admission with concurrent improvement in outcomes. Certainly, the early data provided here, supports the case for screening of colorectal cancer, with good evidence that screening results in earlier diagnosis and therefore presumed better outcomes. Nonetheless, for those who do come to surgery, there can be little doubt that the introduction of minimally invasive/ laparoscopic surgery, combined with enhanced recovery protocols has helped drive the decreasing length of stay reported here and that it is likely modern day figures would report further improvements[192].

The introduction of laparoscopic surgery as recorded here is an excellent example of how population level data can be used to track improvements in patient outcomes through the introduction of new technology. New technology (e.g. laparoscopic surgery, endoluminal stents) inevitably involves a learning curve before its abilities and limitations are fully understood. At a local level, this may prevent uptake of, or persistence with new technologies at the expense of patient outcomes. Population level data allows us to chart the impact of these technologies and to gauge their effectiveness, without the influence of local bias. It further allows us to evaluate where these resources may be best placed or how they may be best delivered for maximum impact on patient care.

Mortality rates at both 30 and 90 days (for English colorectal cancer patients) reported here were consistent with rates reported elsewhere in the medical literature[63]. They also followed the decreasing trend in 30-day mortality reported both for England and Europe[63,139,206,207]. There has been considerable debate over recent years in the medical literature as to the appropriateness of using 30-day mortality alone and whether this was in fact ‘hiding’ mortality that is revealed at 90-days[192,194]. The results presented here confirm an improving trend in relation to mortality at both 30 and 90-days over the period of the study but also highlight the marked increase in mortality seen in patients aged >80 at all time periods. The analysis of mortality rates by Trust also replicates the wide variations in outcomes reported by others for English colorectal cancer patients, although there appeared to be little association with volume of work and interestingly, those Trusts with a high elective mortality were not necessarily the same as those with a high emergency mortality[62,63].

This variation in mortality rates will of course, have a variety of causes, not least because of variability in the demographics that individual hospital Trusts serve. Nonetheless, there is increasing evidence that a key factor behind the variability in outcome in England relates to the provision of critical care beds for high risk surgical patients and of a 'failure to rescue' the deteriorating patient[102,104,208,209]. Critical care bed provision in England (and the United Kingdom as a whole) has been recognised as an issue for over 20 years[208]. The United Kingdom has, on average far fewer critical care beds than other, equivalent income European countries and yet the number of ICU beds in a hospital has been shown to be an independent predictor of decreased mortality amongst high risk general surgical patients[209].

The availability of and access to ICU beds for the post-operative colorectal cancer patient represents only one facet of their care however. Alongside ICU bed provision must be the ability to recognise and react to the deteriorating patient. Again, the United Kingdom compares poorly to other equivalent countries in relation to the number of intensivists caring for patients. UK Government statistics report that the maximum number of patients one consultant intensivist may look after at any one time is 15. In the Netherlands this ratio is 1:12 and in Sweden 1:6. Further, pharmacy services in the United Kingdom are only required to be provided in working hours Monday to Friday, whereas many other countries require these services to be available 24/7[210].Thus opportunities to address a patient's deteriorating condition may be being missed, with associated deleterious effects on outcomes.

ICU bed provision, number of intensivists and such like are linked to 'Failure to Rescue' the deteriorating patient. Failure to rescue simply represents a hospital's ability to allow patients who suffer a serious complication to survive. Henneman et al. have reported that in relation to complication rates, high mortality hospitals only have a slightly higher rate than their low mortality counterparts do[102]. However, the failure to rescue rate was 3 times higher in high mortality hospitals. Henneman et al in a separate study also go on to report that whilst high volume and teaching status are associated with decreased failure to rescue rates, there is also a significant association with higher levels of ICU provision (and decreased mortality)[211].

Almoudaris et al report that in relation to English colorectal cancer units, there is significant variation in failure to rescue rates and in particular, through looking at management of surgical complications, significant variability in complication management. They report that reoperation rates are similar between hospital Trusts with the highest and lowest mortality rates but are

widely different when it comes to failure to rescue rates (and therefore by default, in their management of serious complications)[104]. Recent years have seen recognition of this problem and there are now on-going initiatives to audit management of emergency laparotomy/ serious complications (e.g. National Emergency Laparotomy Audit) in order to improve standards and drive outcomes.

The variation in Failure to Rescue rates throughout England may well go some way to explaining the variability in mortality rates demonstrated here, despite accounting for volume of work. Providing evidence of variability in Failure to Rescue through population level data is likely to be vital for the justification of increased expenditure on critical care facilities within England/ the United Kingdom. It will only be through showing how lack of these facilities affects outcomes (particularly in colorectal cancer), that we will be able to drive forward such changes.

In isolation however, ICU bed numbers and failure to rescue rates do not explain England's on-going poor record in relation to CRC outcomes. Yet, when combined with an ageing population, who often present late (and in an acute fashion), a picture begins to emerge of why England has failed to 'catch up' with similar income level countries. Certainly, the results of this study confirm that risk factors for emergency admission remain the same (old age, female sex, increased co-morbidity and socio-economic deprivation) as do risk factors for mortality post-surgery. There is also variation in hospital performance and again, this is displayed in our results[58,63,104,209]. Therefore, to improve outcomes, particular attention should be paid to the on-going efforts aimed at earlier diagnosis, the lack of critical care beds and the management of patients with serious complications. Failure to rescue would seem to be one of the key challenges facing clinicians who must manage an increasingly elderly and frail population with CRC. Improving English colorectal cancer outcomes will require a multi-faceted approach that targets problems within primary and secondary care and even at a societal level (e.g. how much we as a society choose to spend on health).

How the English surgical community responds to variation in outcomes will also be of great importance in the drive to improve standards of care and outcome (in particular in relation to 'outlying' hospital trusts). Whilst attempts should be made to reduce variation in practice, this should not be done on the basis that poor outcomes are always related to poor individual clinical care, with no effort made to look at systemic failings or the context in which that care is

provided. Initiatives such as the reporting of individual surgeon outcomes may be well intentioned, but provide no information as to the influence of the nature of the population that surgeon serves, the effect of chance or the influence of the practices of the multitude of other health care professionals involved in a patients care, all of whom are necessary for safe surgical practice. It is easy to blame the captain for the sinking of the Titanic, in his haste to reach New York. Yet there is evidence that the poor quality of the rivets used in the construction of the Titanic may have caused the hull to fail, following a comparatively low energy impact with the iceberg (the poor quality rivets were used by Harland and Wolff because of pressure to finish the Titanic quickly)[212].

Surgeons and hospital trusts should be supported to improve their outcomes through the dissemination of good practice that has been shown to be effective in their particular locality or region. Population level data and studies such as this have a key role to play in providing 'big picture' evidence of how outcomes are changing (and in relation to others) and illuminating issues smaller studies may miss. If overall screening take-up is 60% of those invited, if take-up is 90% in one area and only 30% in another, it is clear where efforts to improve take–up should be focused. Population level data may also be used to help change practice through the linking of data from comparable hospital trusts/ health systems, providing much clearer evidence of which interventions are likely to have the greatest impacts and where. Nevertheless, vigilance should be used to ensure that population level data is not abused to suit individual or political aims.

Whilst the findings of this study are similar of others in relation to English CRC outcomes (i.e. improving outcomes but still behind those of Europe, North America etc.), these results also continue to question whether English CRC results are being unfairly criticised. The previous criticisms of Autier and Boniol in relation to the poor quality of UK cancer registration relate to data from the early 1990's and have now been resolved[72]. England and the United Kingdom now enjoy some of the most complete and accurate cancer data registry in the world. Indeed it is perhaps unfair to compare English with European outcomes and even with those in parts of the United States, when it is well recognised that some countries (notably France, Germany, Spain and Italy) have poor and incomplete records; we are therefore not comparing 'apples with apples'[213]. Further, by the nature of population level data and cancer registration, analysis must always be historical rather than contemporaneous. Huge effort went into (and continues to go into) improving cancer outcomes in England and the United Kingdom over the period covered by this study (Calman-Hine report, NHS Cancer Plan, Cancer Reform

Strategy). It is likely that only now are we truly beginning to see the effects of these endeavours 'feeding through' in the improved outcomes seen in reports such as EUROCARE-5[214].

The EUROCARE-5 report is not without its problems however. Of the 29 countries who participated, 21 had 100% cancer registration, but 8 did not[215]. There remain issues regarding the lack of sociodemographic information, investigations patients underwent to confirm their diagnosis and staging, the treatments administered, disease recurrence and the second line treatments used[215]. Stating that England has poor outcomes when a comparison is made to countries with incomplete data is demonstrably unfair. It is a rare occurrence indeed, when positive outcome data is not included in any data submission.

Furthermore, EUROCARE-5 covers a period of upheaval in the European population. Over recent years, there has been significant migration both within and into Europe. If a patient is diagnosed in their country of work but returns to their country of origin to die, this artificially inflates the survival rate of the country of work and decreases that of the country of origin. Again it will only be through use of population level data that we are able to keep track of these changes (and account for them)[215]. Finally, England remains a country of huge income inequality. Households in the top 10% of income have a disposable income that is almost 9 times that of the bottom 10%[216]. If a population is unhealthy and therefore not fit for curative treatment, then no amount of enhanced cancer services will improve outcomes.

Improving cancer outcomes is not only about the proportion of individuals who can undergo and survive major resection of course. No matter what systems are in place, there will always be a certain number of patients who present late with incurable disease, or suffer disease recurrence. How these individuals are managed is equally important to those who undergo a major resection. In this study, the use of endoluminal stents as a bridge to surgery was evaluated. It is clear that there has been an enormous increase in their use since their introduction by Dohomoto in 1991. The results presented here would also appear to concur with the results of the CREST and ESCO trials in that their use as a bridge to surgery (in the relief of an obstructing tumour) appears to offer a higher likelihood of primary anastomosis at time of major resection[185,189]. What neither CREST nor ESCO, nor our study here (although this, or similar datasets would be most appropriate to answer this question) have adequately evaluated is the effect on longer-term survival of endoluminal stent use. In the immediate

term, stents offer obvious advantages to the patient in relief of the obstruction and the opportunity for optimisation prior to surgery. The effect on long-term survival of those unfortunate enough to suffer a stent related perforation remains to be seen. Some authors have reported no effect on long-term survival with stent related perforations (Verstockt et al., Ribeiro et al.) whilst others have reported 5-year survival rates of 61% in those without a stent related perforation and 37% in those with (Avlund et al.)[191,217,218].

Endoluminal stents were introduced into clinical practice over the duration of this study and whilst this study has focused on the changing outcomes of those patients suitable for major resection, evaluation of the treatments offered to those not suitable for surgery must occur in order to complete the picture. Endoluminal stents represent just one part of a changing field of non-surgical treatments (e.g. chemotherapy, radiotherapy, chemoembolization, radiofrequency ablation), the outcomes of which must be collated, evaluated and their use tailored to patient need, once again a role to which population level data is highly suited.

Our study, like all population-based studies suffers from its analysis of historical data and of a necessarily limited scope (those undergoing major resection). It is also limited by the issues affecting other databases raised here (accuracy and completeness of recording) and by lack of confounding information, e.g. sociodemographic effects have only been taken into limited account but their effect may be much greater than that demonstrated here. It does however evaluate a complete population over time and as such provides an excellent ‘snapshot’ of the changing face of English colorectal cancer outcomes. It avoids problems such as selection bias associated with smaller studies and demonstrates how interventions such as the NHS Cancer Plan and the introduction of screening for colorectal cancer are beginning to make a tangible difference to outcomes. There will be no magic bullet for English colorectal cancer outcomes, but population level databases have a great deal to contribute and an on-going role to play in the analysis of outcomes and evaluation of the progress being made.

Analysis of population level datasets may allow comparisons of survival of matched patients offered different treatment modalities (including non-operative treatments) to be made. These outcomes could then be linked to quality of life scores and other qualitative measures of cancer treatment (beyond current Patient Reported Outcome Measures). In time therefore, a patient may be offered a suite of potential treatment options from which they are able to choose those that best suit their own needs; after all there is little point chasing quantity of life

if there is no quality of life. The linking of outcome data to demographic data may reveal treatments best suited to different population groups and may support or refute variations in clinical practice depending on the population served. In short, population datasets present challenges, not least through their size and the ethical ownership and management of that data, but their potential to answer questions not previously thought possible is unrivalled.

13. Conclusions

Without doubt, colorectal cancer outcomes in England are improving. Numbers of patients admitted as an emergency are falling and for those suitable for major resection, mortality is decreasing. Systems are now in place to improve rates of early diagnosis through patient education and nationwide screening programs. There is also an increasing realisation of the role of perioperative care through use of pre-assessment and enhanced recovery protocols.

Significant challenges remain however. As early diagnosis is the key to successful treatment in colorectal cancer, on-going efforts must be made to identify patients in the initial stages of their disease. Further, the systems must be in place to offer those patients prompt and individually tailored treatments; current systems such as the two-week wait and 31/62 day targets may not be the best method of driving standards and should continue to be challenged.

Major resectional surgery for colorectal cancer represents a huge physiological insult to a patient, no matter what age they are. In a disease where the majority of patients are elderly, often with co-morbidities, patients must be optimised for surgery as much as possible beforehand, but there must also be adequate facilities to care for them thereafter. There seems little point investing in earlier diagnosis if we are then unable to perform a safe operation from which the patient has the best possible chance of surviving. The variability in failure to rescue must be addressed not only through increased provision of critical care beds and the dissemination of good practice but also through initiatives which have already begun such as the perioperative care physician and Care of the Elderly physicians reviewing post-operative colorectal cancer patients.

Care for those who are unsuitable for surgical intervention must also be reviewed in the same light as those for whom surgery is an option. Their treatment must be optimised and novel technologies such as endoluminal stents have a role to play in avoidance of operative procedures (e.g. defunctioning stoma) and in providing the patient with the greatest quality of life for as long as possible. Our efforts to improve outcomes must not solely focus on surgery.

Out with the surgical sphere of influence, there remains huge variability in income distribution and access to healthcare in England. There will always be variability in income, but there is no reason in a nationalised health service that there should be variability in access to healthcare. Further efforts need to be made to address these shortcomings, alongside efforts to improve healthy living standards. Outcomes cannot improve if the population itself is not well enough to undergo the treatment.

At present, we have achieved only a ‘frame shift’ in English colorectal cancer outcomes. Our outcomes have improved and it is questionable whether previously reported poor outcomes are indeed a true reflection, but so have everyone else’s. In order for us to ‘catch up’ improvements must be made in three domains: access to healthcare and improved public health, early diagnosis through education and screening and access to optimal treatments and post-operative care, in particular focusing on the needs of an increasingly frail and elderly population. Population level data has a key role to play in documenting changing outcomes but also in identify where effort and resources may best be allocated. Much work has been done to improve English colorectal cancer care, but there remains much work to do.

14. References

1. Coleman MP, Allemani C. Cancer: the elephant in the room. The Lancet. 2015 Mar;385(9973):1047–8.

2. Bowel cancer incidence statistics : Cancer Research UK [Internet]. [cited 2013 Aug 13]. Available from: http://www.cancerresearchuk.org/cancer-info/cancerstats/types/bowel/incidence/#prevalence

3. National Institute for Health and Care Excellence. Colorectal cancer Guidance CG131 [Internet]. [cited 2013 Jul 12]. Available from: http://publications.nice.org.uk/colorectal-cancer-cg131/guidance

4. Bowel cancer incidence statistics : Cancer Research UK [Internet]. [cited 2013 Feb 5]. Available from: http://www.cancerresearchuk.org/cancer-info/cancerstats/types/bowel/incidence/uk-bowel-cancer-incidence-statistics#source1

5. Whynes D., Frew E., Manghan C., Scholefield J., Hardcastle J. Colorectal cancer, screening and survival: the influence of socio-economic deprivation. Public Health. 2003 Nov;117(6):389–95.

6. Harris AR, Bowley DM, Stannard A, Kurrimboccus S, Geh JI, Karandikar S. Socioeconomic deprivation adversely affects survival of patients with rectal cancer. Br J Surg. 2009 Jul 1;96(7):763–8.

7. Møller H, Sandin F, Robinson D, Bray F, Klint Å, Linklater KM, et al. Colorectal cancer survival in socioeconomic groups in England: Variation is mainly in the short term after diagnosis. Eur J Cancer. 2012 Jan;48(1):46–53.

8. Dennis R, Tou S, Miller R. Colorectal cancer: prevention and early diagnosis. Gastroenterol Part 4 4. 2011 May;39(5):243–9.

9. Ponz de Leon M, Benatti P, Borghi F, Pedroni M, Scarselli A, Di Gregorio C, et al. Aetiology of colorectal cancer and relevance of monogenic inheritance. Gut. 2004 Jan 1;53(1):115–22.

10. Giovannucci E. Modifiable risk factors for colon cancer. Gastroenterol Clin North Am. 2002 Dec;31(4):925–43.

11. Winawer SJ. Natural history of colorectal cancer. Am J Med. 1999 Jan;106(1):3–6.

12. Arnold M, Karim-Kos HE, Coebergh JW, Byrnes G, Antilla A, Ferlay J, et al. Recent trends in incidence of five common cancers in 26 European countries since 1988: Analysis of the European Cancer Observatory. Eur J Cancer [Internet]. 2013 Oct [cited 2014 Feb 10]; Available from: http://linkinghub.elsevier.com/retrieve/pii/S0959804913008423

13. Iwama T. NSAIDs and colorectal cancer prevention. J Gastroenterol. 2009 Jan 16;44(S19):72–6.

14. Nan H, Hutter CM, Lin Y, Jacobs EJ, Ulrich CM, White E, et al. Association of Aspirin and NSAID Use With Risk of Colorectal Cancer According to Genetic Variants. JAMA. 2015 Mar 17;313(11):1133.

15. Fodde R. The APC gene in colorectal cancer. Eur J Cancer. 2002 May;38(7):867–71.

16. Jager AC, Rasmussen M, Bisgaard HC, Singh KK, Nielsen FC, Rasmussen LJ. HNPCC mutations in the human DNA mismatch repair gene hMLH1 influence assembly of hMutLalpha and hMLH1-hEXO1 complexes. Oncogene. 20(27):3590–5.

17. Munkholm P. Review article: the incidence and prevalence of colorectal cancer in inflammatory bowel disease. Aliment Pharmacol Ther. 2003 Sep 1;18:1–5.

18. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, et al. Cancer Statistics, 2008. CA Cancer J Clin. 2008 Jan 28;58(2):71–96.

19. Larsson SC, Orsini N, Wolk A. Diabetes Mellitus and Risk of Colorectal Cancer: A Meta-Analysis. J Natl Cancer Inst. 16;97(22):1679–87.

20. Bingham SA, Day NE, Luben R, Ferrari P, Slimani N, Norat T, et al. Dietary fibre in food and protection against colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC): an observational study. The Lancet. 2003 May 3;361(9368):1496–501.

21. Marchand LL, Wilkens LR, Kolonel LN, Hankin JH, Lyu L-C. Associations of Sedentary Lifestyle, Obesity, Smoking, Alcohol Use, and Diabetes with the Risk of Colorectal Cancer. Cancer Res. 1997 Nov 1;57(21):4787–94.

22. American Joint Committee on Cancer Colon and Rectum Cancer Staging 7th Edition [Internet]. Available from: http://www.cancerstaging.org/staging/posters/colon8.5x11.pdf

23. Dukes CE. The classification of cancer of the rectum. J Pathol Bacteriol. 1932;35(3):323–32.

24. ASTLER VB, COLLER FA. The prognostic significance of direct extension of carcinoma of the colon and rectum. Ann Surg. 1954 Jun;139(6):846–52.

25. Colon Cancer Treatment (PDQ®) - National Cancer Institute [Internet]. [cited 2014 Feb 13]. Available from: http://www.cancer.gov/cancertopics/pdq/treatment/colon/HealthProfessional/Page3#Section_331

26. Astin M, Griffin T, Neal RD, Rose P, Hamilton W. The diagnostic value of symptoms for colorectal cancer in primary care: a systematic review. Br J Gen Pract. 2011 May 1;61(586):e231–43.

27. Scott N, Hill J, Smith J. National Bowel Cancer Audit Annual Report 2013 [Internet]. Health and Social Care Information Centre; 2013 [cited 2013 May 7]. Available from: http://www.hscic.gov.uk/searchcatalogue?productid=11877&q=title%3a%22bowel+cancer%22&sort=Relevance&size=10&page=1#top

28. Guideline 126: Diagnosis and management of colorectal cancer [Internet]. [cited 2014 Dec 19]. Available from: http://www.sign.ac.uk/guidelines/fulltext/126/

29. Guidelines for the Management of Colorectal Cancer - The Association of Coloproctology of Great Britain and Ireland | The Association of Coloproctology of Great Britain and Ireland [Internet]. [cited 2014 Dec 19]. Available from: http://www.acpgbi.org.uk/resources/guidelines/guidelines-for-the-management-of-colorectal-cancer/

30. Williams NS, Dixon MF, Johnston D. Reappraisal of the 5 centimetre rule of distal excision for carcinoma of the rectum: A study of distal intramural spread and of patients' survival. Br J Surg. 1983 Mar;70(3):150–4.

31. Ludwig KA. Sphincter-Sparing Resection for Rectal Cancer. Clin Colon Rectal Surg. 2007 Aug;20(3):203–12.

32. Law WL, Chu KW. Anterior Resection for Rectal Cancer With Mesorectal Excision: A Prospective Evaluation of 622 Patients. Ann Surg. 2004 Aug;240(2):260–8.

33. Heald RJ, Moran BJ, Ryall RD, Sexton R, MacFarlane JK. Rectal cancer: the Basingstoke experience of total mesorectal excision, 1978-1997. Arch Surg Chic Ill 1960. 1998 Aug;133(8):894–9.

34. Enker WE, Thaler HT, Cranor ML, Polyak T. Total mesorectal excision in the operative treatment of carcinoma of the rectum. J Am Coll Surg. 1995 Oct;181(4):335–46.

35. Heald RJ. Total mesorectal excision is optimal surgery for rectal cancer: A Scandinavian consensus. Br J Surg. 1995 Oct;82(10):1297–9.

36. Surgery for bowel cancer- Cancer Council SA Information Portal [Internet]. [cited 2014 Dec 19]. Available from: http://www.cancersa.org.au/information/a-z-index/surgery-for-bowel-cancer#Surgery%20for%20rectal%20and%20anal%20cancers

37. Figueredo A, Rumble RB, Maroun J, Earle CC, Cummings B, McLeod R, et al. Follow-up of patients with curatively resected colorectal cancer: a practice guideline. BMC Cancer. 2003 Oct 6;3:26.

38. Colorectal Cancer Collaborative Group. Palliative chemotherapy for advanced colorectal cancer: systematic review and meta-analysis. BMJ. 2000 Sep 2;321(7260):531–5.

39. Colorectal cancer | about-this-guideline | Guidance and guidelines | NICE [Internet]. [cited 2015 Jan 11]. Available from: https://www.nice.org.uk/guidance/cg131/chapter/about-this-guideline

40. Bowel cancer statistics : Cancer Research UK [Internet]. [cited 2013 Jul 3]. Available from: http://www.cancerresearchuk.org/cancer-info/cancerstats/types/bowel/

41. Cancer survival statistics for common cancers : Cancer Research UK [Internet]. [cited 2013 Jul 3]. Available from: http://www.cancerresearchuk.org/cancer-info/cancerstats/survival/common-cancers/#source1

42. Munro AJ. Comparative cancer survival in European countries. Br Med Bull. 2014 Jun 1;110(1):5–22.

43. National bowel cancer audit programme (NBOCAP) [Internet]. [cited 2014 Apr 24]. Available from: http://www.hqip.org.uk/national-bowel-cancer-audit-programme-nbocap/

44. Worldwide cancer incidence statistics : Cancer Research UK [Internet]. [cited 2014 Dec 29]. Available from: http://www.cancerresearchuk.org/cancer-info/cancerstats/world/incidence/

45. Jemal A, Center MM, DeSantis C, Ward EM. Global Patterns of Cancer Incidence and Mortality Rates and Trends. Cancer Epidemiol Biomarkers Prev. 2010 Aug 1;19(8):1893–907.

46. Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang X-S, et al. Global surveillance of cancer survival 1995–2009: analysis of individual data for 25 676 887 patients from 279 population-based registries in 67 countries (CONCORD-2). The Lancet. 385(9972):977–1010.

47. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon Fr Int Agency Res Cancer [Internet]. 2013 [cited 2014 Dec 30]; Available from: Available from: http://globocan.iarc.fr

48. Gatta G, Capocaccia R, Coleman MP, Gloeckler Ries LA, Hakulinen T, Micheli A, et al. Toward a comparison of survival in American and European cancer patients. Cancer. 2000 Aug 15;89(4):893–900.

49. Cutler SJ, editor. International symposium on end result of cancer therapy National Cancer Institute Monograph No. 15. Bethesda, MD. Government Printing Office; 1964.

50. Berrino F, Sant M, Verdecchia V, Capocaccia R, Hakulinen T, Estéve J. Survival of cancer patients in Europe: the EUROCARE Study. ARC Sci Publ. 1995;132.

51. Sant M, Capocaccia R, Verdecchia A, Gatta G, Micheli A, Mariotto A, et al. Comparisons of colon–cancer survival among european countries: The eurocare study. Int J Cancer. 1995 Sep 27;63(1):43–8.

52. Berrino F, Gatta G, Chessa E, Valente F, Capocaccia R. The EUROCARE II study. Eur J Cancer. 34(14):2139–53.

53. Gatta G, Faivre J, Capocaccia R, Ponz de Leon M. Survival of colorectal cancer patients in Europe during the period 1978–1989. Eur J Cancer. 1998 Dec;34(14):2176–83.

54. Gatta G. Understanding variations in survival for colorectal cancer in Europe: a EUROCARE high resolution study. Gut. 2000 Oct 1;47(4):533–8.

55. Sant M, Aareleid T, Berrino F, Bielska Lasota M, Carli PM, Faivre J, et al. EUROCARE-3: survival of cancer patients diagnosed 1990–94—results and commentary. Ann Oncol. 2003 Dec 1;14(suppl 5):v61–118.

56. Berrino F, De Angelis R, Sant M, Rosso S, Lasota MB, Coebergh JW, et al. Survival for eight major cancers and all cancers combined for European adults diagnosed in 1995–99: results of the EUROCARE-4 study. Lancet Oncol. 2007 Sep;8(9):773–83.

57. De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, et al. Cancer survival in Europe 1999–2007 by country and age: results of EUROCARE-5—a population-based study. Lancet Oncol. 2014 Jan;15(1):23–34.

58. Dejardin O, Rachet B, Morris E, Bouvier V, Jooste V, Haynes R, et al. Management of colorectal cancer explains differences in 1-year relative survival between France and England for patients diagnosed 1997-2004. Br J Cancer [Internet]. 2013 Feb 7; Available from: http://dx.doi.org/10.1038/bjc.2013.33

59. Engholm G, Kejs AMT, Brewster DH, Gaard M, Holmberg L, Hartley R, et al. Colorectal cancer survival in the Nordic countries and the United Kingdom: excess mortality risk analysis of 5 year relative period survival in the period 1999 to 2000. Int J Cancer J Int Cancer. 2007 Sep 1;121(5):1115–22.

60. Morris EJA, Sandin F, Lambert PC, Bray F, Klint A, Linklater K, et al. A population-based comparison of the survival of patients with colorectal cancer in England, Norway and Sweden between 1996 and 2004. Gut. 2011 Feb 8;60(8):1087–93.

61. Iversen LH, Pedersen L, Riis A, Friis S, Laurberg S, Sørensen HT. Age and Colorectal Cancer With Focus on the Elderly: Trends in Relative Survival and Initial Treatment From a Danish Population-Based Study. Dis Colon Rectum. 2005 Sep 1;48(9):1755–63.

62. Downing A, Aravani A, Macleod U, Oliver S, Finan PJ, Thomas JD, et al. Early mortality from colorectal cancer in England: a retrospective observational study of the factors associated with death in the first year after diagnosis. Br J Cancer. 2013 Feb 19;108(3):681–5.

63. Morris EJA, Taylor EF, Thomas JD, Quirke P, Finan PJ, Coleman MP, et al. Thirty-day postoperative mortality after colorectal cancer surgery in England. Gut. 2011 Apr 12;60(6):806–13.

64. Osler M, Iversen LH, Borglykke A, Mårtensson S, Daugbjerg S, Harling H, et al. Hospital Variation in 30-Day Mortality After Colorectal Cancer Surgery in Denmark. Ann Surg. 2011 Apr;253(4):733–8.

65. McPhail S, Elliss-Brookes L, Shelton J, Ives A, Greenslade M, Vernon S, et al. Emergency presentation of cancer and short-term mortality. Br J Cancer. 2013 Sep 17;109(8):2027–34.

66. Coleman MP, Quaresma M, Berrino F, Lutz J-M, De Angelis R, Capocaccia R, et al. Cancer survival in five continents: a worldwide population-based study (CONCORD). Lancet Oncol. 2008 Aug;9(8):730–56.

67. Allemani C, Rachet B, Weir HK, Richardson LC, Lepage C, Faivre J, et al. Colorectal cancer survival in the USA and Europe: a CONCORD high-resolution study. BMJ Open. 2013 Sep 10;3(9):e003055–e003055.

68. Yu XQ, O'Connell DL, Forman D. Comparison of cancer survival in UK and Australia: rates are higher in Australia for three major sites. Br J Cancer. 2004 Nov 1;91(9):1663–5.

69. Cookson JB. Cancer Survival. The Lancet. 2000;356(4):1611.

70. Woodman CBJ, Gibbs A, Scott N, Haboubi NY, Collins S. Are differences in stage at presentation a credible explanation for reported differences in the survival of patients with colorectal cancer in Europe? Br J Cancer. 2001 Jun 1;85(6):787–90.

71. Maringe C, Walters S, Rachet B, Butler J, Fields T, Finan P, et al. Stage at diagnosis and colorectal cancer survival in six high-income countries: a population-based study of patients diagnosed during 2000-2007. Acta Oncol Stockh Swed. 2013 Jun;52(5):919–32.

72. Autier, Philippe, Boniol, Mathieu. Caution needed for country-specifi c cancer survival. The Lancet. 2008 Jan 8;377:100–1.

73. Beral V, Peto R. UK cancer survival statistics. BMJ. 2010 Aug 11;341(aug11 1):c4112–c4112.

74. McPherson K, Brown M. UK cancer survival statistics. BMJ. 2010;341:4112.

75. Scott NA, Jeacock J, Kingston RD. Risk factors in patients presenting as an emergency with colorectal cancer. Br J Surg. 1995 Mar;82(3):321–3.

76. Amri R, Bordeianou LG, Sylla P, Berger DL. Colon cancer surgery following emergency presentation: effects on admission and stage-adjusted outcomes. Am J Surg. 2015 Feb;209(2):246–53.

77. Black RJ, Bray F, Ferlay J, Parkin DM. Cancer incidence and mortality in the European Union: Cancer registry data and estimates of national incidence for 1990. Eur J Cancer. 1997 Jun;33(7):1075–107.

78. Stower MJ, Hardcastle JD. The results of 1115 patients with colorectal cancer treated over an 8-year period in a single hospital. Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol. 1985 Jun;11(2):119–23.

79. Umpleby HC, Bristol JB, Rainey JB, Williamson RC. Survival of 727 patients with single carcinomas of the large bowel. Dis Colon Rectum. 1984 Dec;27(12):803–10.

80. Mitchell E, Macdonald S, Campbell NC, Weller D, Macleod U. Influences on pre-hospital delay in the diagnosis of colorectal cancer: a systematic review. Br J Cancer. 2007 Dec 4;98(1):60–70.

81. Rubin G, McPhail S, Elliott K. National Audit of Cancer Diagnosis in Primary Care. Royal College of General Practitioners: London, England; 2011.

82. Hamilton W, Lancashire R, Sharp D, Peters TJ, Cheng K, Marshall T. The risk of colorectal cancer with symptoms at different ages and between the sexes: a case-control study. BMC Med. 2009;7(1):17.

83. Pescatori M, Maria G, Beltrani B, Mattana C. Site, emergency, and duration of symptoms in the prognosis of colorectal cancer. Dis Colon Rectum. 1982 Jan 1;25(1):33–40.

84. Jullumstrø E, Lydersen S, Møller B, Dahl O, Edna T-H. Duration of symptoms, stage at diagnosis and relative survival in colon and rectal cancer. Eur J Cancer. 2009 Sep;45(13):2383–90.

85. Mulcahy HE, O'Donoghue DP. Duration of colorectal cancer symptoms and survival: the effect of confounding clinical and pathological variables. Eur J Cancer. 1997 Aug;33(9):1461–7.

86. Hamilton W, Coleman MG, Rubin G. Colorectal cancer. BMJ. 2013 May 21;346(may20 7):f3172–f3172.

87. Wallace D, Walker K, Kuryba A, Finan P, Scott N, van der Meulen J. Identifying patients at risk of emergency admission for colorectal cancer. Br J Cancer [Internet]. 2014 Jun 12; Available from: http://dx.doi.org/10.1038/bjc.2014.300

88. Rabeneck L, Paszat LF, Li C. Risk Factors for Obstruction, Perforation, or Emergency Admission at Presentation in Patients with Colorectal Cancer: A Population-Based Study. Am J Gastroenterol. 2006 May;101(5):1098–103.

89. Cleary J, Peters TJ, Sharp D, Hamilton W. Clinical features of colorectal cancer before emergency presentation: a population-based case-control study. Fam Pract. 2006 Oct 18;24(1):3–6.

90. Stapley S, Peters TJ, Sharp D, Hamilton W. The mortality of colorectal cancer in relation to the initial symptom at presentation to primary care and to the duration of symptoms: a cohort study using medical records. Br J Cancer. 2006 Sep 21;95(10):1321–5.

91. Gunnarsson H, Holm T, Ekholm A, Olsson LI. Emergency presentation of colon cancer is most frequent during summer: Emergency presentation of colon cancer. Colorectal Dis. 2011 Jun;13(6):663–8.

92. Elliss-Brookes L, McPhail S, Ives A, Greenslade M, Shelton J, Hiom S, et al. Routes to diagnosis for cancer – determining the patient journey using multiple routine data sets. Br J Cancer. 2012 Sep 20;107(8):1220–6.

93. Jones R. Is the two week rule for cancer referrals working? BMJ. 2001 Jun 30;322(7302):1555–6.

94. Kiran PR, Glass RE. Duration of symptoms and spread of colorectal cancer: a short history does not mean early disease. Ann R Coll Surg Engl. 2002 Nov;84(6):381–5.

95. Holliday H, Hardcastle J. Delay in Diagnosis and Treatment of Symptomatic Colorectal Cancer. The Lancet. 1979 Feb 10;313(8111):309–11.

96. Lyratzopoulos G, Neal RD, Barbiere JM, Rubin GP, Abel GA. Variation in number of general practitioner consultations before hospital referral for cancer: findings from the 2010 National Cancer Patient Experience Survey in England. Lancet Oncol. 2012 Apr;13(4):353–65.

97. Olsson L, Bergkvist L, Ekbom A. Symptom duration versus survival in non-emergency colorectal cancer. Scand J Gastroenterol. 2004 Mar;39(3):252–8.

98. Hargarten SW, Roberts MJS, Anderson AJ. Cancer presentation in the emergency department: A failure of primary care. Am J Emerg Med. 1992 Jul;10(4):290–3.

99. Center MM, Jemal A, Smith RA, Ward E. Worldwide Variations in Colorectal Cancer. CA Cancer J Clin. 2009 Nov 1;59(6):366–78.

100. Coleman M, Forman D, Bryant H, Butler J, Rachet B, Maringe C, et al. Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995–2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data. The Lancet. 2011 Jan;377(9760):127–38.

101. Warwick J, Will O, Allgood P, Miller R, Duffy S, Greenberg D. Variation in colorectal cancer treatment and survival: a cohort study covering the East Anglia region. Colorectal Dis. 2013 Oct;15(10):1243–52.

102. Henneman D, Snijders HS, Fiocco M, Leersum NJ, Kolfschoten NE, Wiggers T, et al. Hospital Variation in Failure to Rescue after Colorectal Cancer Surgery: Results of the Dutch Surgical Colorectal Audit. Ann Surg Oncol. 2013 Feb 16;20(7):2117–23.

103. Adhikari NK, Fowler RA, Bhagwanjee S, Rubenfeld GD. Critical care and the global burden of critical illness in adults. The Lancet. 2010 Oct;376(9749):1339–46.

104. Almoudaris AM, Burns EM, Mamidanna R, Bottle A, Aylin P, Vincent C, et al. Value of failure to rescue as a marker of the standard of care following reoperation for complications after colorectal resection. Br J Surg. 2011 Dec;98(12):1775–83.

105. Haward RA. The Calman–Hine report: a personal retrospective on the UK's first comprehensive policy on cancer services. Lancet Oncol. 7(4):336–46.

106. [ARCHIVED CONTENT] A policy framework for commissioning cancer services : A report by the Expert Advisory Group on Cancer to the Chief Medical Officers of England

and Wales : Department of Health - Publications [Internet]. [cited 2015 Jan 10]. Available from: http://webarchive.nationalarchives.gov.uk/20080814090336/dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4071083

107. Morris E, Haward R, Gilthorpe M, Craigs C, Forman D. The impact of the Calman-Hine report on the processes and outcomes of care for Yorkshire's breast cancer patients. Ann Oncol [Internet]. 2007 Jan 1; Available from: http://annonc.oxfordjournals.org/content/early/2007/09/04/annonc.mdm432.abstract

108. Morris E, Haward RA, Gilthorpe MS, Craigs C, Forman D. The impact of the Calman-Hine report on the processes and outcomes of care for Yorkshire's colorectal cancer patients. Br J Cancer. 95(8):979–85.

109. PhD BKB, Chris Hawkins MA BA Grad Dip Phys MCSP SRP2, PhD EFB. Calman-Hine reassessed: a survey of cancer network development in England, 1999-2000. J Eval Clin Pract. 2002 Aug;8(3):303–11.

110. Munro AJ. The Calman–Hine report: its causes and consequences. Eur J Cancer Care (Engl). 2001;10(3):213–5.

111. The NHS Cancer Plan [Internet]. Department of Health; 2000. Available from: http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4014513.pdf

112. Rachet B, Maringe C, Nur U, Quaresma M, Shah A, Woods LM, et al. Population-based cancer survival trends in England and Wales up to 2007: an assessment of the NHS cancer plan for England. Lancet Oncol. 10(4):351–69.

113. Raptis DA, Fessas C, Belasyse-Smith P, Kurzawinski TR. Clinical presentation and waiting time targets do not affect prognosis in patients with pancreatic cancer. The Surgeon. 8(5):239–46.

114. Raje D, Touche S, Mukhtar H, Oshowo A, Ingham Clark C. Changing trends in the management of colorectal cancers and its impact on cancer waiting times. Colorectal Dis. 2006 Feb;8(2):140–4.

115. Currie AC, Evans J, Smith NJ, Brown G, Abulafi AM, Swift RI. The impact of the two-week wait referral pathway on rectal cancer survival: Two-week wait impact in rectal cancer. Colorectal Dis. 2012 Jul;14(7):848–53.

116. Leung E, Grainger J, Bandla N, Wong L. The effectiveness of the '2-week wait' referral service for colorectal cancer: Effectiveness of 2-week wait service. Int J Clin Pract. 2010 Nov;64(12):1671–4.

117. Debnath D. Guidelines, compliance, and effectiveness: a 12 months' audit in an acute district general healthcare trust on the two week rule for suspected colorectal cancer. Postgrad Med J. 2002 Dec 1;78(926):748–51.

118. Chohan DPK, Goodwin K, Wilkinson S, Miller R, Hall NR. How has the 'two-week wait' rule affected the presentation of colorectal cancer? Colorectal Dis. 2005 Sep;7(5):450–3.

119. Trickett JP, Donaldson DR, Bearn PE, Scott HJ, Hassall AC. A study on the routes of referral for patients with colorectal cancer and its affect on the time to surgery and pathological stage. Colorectal Dis. 2004 Nov;6(6):428–31.

120. Flashman K. The Department of Health's 'two week standard' for bowel cancer: is it working? Gut. 2004 Mar 1;53(3):387–91.

121. [ARCHIVED CONTENT] The NHS Cancer plan: a plan for investment, a plan for reform : Department of Health - Publications [Internet]. [cited 2015 Jan 11]. Available from: http://webarchive.nationalarchives.gov.uk/+/www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyandGuidance/DH_4009609

122. The national cancer strategy - Publications - GOV.UK [Internet]. [cited 2015 Jan 21]. Available from: https://www.gov.uk/government/publications/the-national-cancer-strategy

123. Garborg K, Holme O, Loberg M, Kalager M, Adami HO, Bretthauer M. Current status of screening for colorectal cancer. Ann Oncol. 2013 Apr 25;24(8):1963–72.

124. NHS Bowel Cancer Screening Programme (NHSBCSP) [Internet]. [cited 2013 Nov 14]. Available from: http://www.cancerscreening.nhs.uk/bowel/index.html

125. Logan RFA, Patnick J, Nickerson C, Coleman L, Rutter MD, von Wagner C, et al. Outcomes of the Bowel Cancer Screening Programme (BCSP) in England after the first 1 million tests. Gut. 2011 Dec 7;61(10):1439–46.

126. Goodyear SJ, Leung E, Menon A, Pedamallu S, Williams N, Wong LS. The effects of population-based faecal occult blood test screening upon emergency colorectal cancer admissions in Coventry and north Warwickshire. Gut. 2008 Feb 1;57(2):218–22.

127. Scholefield JH, Robinson MHE, Mangham CM, Hardcastle JD. Screening for colorectal cancer reduces emergency admissions. Eur J Surg Oncol EJSO. 1998 Feb;24(1):47–50.

128. National bowel cancer audit programme - Health Foundation [Internet]. [cited 2015 Jan 12]. Available from: http://www.health.org.uk/areas-of-work/programmes/engaging-with-quality/related-projects/national-bowel-cancer-audit-programme/

129. NCRAS for Analysts [Internet]. [cited 2018 Mar 30]. Available from: http://www.ncin.org.uk/about_ncin/audiences/analysts

130. WHO | International Classification of Diseases (ICD) [Internet]. [cited 2013 Aug 21]. Available from: http://www.who.int/classifications/icd/en/

131. Doran T, Drever F, Whitehead M. Is there a north-south divide in social class inequalities in health in Great Britain? Cross sectional study using data from the 2001 census. BMJ. 2004 Apr 29;328(7447):1043–5.

132. Hansen R, Olesen F, Sørensen H, Sokolowski I, Søndergaard J. Socioeconomic patient characteristics predict delay in cancer diagnosis: a Danish cohort study. BMC Health Serv Res. 2008;8(1):49.

133. Frederiksen BL, Osler M, Harling H, Ladelund S, Jørgensen T. The impact of socioeconomic factors on 30-day mortality following elective colorectal cancer surgery: A nationwide study. Eur J Cancer. 2009 May;45(7):1248–56.

134. Panis Y, Maggiori L, Caranhac G, Bretagnol F, Vicaut E. Mortality After Colorectal Cancer Surgery. Ann Surg. 2011 Nov;254(5):738–44.

135. Marcella S, Miller JE. Racial differences in colorectal cancer mortality. The importance of stage and socioeconomic status. J Clin Epidemiol. 2001 Apr;54(4):359–66.

136. McArdle CS, Hole DJ. Emergency presentation of colorectal cancer is associated with poor 5-year survival. Br J Surg. 2004 May;91(5):605–9.

137. Bass G, Fleming C, Conneely J, Martin Z, Mealy K. Emergency First Presentation of Colorectal Cancer Predicts Significantly Poorer Outcomes. Dis Colon Rectum. 2009 Apr;52(4):678–84.

138. Anderson JH, Hole D, McArdle CS. Elective versus emergency surgery for patients with colorectal cancer. Br J Surg. 1992;79(7):706–9.

139. Iversen LH, Ingeholm P, Gögenur I, Laurberg S. Major reduction in 30-day mortality after elective colorectal cancer surgery: a nationwide population-based study in Denmark 2001-2011. Ann Surg Oncol. 2014 Jul;21(7):2267–73.

140. Sterne JAC, Sutton AJ, Ioannidis JPA, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ. 2011 Jul 22;343(jul22 1):d4002–d4002.

141. Cuffy M, Abir F, Audisio RA, Longo WE. Colorectal cancer presenting as surgical emergencies. Surg Oncol. 2004 Aug;13(2–3):149–57.

142. Morris EJA, Sandin F, Lambert PC, Bray F, Klint A, Linklater K, et al. A population-based comparison of the survival of patients with colorectal cancer in England, Norway and Sweden between 1996 and 2004. Gut. 2011 Feb 8;60(8):1087–93.

143. Bailey CE, Hu C-Y, You YN, Bednarski BK, Rodriguez-Bigas MA, Skibber JM, et al. Increasing Disparities in the Age-Related Incidences of Colon and Rectal Cancers in the United States, 1975-2010. JAMA Surg. 2015 Jan 1;150(1):17.

144. Libby G, Brewster DH, Steele RJC. Impact of faecal occult blood test screening on emergency admissions and short-term outcomes for colorectal cancer: Faecal occult blood test screening for colorectal cancer. Br J Surg. 2014 Nov;101(12):1607–15.

145. Mayor S. Screening for bowel cancer halves numbers of emergency admissions and deaths. BMJ. 2007 Nov 29;335(7631):1177–1177.

146. Logan RFA, Patnick J, Nickerson C, Coleman L, Rutter MD, von Wagner C, et al. Outcomes of the Bowel Cancer Screening Programme (BCSP) in England after the first 1 million tests. Gut. 2012 Oct 1;61(10):1439–46.

147. Routes to diagnosis [Internet]. [cited 2018 Mar 30]. Available from: http://www.ncin.org.uk/publications/routes_to_diagnosis

148. Birkmeyer JD, Siewers AE, Finlayson EVA, Stukel TA, Lucas FL, Batista I, et al. Hospital Volume and Surgical Mortality in the United States. N Engl J Med. 2002 Apr 11;346(15):1128–37.

149. Borowski DW, Kelly SB, Bradburn DM, Wilson RG, Gunn A, Ratcliffe AA, et al. Impact of surgeon volume and specialization on short-term outcomes in colorectal cancer surgery. Br J Surg. 2007 Jul;94(7):880–9.

150. Faiz O, Brown T, Bottle A, Burns EM, Darzi AW, Aylin P. Impact of Hospital Institutional Volume on Postoperative Mortality After Major Emergency Colorectal Surgery in English National Health Service Trusts, 2001 to 2005. Dis Colon Rectum. 2010 Apr;53(4):393–401.

151. Bülow S, Harling H, Iversen LH, Ladelund S, on behalf of The Danish Colorectal Cancer Group. Improved survival after rectal cancer in Denmark. Colorectal Dis. 2010 Jul 1;12(7Online):e37–42.

152. Iversen LH, Pedersen L, Riis A, Friis S, Laurberg S, Sørensen HT. Population-based study of short- and long-term survival from colorectal cancer in Denmark, 1977–1999. Br J Surg. 2005 Jul 1;92(7):873–80.

153. Adamson J, Ben-Shlomo Y, Chaturvedi N, Donovan J. Ethnicity, socio-economic position and gender—do they affect reported health—care seeking behaviour? Soc Sci Med. 2003 Sep;57(5):895–904.

154. Richards MA. The size of the prize for earlier diagnosis of cancer in England. Br J Cancer. 2009 Dec 3;101(Suppl 2):S125–9.

155. Hole DJ, McArdle CS. Impact of socioeconomic deprivation on outcome after surgery for colorectal cancer. Br J Surg. 2002 May;89(5):586–90.

156. Ries LAG, Wingo PA, Miller DS, Howe HL, Weir HK, Rosenberg HM, et al. The annual report to the nation on the status of cancer, 1973–1997, with a special section on colorectal cancer. Cancer. 2000 May 15;88(10):2398–424.

157. Center MM, Jemal A, Ward E. International Trends in Colorectal Cancer Incidence Rates. Cancer Epidemiol Biomarkers Prev. 2009 Jun 8;18(6):1688–94.

158. Cancer Trends in England and Wales , 1950-1999, SMPS No. 66 - ONS [Internet]. [cited 2015 Sep 7]. Available from: http://www.ons.gov.uk/ons/rel/cancer-unit/cancer-trends-in-england-and-wales/smps-no--66/index.html

159. Moghadamyeghaneh Z, Alizadeh RF, Phelan M, Carmichael JC, Mills S, Pigazzi A, et al. Trends in Colorectal Cancer Admissions and Stage at Presentation-Impact of Screening. Surg Endosc. 2016 Aug;30(8):3604–10.

160. Center MM, Jemal A, Ward E. International Trends in Colorectal Cancer Incidence Rates. Cancer Epidemiol Biomark Amp Prev. 2009 Jun 1;18(6):1688.

161. Singh KE, Taylor TH, Pan C-JG, Stamos MJ, Zell JA. Colorectal Cancer Incidence Among Young Adults in California. J Adolesc Young Adult Oncol. 2014 Dec 1;3(4):176–84.

162. Austin H, Henley SJ, King J, Richardson LC, Eheman C. Changes in colorectal cancer incidence rates in young and older adults in the United States: what does it tell us about screening. Cancer Causes Control CCC. 2014 Feb;25(2):191–201.

163. Slattery ML. Physical activity and colorectal cancer. Sports Med Auckl NZ. 2004;34(4):239–52.

164. Demeyer D, Mertens B, De Smet S, Ulens M. Mechanisms Linking Colorectal Cancer to the Consumption of (Processed) Red Meat: A Review. Crit Rev Food Sci Nutr. 2016 Dec 9;56(16):2747–66.

165. Chohan DPK, Goodwin K, Wilkinson S, Miller R, Hall NR. How has the ‘two-week wait’ rule affected the presentation of colorectal cancer? Colorectal Dis. 2005 Sep;7(5):450–3.

166. Hanna SJ, Muneer A, Khalil KH. The 2-week wait for suspected cancer: time for a rethink? Int J Clin Pract. 2005 Nov 1;59(11):1334–9.

167. Leung E, Grainger J, Bandla N, Wong L. The effectiveness of the ‘2-week wait’ referral service for colorectal cancer: Effectiveness of 2-week wait service. Int J Clin Pract. 2010 Nov;64(12):1671–4.

168. Rai S, Kelly MJ. Prioritization of colorectal referrals: a review of the 2-week wait referral system. Colorectal Dis. 2007 Mar;9(3):195–202.

169. Zafar A, Mak T, Whinnie S, Chapman MAS. The 2-week wait referral system does not improve 5-year colorectal cancer survival. Colorectal Dis. 2012 Apr 1;14(4):e177–80.

170. Pignone M, Rich M, Teutsch SM, Berg AO, Lohr KN. Screening for Colorectal Cancer in Adults at Average Risk: A Summary of the Evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2002 Jul 16;137(2):132.

171. Jayne DG, Guillou PJ, Thorpe H, Quirke P, Copeland J, Smith AMH, et al. Randomized Trial of Laparoscopic-Assisted Resection of Colorectal Carcinoma: 3-Year Results of the UK MRC CLASICC Trial Group. J Clin Oncol. 2007 Jul 20;25(21):3061–8.

172. Bonjer HJ, Deijen CL, Abis GA, Cuesta MA, van der Pas MHGM, de Lange-de Klerk ESM, et al. A Randomized Trial of Laparoscopic versus Open Surgery for Rectal Cancer. N Engl J Med. 2015 Apr 2;372(14):1324–32.

173. sitecore\julie@redweb.com. Search [Internet]. Royal College of Surgeons. [cited 2018 Apr 2]. Available from: https://www.rcseng.ac.uk/search/

174. Office for National Statistics. Cancer Incidence and Mortality in the United Kingdom, 2008-10 [Internet]. [cited 2013 Feb 5]. Available from: http://www.ons.gov.uk/ons/dcp171778_289890.pdf

175. Finan PJ, smith, J, Scott, N. National Bowel Cancer Audit 2012 [Internet]. Association of Coloprotcology of Great Britain and Ireland; 2012. Available from: https://catalogue.ic.nhs.uk/publications/clinical/bowel/nati-clin-audi-supp-prog-bowe-canc-2012/nati-clin-audi-supp-prog-bowe-canc-2012-rep.pdf

176. Turner P, Burke D, Finan P. Non-Resectional Management of Colorectal Cancer: Factors that Influence Treatment Strategy. Colorectal Dis. 2013 Jun;n/a-n/a.

177. Álvarez J, Baldonedo RF, Bear IG, Truán N, Pire G, Álvarez P. Obstructing Colorectal Carcinoma: Outcome and Risk Factors for Morbidity and Mortality. Dig Surg. 2005;22(3):174–81.

178. Khot UP, Lang AW, Murali K, Parker MC. Systematic review of the efficacy and safety of colorectal stents. Br J Surg. 2002 Sep 1;89(9):1096–102.

179. Finan PJ, Campbell S, Verma R, MacFie J, Gatt M, Parker MC, et al. The Management of Malignant Large Bowel Obstruction: ACPGBI Position Statement. Colorectal Dis. 2007 Oct;9(s4):1–17.

180. Dohmoto M. Endoscopic implantation of rectal stent in palliative treatment of malignant stenosis. Endosc Dig. 1991;3:1507–12.

181. Khot UP, Lang AW, Murali K, Parker MC. Systematic review of the efficacy and safety of colorectal stents. Br J Surg. 2002 Sep;89(9):1096–102.

182. Kavanagh DO, Nolan B, Judge C, Hyland JMP, Mulcahy HE, O’Connell PR, et al. A Comparative Study of Short- and Medium-term Outcomes Comparing Emergent Surgery

and Stenting as a Bridge to Surgery in Patients With Acute Malignant Colonic Obstruction. Dis Colon Rectum [Internet]. 2013;56(4). Available from: http://journals.lww.com/dcrjournal/Fulltext/2013/04000/A_Comparative_Study_of_Short__and_Medium_term.6.aspx

183. van Hooft J, Fockens P, Marinelli A, Timmer R, van Berkel A, Bossuyt P, et al. Early closure of a multicenter randomized clinical trial of endoscopic stenting versus surgery for stage IV left-sided colorectal cancer. Endoscopy. 2008 Mar;40(3):184–91.

184. Pirlet IA, Slim K, Kwiatkowski F, Michot F, Millat BL. Emergency preoperative stenting versus surgery for acute left-sided malignant colonic obstruction: a multicenter randomized controlled trial. Surg Endosc. 2010 Dec 18;25(6):1814–21.

185. Hill J, Kay C, Morton D, Magill L, Handley K, Gray RG. CREST: Randomised phase III study of stenting as a bridge to surgery in obstructing colorectal cancer—Results of the UK ColoRectal Endoscopic Stenting Trial (CREST). J Clin Oncol. 2016 May 20;34(15_suppl):3507–3507.

186. NHS treated cancer patients receiving major surgical resections [Internet]. [cited 2013 Sep 19]. Available from: http://www.ncin.org.uk/publications/data_briefings/major_resection

187. Fiori E, Lamazza A, Schillaci A, Femia S, DeMasi E, DeCesare A, et al. Palliative management for patients with subacute obstruction and stage IV unresectable rectosigmoid cancer: colostomy versus endoscopic stenting: final results of a prospective randomized trial. Am J Surg. 204(3):321–6.

188. Fugazza A, Galtieri PA, Repici A. Using stents in the management of malignant bowel obstruction: the current situation and future progress. Expert Rev Gastroenterol Hepatol. 2017 Jul 3;11(7):633–41.

189. Arezzo A, Balague C, Targarona E, Borghi F, Giraudo G, Ghezzo L, et al. Colonic stenting as a bridge to surgery versus emergency surgery for malignant colonic obstruction: results of a multicentre randomised controlled trial (ESCO trial). Surg Endosc. 2017 Aug 1;31(8):3297–305.

190. Sloothaak DAM, van den Berg MW, Dijkgraaf MGW, Fockens P, Tanis PJ, van Hooft JE, et al. Oncological outcome of malignant colonic obstruction in the Dutch Stent-In 2 trial. Br J Surg. 2014 Dec;101(13):1751–7.

191. Avlund TH, Erichsen R, Ravn S, Ciplys Z, Andersen JC, Laurberg S, et al. The prognostic impact of bowel perforation following self-expanding metal stent as a bridge to surgery in colorectal cancer obstruction. Surg Endosc [Internet]. 2017 Jun 29; Available from: https://doi.org/10.1007/s00464-017-5680-0

192. Suárez J, Jimenez-Pérez J. Long-term outcomes after stenting as a ‘bridge to surgery’ for the management of acute obstruction secondary to colorectal cancer. World J Gastrointest Oncol. 2016 Jan 15;8(1):105–12.

193. Allievi N, Ceresoli M, Fugazzola P, Montori G, Coccolini F, Ansaloni L. Endoscopic Stenting as Bridge to Surgery versus Emergency Resection for Left-Sided Malignant Colorectal Obstruction: An Updated Meta-Analysis. Int J Surg Oncol. 2017;2017:1–11.

194. De Ceglie A, Filiberti R, Baron TH, Ceppi M, Conio M. A meta-analysis of endoscopic stenting as bridge to surgery versus emergency surgery for left-sided colorectal cancer obstruction. Crit Rev Oncol Hematol. 2013 Nov;88(2):387–403.

195. Pisani P, Parkin DM, Ferlay J. Estimates of the worldwide mortality from eighteen major cancers in 1985. Implications for prevention and projections of future burden. Int J Cancer. 1993 Dec 2;55(6):891–903.

196. Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of eighteen major cancers in 1985. Int J Cancer. 1993 Jun 19;54(4):594–606.

197. Ng O, Watts E, Bull C, Morris R, Acheson A, Banerjea A. Colorectal cancer outcomes in patients aged over 85 years. Ann R Coll Surg Engl. 2016 Mar;98(3):216–21.

198. Siegel RL, Miller KD, Jemal A. Colorectal Cancer Mortality Rates in Adults Aged 20 to 54 Years in the United States, 1970-2014. JAMA. 2017 Aug 8;318(6):572.

199. Overview of the UK population - Office for National Statistics [Internet]. [cited 2018 Jan 23]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/articles/overviewoftheukpopulation/july2017

200. Gross CP, McAvay GJ, Krumholz HM, Paltiel AD, Bhasin D, Tinetti ME. The Effect of Age and Chronic Illness on Life Expectancy after a Diagnosis of Colorectal Cancer: Implications for Screening. Ann Intern Med. 2006 Nov 7;145(9):646.

201. Askari A, Nachiappan S, Currie A, Bottle A, Athanasiou T, Abercrombie J, et al. PWE-261 Elderly, ethnic minorities and socially deprived patients at high risk of requiring emergency surgery for colorectal cancer. Gut. 2015 Jun 1;64(Suppl 1):A327.

202. Greenfield P. Andrew Lansley calls for better NHS screening after revealing bowel cancer [Internet]. the Guardian. 2018 [cited 2018 Apr 4]. Available from: http://www.theguardian.com/society/2018/apr/03/lord-lansley-calls-for-better-screening-after-revealing-cancer

203. Badshah N. Cuts meant my cancer was missed, says Andrew Lansley, Tory who pioneered screening. The Times [Internet]. 2018 Apr 3 [cited 2018 Apr 4]; Available from: https://www.thetimes.co.uk/article/cuts-meant-my-cancer-was-missed-says-andrew-lansley-the-tory-who-pioneered-screening-68wmbbgqv

204. Brandenbarg D, Groenhof F, Siewers IM, van der Voort A, Walter FM, Berendsen AJ. Possible missed opportunities for diagnosing colorectal cancer in Dutch primary care: a multimethods approach. Br J Gen Pract [Internet]. 2017 Dec 5; Available from: http://bjgp.org/content/early/2017/12/04/bjgp17X693905.abstract

205. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012: Global Cancer Statistics, 2012. CA Cancer J Clin. 2015 Mar;65(2):87–108.

206. Rutegård M, Haapamäki M, Matthiessen P, Rutegård J. Early postoperative mortality after surgery for rectal cancer in Sweden, 2000–2011. Colorectal Dis. 2014 Jun 1;16(6):426–32.

207. Andreoni B, Chiappa A, Bertani E, Bellomi M, Orecchia R, Zampino M, et al. Surgical outcomes for colon and rectal cancer over a decade: results from a consecutive monocentric experience in 902 unselected patients. World J Surg Oncol. 2007;5(1):73.

208. Vincent JL, Suter P, Bihari D, Braining H. Organization of intensive care units in Europe: lessons from the EPIC study. Intensive Care Med. 1997 Nov;23(11):1181–4.

209. Symons NRA, Moorthy K, Almoudaris AM, Bottle A, Aylin P, Vincent CA, et al. Mortality in high-risk emergency general surgical admissions. Br J Surg. 2013 Sep 1;100(10):1318–25.

210. International comparisons of selected service lines in seven health systems ANNEX 3 – REVIEW OF SERVICE LINES: CRITICAL CARE [Internet]. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/382845/Annex_3_Critical_Care1.pdf

211. Henneman D, van Leersum NJ, ten Berge M, Snijders HS, Fiocco M, Wiggers T, et al. Failure-to-Rescue After Colorectal Cancer Surgery and the Association with Three Structural Hospital Factors. Ann Surg Oncol. 2013 Oct;20(11):3370–6.

212. What really sank the Titanic? Available from: https://www.materialstoday.com/metals-alloys/news/what-really-sank-the-titanic/

213. Quinn MJ. Cancer Trends in the United States--A View From Europe. CancerSpectrum Knowl Environ. 2003 Sep 3;95(17):1258–61.

214. Holleczek B, Rossi S, Domenic A, Innos K, Minicozzi P, Francisci S, et al. On-going improvement and persistent differences in the survival for patients with colon and rectum cancer across Europe 1999–2007 – Results from the EUROCARE-5 study. Eur J Cancer. 2015 Oct;51(15):2158–68.

215. Munro AJ. Interpretation of EUROCARE-5. Lancet Oncol. 15(1):2–3.

216. The Scale of Economic Inequality in the UK | The Equality Trust [Internet]. [cited 2018 Jan 25]. Available from: https://www.equalitytrust.org.uk/scale-economic-inequality-uk

217. Verstockt B, Van Driessche A, De Man M, van der Spek P, Hendrickx K, Casneuf V, et al. Ten-year survival after endoscopic stent placement as a bridge to surgery in obstructing colon cancer. Gastrointest Endosc [Internet]. 2017 Jun [cited 2018 Jan 25]; Available from: http://linkinghub.elsevier.com/retrieve/pii/S0016510717319867

218. Ribeiro I, Pinho R, Leite M, Proença L, Silva J, Ponte A, et al. Reevaluation of Self-Expanding Metal Stents as a Bridge to Surgery for Acute Left-Sided Malignant Colonic Obstruction: Six Years Experience. GE Port J Gastroenterol. 2016 Mar;23(2):76–83.