A comparison of the management and outcomes of colorectal cancer in Denmark and the Yorkshire region of the United Kingdom

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Intellectual property and publications

I confirm that the work submitted is my own, except where work which has formed part of jointly authored publications has been included. My contribution and the other authors to this work has been explicitly indicated below. I confirm that appropriate credit has been given within the thesis where reference has been made to the work of others.

Publications

This thesis is submitted as an alternative style of doctoral thesis including published material. The reason for the use of an alternative style was because I sought from the outset to report my research as journal articles, to complement my position as epidemiologist at the University of Leeds, funded by Yorkshire Cancer Research.

A review of the literature, the overall research design, data acquisition and methods are included in the Introduction (Chapter 1). This is followed by three published papers, listed below, which constitute the main body of work (Chapters 2 to 4). Additional descriptions of the methods as well as results that were not included in the final published work are included at the end of each chapter. This is followed by an overall discussion of the three papers, highlighting the main contributions of this work, strengths and limitation, and recommendations for future work (Chapter 5).

The three publications used in alternative style format in this thesis are as follows:

Paper 1 (Chapter 2)

Influence of age on surgical treatment and postoperative outcomes of patients with colorectal cancer in Denmark and Yorkshire, England.

Colorectal Disease (2021) 23(12):3152–3161 [https://doi.org/10.1111/codi.15910]

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Contribution of other authors: EJAM, PQ, LP and LHI contributed to the concept and acquired the data. DB, PJF and SH provided input into the clinical aspects of the work. MMI contributed to the statistical interpretation of the data.

Paper 2 (Chapter 3)

Differences in the management of patients requiring an emergency resection for colonic cancer in two European populations

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Paper 3 (Chapter 4)

Minimally invasive surgery for colorectal cancer: Benchmarking English uptake against Denmark for a regional improvement programme

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The following publications were also produced during the PhD and are referred to in the introduction and discussion, but not included as a main paper:

Regional multidisciplinary team intervention programme to improve colorectal cancer outcomes: study protocol for the Yorkshire Cancer Research Bowel Cancer Improvement Programme (YCR BCIP)

BMJ Open (2019) 9(11):e030618 [https://doi.org/10.1136/bmjopen-2019-030618]

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A comparison of frailty measures in population-based data for patients with colorectal cancer

Age and Ageing 53(5):afae105 (2024) [https://doi.org/10.1093/ageing/afae105]

Birch R*, Taylor J*, Rahman T, Audisio R, Pilleron S, Quirke P, Howell S, Downing A#, Morris E# (* joint first author, # joint senior author)

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Abstract

Survival differences for patients with colorectal cancer have caused considerable concern in Denmark and the UK where rates have compared unfavourably with many other countries with similar health systems. Interventions in Denmark have included detailed reviews of observational data to quantify patterns of practice and identify areas of concern. There is strong evidence this has radically changed practice and improved patient outcomes. The aim of the research described in this thesis was to identify differences in the surgical management of patients with colorectal cancer between Denmark and a representative region of the UK (Yorkshire).

Data from the cancer registry in England and clinical data from Denmark were collated to compare surgical treatment and outcomes for patients with colorectal cancer in Yorkshire and Denmark. Three aspects of surgical treatment were identified for comparison, these were the use of: major surgical resection, emergency surgery and minimally invasive surgery (MIS).

The use of major surgical resection was higher in Denmark than Yorkshire, especially in more elderly patients, corresponding to an increased postoperative 30-day mortality, but higher 1-year overall survival from diagnosis. A larger decrease in overall postoperative mortality in Denmark has coincided with a reduction in the use of emergency resection and an increase in stenting procedures. Uptake of MIS in patients undergoing elective surgery for colorectal cancer in Yorkshire was slower than in Denmark, for both laparoscopic and robotic procedures.

This study's data-driven approach identified several differences in the surgical management of patients with colorectal cancer between Yorkshire and Denmark. Teams managing elderly patients should balance the short-term risk versus the long-term benefit of major surgery. Consensus guidelines for converting potential emergency resections into elective resections may help lower rates of emergency surgery in Yorkshire. Ensuring adequate training and access to laparoscopic equipment should increase use of MIS in Yorkshire.

Abbreviations

APE	Abdominoperineal excision
ASA	American Society of Anesthesiologists
CCI	Charlson Comorbidity Index
CGA	Comprehensive geriatric assessment
CI	Confidence interval
CME	Complete mesocolic excision
CORECT-R	Colorectal cancer Repository
COSD	Cancer Outcomes and Services Data Set
COVID	Coronavirus disease
CRM	Circumferential resection margin
CRN	Clinical Research Network
DCCG	Danish Colorectal Cancer Group
DCR	Danish Cancer Registry
DPR	Danish Pathology Register
ELAPE	Extralevator abdominoperineal excision
EMR	Endoscopic mucosal resection
ERAS	Enhanced recovery after surgery
FIT	Faecal immunochemical test
FOBT	Faecal occult blood test
GP	General practitioner
HES	Hospital Episode Statistics
ICD	International Classification of Diseases
IMD	Index of Multiple Deprivation
LAPCO	National Training Program for Laparoscopic Colorectal Surgery
LARS	Low anterior resection syndrome
MDT	Multidisciplinary team
MET	Metabolic equivalent of task
MIS	Minimally invasive surgery
MOR	Median odds ratio
MRI	Magnetic resonance imaging
NBOCA	National Bowel Cancer Audit
NCEPOD	National Confidential Enquiry into Patient Outcome and Death
NCRAS	National Cancer Registration and Analysis Service
NELA	National Emergency Laparotomy Audit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NOC	Not otherwise classified

NPR	National Patient Regis
NUTS	Nomenclature of Territorial Units for Statistics
OPCS	Office of Population Censuses and Surveys
OR	Odd ratio
PME	Partial mesorectal excision
PROMs	Patient-reported outcome measures
QPI	Quality performance indicator
RCRD	Rapid cancer registration dataset
RR	Risk ratio
RTDS	Radiotherapy Dataset
SACT	Systemic anti-cancer therapy
SBTS	Stent as bridge to surgery
SCRT	Short-course radiotherapy
SEMS	Self-expandable metallic stent
TAMIS	Transanal Minimally Invasive Surgery
TEM	Transanal endoscopic microsurgery
TEO	Transanal endoscopic operation
TME	Total mesorectal excision
TNM	Tumour Node Metastasis
UICC	Union for International Cancer Control
UK	United Kingdom
YCR BCIP	Yorkshire Cancer Research Bowel Cancer Improvement Programme

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Chapter 1. Introduction

1.1. Colorectal cancer

1.1.1. Epidemiology

Colorectal cancer is estimated to be the second most common cancer in Europe and the second most common cause of death from cancer, with an estimated 500,000 new cases and 243,000 deaths in 2018[1]. In the UK alone, there are approximately 43,000 new cases of bowel cancer each year, accounting for 11% of all new cancer cases[2]. Incidence and mortality rates vary widely geographically, in Europe alone a five-fold variation in incidence rates between countries has been reported[1].

The variation in incidence and mortality rates observed may be attributable to a combined effect of numerous factors which include environmental exposures, genetics, differences in life expectancy, detection through screening, development of new treatments and the quality of cancer registries. The risk of sporadic colorectal cancer increases rapidly in individuals over the age of 50 years, with 75% of patients with rectal cancer and 80% of patients with colon cancer having an age at diagnosis >60 years[3].

The majority of colorectal cases are sporadic, with twin studies estimating a heritability component of approximately 35%-40%[4-6]. While approximately 25% of cases have a family history, less than 10% have a known hereditary cancer syndrome such as Lynch syndrome[7]. Consequently, a positive family history greatly increases an individual's risk of developing colorectal cancer.

Several modifiable life-style factors are known to be associated with the risk of developing colorectal cancer. Smoking increases the risk of colorectal cancer by 15-20%, rising to 25-30% in those who smoke with the highest intensity or duration[8]. Increased risk is also reported with moderate (20%) and heavy (50%) alcohol drinking[9]. The Word Cancer Research Fund and American Institute for Cancer Research publishes regular systematic reviews to assess the evidence of associations between diet, nutrition and physical activity with colorectal cancer[10]. The 2018 report found strong evidence of increased risk with Body Mass Index (5% increase in risk per 5kg/m^2) and consumption of processed meat (16% increase per 50g/day) and reduced risk with increased physical activity (8% reduction per 5 MET-hours/week in colon cancer). Additional evidence of dietary associated factors includes red meat (12% increase per 100g/day), fibre (7% reduction per 10g/day) and whole grains (17% reduction per 90g/day). A reduction in the risk of colorectal cancer has also been reported with aspirin and calcium intake[11,12].

Most colorectal cancer tumours arise from the development of an aberrant crypt in the lining of the colon, into a neoplastic precursor lesion (commonly known as a polyp). Over the course of 10–15 years, an accumulation of genetic and epigenetic alterations causes the progression of the polyp into a colorectal cancer[13]. Between 70–90% of colorectal cancers develop through the adenoma-carcinoma pathway, but it is important to note that only approximately 10% of adenomas progress to colorectal cancer[3]. Between 10–20% of colorectal cancers develop through the serrated neoplasia pathway, leading to both microsatellite stable and unstable tumours. Microsatellite instability is caused by DNA mismatch repair (MMR) deficiency. Is it estimated that 2–7% of colorectal cancers develop through a germline mutation in MMR genes, such as Lynch syndrome[13].

The prognosis of patients with colorectal cancer is largely influenced by the tumour stage at the time of diagnosis, as 5-year net survival decreases rapidly with increasing stage. Figures for UK patients in 2010-2014 demonstrate this in both colon cancer (96% stage I, 85% stage II, 63% stage III and 9% stage IV) and rectal cancer (92% stage I, 75% stage II, 64% stage III and 9% stage IV)[14]. Age at diagnosis is also an important prognostic factor. Net 1-year survival rates for patients in the UK aged <50 years are much higher (87% colon cancer, 91% rectal cancer) than those aged ≥80 years (58% colon cancer, 70% rectal cancer)[14]. Survival estimates vary greatly across Europe and high-income countries. While most Western European countries have a net 5-year survival ranging 60–69% for both colon cancer and rectal cancer and rates have generally increased by 5–10% over the past 15 years, differences are still apparent[15].

1.1.2. Surgical management

To ensure timely treatment and appropriate clinical decision-making, the treatment of patients with colorectal cancer is managed by multidisciplinary teams (MDTs)[16]. The MDT consists of a team of specialists whose core members include: a surgeon, an oncologist, a radiologist, a pathologist, and a clinical nurse specialist. Several benefits of this treatment strategy have been reported including increased use of MRI and adjuvant therapy, and reduced perioperative mortality and positive circumferential resection margin[17].

Major surgical resection to remove the tumour and surrounding tissue, termed bowel resection including regional lymphadenectomy, is the mainstay of treatment for colorectal cancer[18]. Surgery requires differing approaches for colon cancer and rectal cancer, and patient outcome is strongly related to the quality of this surgery[3]. The surgery is performed using either a traditional open approach or using minimally invasive surgery (MIS) such as a laparoscopic or robot-assisted approach.

In rectal cancer, major surgical resection is based around the concept of total mesorectal excision (TME)[19]. The TME procedure involves removal of the rectum along with the surrounding mesorectum which contains the involved lymph nodes and tumour deposits. The circumferential resection margin (CRM) is the distance between the resection margin and the tumour border. A CRM ≤1mm (positive or involved) has been associated with an increased risk of local recurrence and distant metastases[20]. Several surgical techniques have been developed to treat some early-stage rectal cancers in the absence of high-risk features, and include transanal microscopy surgery (TEM), transanal endoscopic operation (TEO) and transanal minimally invasive surgery (TAMIS). Since these local excision techniques involve only the removal of the tumour, and not the removal of the rectum and mesorectum, they have the benefit of a less invasive procedure associated with improved functional outcome but a higher risk of local recurrence[21].

Major resections for colon cancer involve the removal of the tumour and corresponding lymph vessels. Complete mesocolic excision (CME) has also been proposed, using the same principles to that of TME. Although currently lacking the strong evidence of that found in TME, CME has been reported to be associated with lower rates of recurrence[22]. For patients presenting with obstructing colon cancer, the approach to surgery may differ depending on the location of the tumour. Emergency surgery with ileocolic anastomosis is commonly considered for obstructing right-sided tumours. For left-sided tumours, emergency surgery may also be considered, but use of self-expanding colonic stents as a bridge to surgery is also an option[23].

Patients with colorectal cancer may receive additional treatment pre- or post-surgery, dependent on their tumour staging and individual patient factors, such as fitness. Treatment with radiotherapy (short-course or long-course chemoradiotherapy) before surgery may reduce the risk of recurrence in patients with locally advanced rectal cancer[20]. Neoadjuvant radiotherapy may also be used to achieve downsizing or downstaging of the tumour. Adjuvant chemotherapy after surgery is associated with increased survival and is recommended for most patients with stage 3 colon cancer and some stage 2 patients with high-risk features. Patients with metastases in the lung or liver, may also be treated with surgery if it is deemed that the metastases are resectable[17].

1.1.3. Study overview

The differences in survival for patients with colorectal cancer have caused considerable concern in Denmark and the UK where rates have compared unfavourably with many other countries with similar health systems and populations. Understanding what is driving these survival deficits is important but, to date, there is little evidence to explain their origin. Differences in the extent of disease at diagnosis, treatment and co-morbidities may contribute to some of the variation observed, but variation in management and the quality of care delivered may also be relevant. Further detailed studies are required to understand why some countries have a lower survival proportion relative to many of their economic neighbours.

Despite the lack of consensus about what is driving the survival differences, both the UK and Denmark have instigated interventions that seek to improve outcomes from this disease[24]. In Denmark, these interventions have included detailed reviews of observational data to quantify patterns of practice, identify areas of concern and then take action to improve care. There is strong evidence this has radically changed both practice and outcome with, for example, 30-day postoperative mortality rates falling dramatically[25].

Recently, in the Yorkshire region of the UK, a similar programme commenced[26]. Again, it aims to make use of routinely available health service data but also supplement it with prospective data captured directly from patients, to quantify in more depth than has previously been possible the patterns of care and outcome. Based on what is observed, interventions will then be developed by Yorkshire's clinical colorectal cancer community to seek to eliminate any disparities in quality and improve outcomes. Given Denmark's improvement in outcomes, a key strategic approach of the programme was to compare management of Yorkshire's colorectal cancer population and benchmark that with those in Denmark. It was reasoned that Denmark would be a suitable comparator given its similar sized population and healthcare provision financed through taxation.

The aim of the research described in this thesis is to identify differences in the surgical management of patients with colorectal cancer between Denmark and Yorkshire. To achieve this aim, the following three objectives are addressed:

1. To explore the strategies employed by Denmark to achieve improved survival of patients with colorectal cancer.

2. Investigate and collate data common to both colorectal cancer populations that can be used to assess differences in surgical management.

3. Identify differences in the surgical management of patients with colorectal cancer that may impact on differences in survival.

This thesis is based upon three published papers. Objectives (1) and (2) are addressed in the Introduction (Chapter 1) through literature review and extended descriptions of the data acquisition. Objective (3) is addressed through presentation of the three published papers (Chapters 2 to 4), with additional description of the methods and results that were not included in the final published work. The results of the three papers are then discussed, highlighting the main contributions of this work, strengths and limitations, and recommendations for future work.

1.2. The Danish and Yorkshire populations

1.2.1. Geography and demographics

Denmark is a country located in Northern Europe with a population of approximately 5.7 million (Figure 1.1). Denmark consists of 5 Regions at Level 2 Nomenclature of Territorial Units for Statistics (NUTS): North Denmark Region (the least populated), the Region Zealand, Region of Southern Denmark, the Central Denmark Region and the Capital Region of Denmark (the most populated). The 5 Regions are further divided into 98 Municipalities. Yorkshire is a region of England, located in the Northern part of the country. The administrative geography of Yorkshire is slightly more complicated than Denmark but also with a population size of approximately 5.7 million, divided into 4 counties at the equivalent Level 2 NUTS West Yorkshire (the most populated); South Yorkshire; East Riding and North Lincolnshire; and North Yorkshire (the least populated) which are made up of a mixture of 24 unitary authorities and districts in total. In addition to a similar sized population, the age-structure of Danish and Yorkshire populations is similar. When compared to English averages, Yorkshire generally has poorer public health outcomes and the overall healthy life expectancy (the number of years a person can expect to live in good health) is two years less than the English average[27].

The Danish health care system is largely financed through taxation, which finances 84% of total health care expenditure. Primary and secondary health care services are overseen by the 5 regions that own and operate public hospitals. As in the UK, the first point of contact for most patients is through General Practitioners[28]. Denmark has recently seen an increase in the number of people additionally covered by private health insurance from 21% in 2010 to 29% in 2017, which is substantially more than that in the UK (10% in 2017)[29].

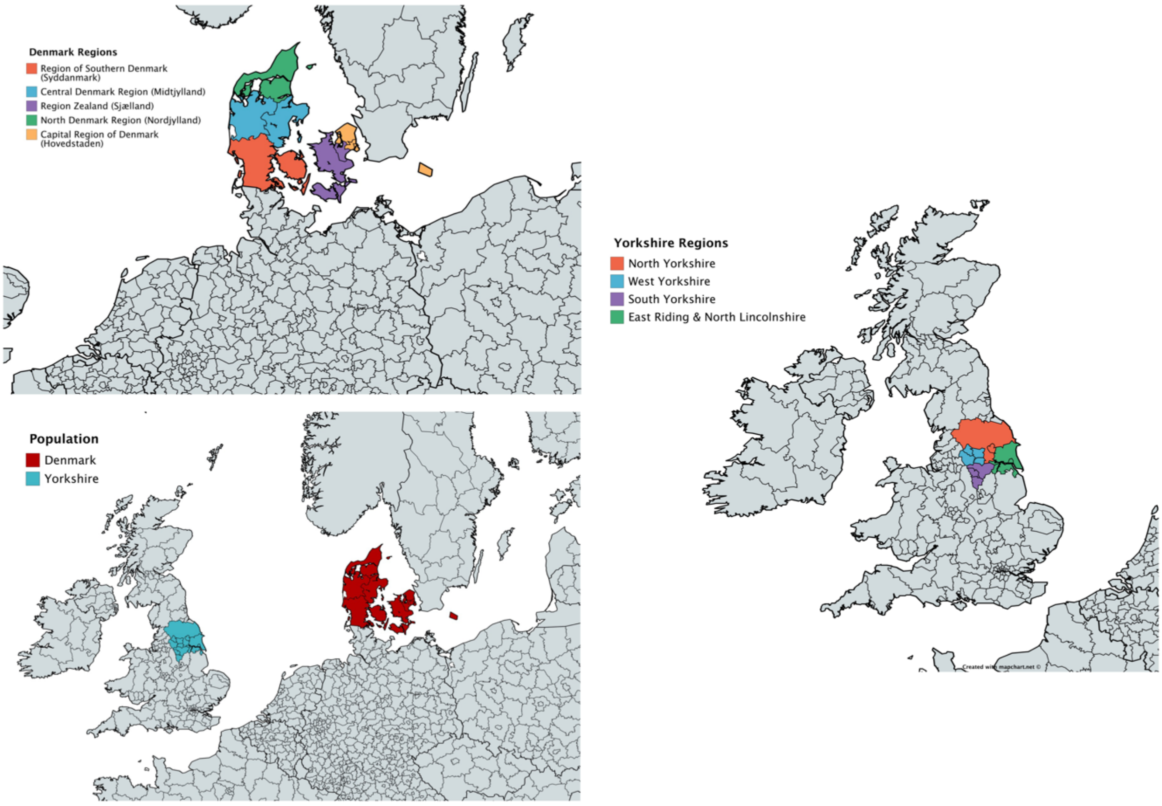

Figure 1.1 Geographical location of the study populations. Created with MapChart[30].

In 2016 it was estimated that Denmark spent more on health as a percentage of total national gross domestic product (10.8%) than the UK (9.7%) and furthermore used a higher proportion of its healthcare expenditure in the inpatient and outpatient sectors than did the UK[31]. Denmark has a higher number of practicing doctors (4.0 *per* 1000 population in Denmark vs 2.8 *per* 1000 in the UK) and nurses (10 v 7.8) than the UK, but a similar number of GPs (0.8 vs 0.8) and beds (2.6 vs 2.5)[29].

The percentage of the population aged ≥65 years is approximately 18% in Denmark, compared with 17% in the UK[32,33]. In 2015, Denmark and the UK were reported to have a similar Healthcare Access and Quality Index[34]. While lifestyle factors such as smoking and alcohol consumption are broadly the same, Denmark has higher reported admission rates for diabetes (type 1 or type 2) and chronic obstructive pulmonary disease but considerably lower rates of obesity[29]. Life expectancy in 2016 was broadly the same in the Danish (male 78.9, female 82.8) and Yorkshire (male 78.7, female 82.4) populations. However it is worth noting that Danish life expectancy improved in the 2000s to at least match that of the UK (Figure 1.2).

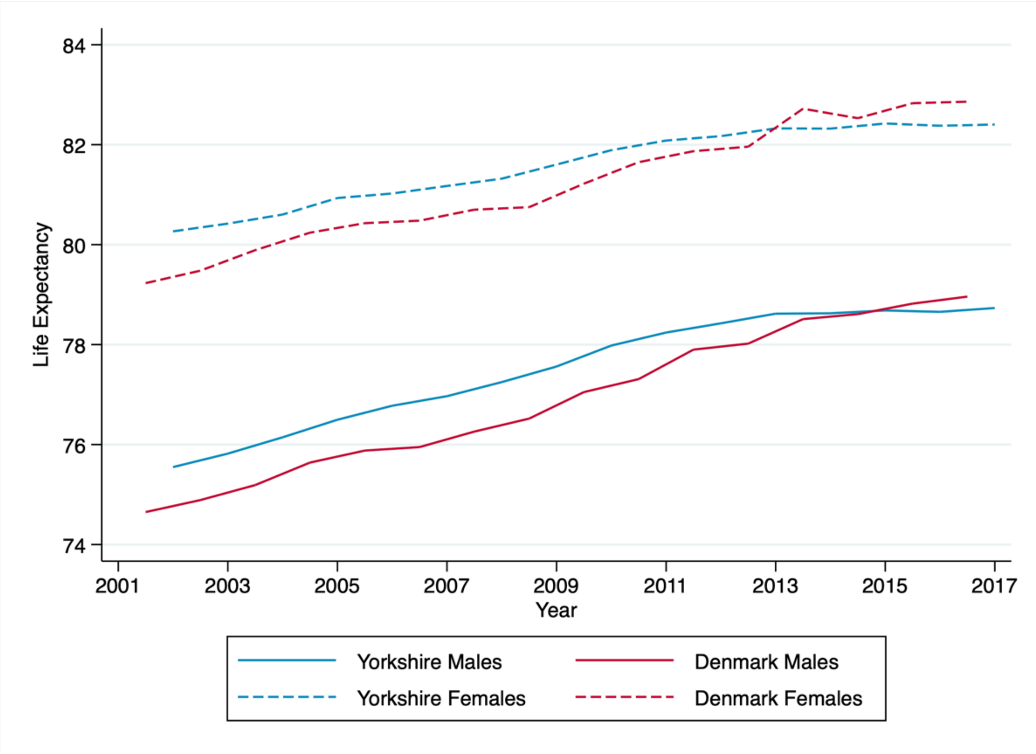

Figure 1.2 Life expectancy of the study populations. Source data[32,33].

1.2.2. Incidence and survival

International cancer incidence and mortality estimates are available from the Global Cancer Observatory[35], enabling the comparison of rates between countries over a period of time. Colon and rectal (including anal) cancer incidence rates for Denmark and the UK (as detailed Yorkshire data is not available) over the period 1990 to 2017/18 are shown Figure 1.3. Here, incidence is defined as the number of new colorectal cancer cases in the specified population for that year. Mortality is defined as the number of deaths due to colorectal cancer in the specified population for that year. Colon cancer incidence remained reasonably stable in the UK, as opposed to Denmark which saw a steady increase in colon cancer incidence from the 1990s, followed by a sharp increase in the 2010s. Rectal cancer incidence has remained relatively stable in both countries.

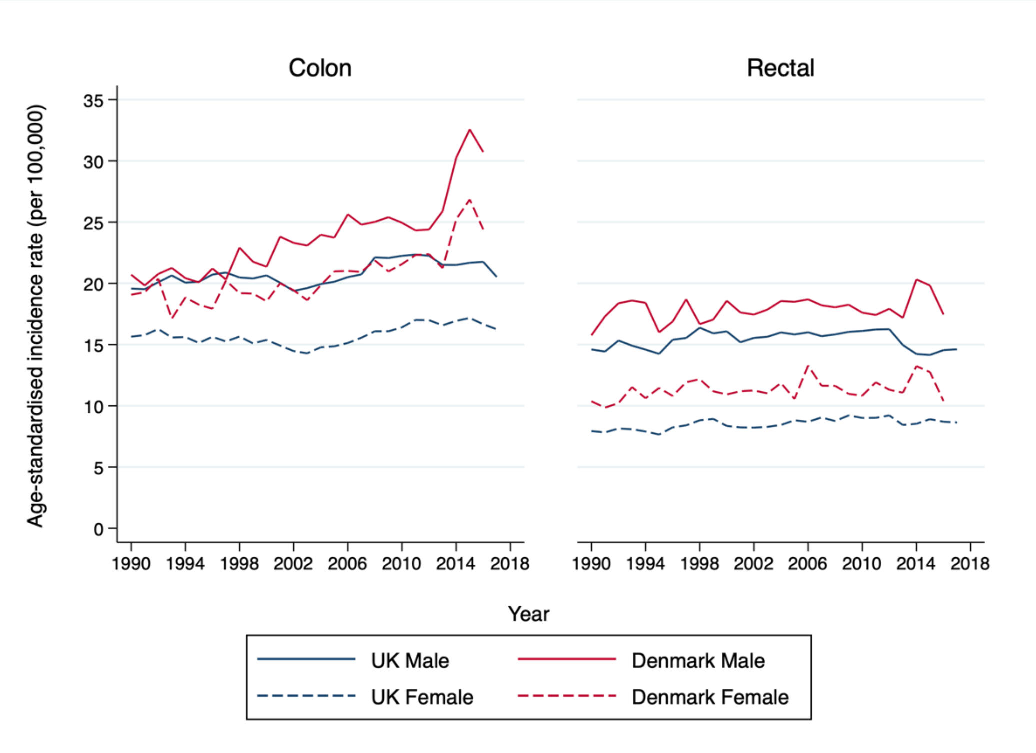

Figure 1.3 Incidence rates for colorectal cancer in the UK and Denmark. Source data[35].

Mortality rates for Denmark and the UK over the period 1980-2018 are show in Figure 1.4. Mortality rates for colon cancer have dropped sharply for both Denmark and the UK since the 1990s, with rates for Denmark consistently higher. Mortality rates for rectal cancer have also dropped in both countries. However, since the late 1990s, the UK mortality rate has stabilised whereas rates in Denmark have continued to fall.

Denmark's improvement in outcomes is illustrated by the trends in 5-year survival. The SURVMARK-2 project compared cancer survival across 7 high-income countries (Denmark, UK, Australia, Canada, Ireland, New Zealand and Norway)[36]. In 1995-1999, Denmark and the UK had respectively the 5th and 6th best 5-year survival rates for both colon and rectal cancer across the 7 countries (colon cancer: Denmark=49.1%, UK=47.0%, rectal cancer: Denmark=48.1%, UK=47.8%). By 2010-2014, Denmark had the 3rd best rate for colon cancer and 2nd best rate for rectal cancer, whereas the UK ranked 7th in both (colon cancer: Denmark=65.7%, UK=58.9%, rectal cancer: Denmark=69.1%, UK=62.1%). It was also noticeable that the improvements for colon and rectal cancer observed for Denmark showed the greatest improvement among all the cancers included in the study. Survival rates in Yorkshire appear to be slightly lower than that of English rates, with estimates of 5-year survival up to 1% lower than the national average[37].

Further evidence of Danish improvements in comparison with the other Scandinavian countries has been documented[38]. In 1996-2000, the Danish 5-year survival rate for colorectal cancer was considerably lower than that of the other Scandinavian countries (Denmark=48.1%, Norway=57.0%, Sweden=,57.0% Finland=57.4%); by 2011-2015 Denmark had the highest survival rate (Denmark=69.2%, Norway=67.3%, Sweden=67.1%, Finland=65.6%)[39].

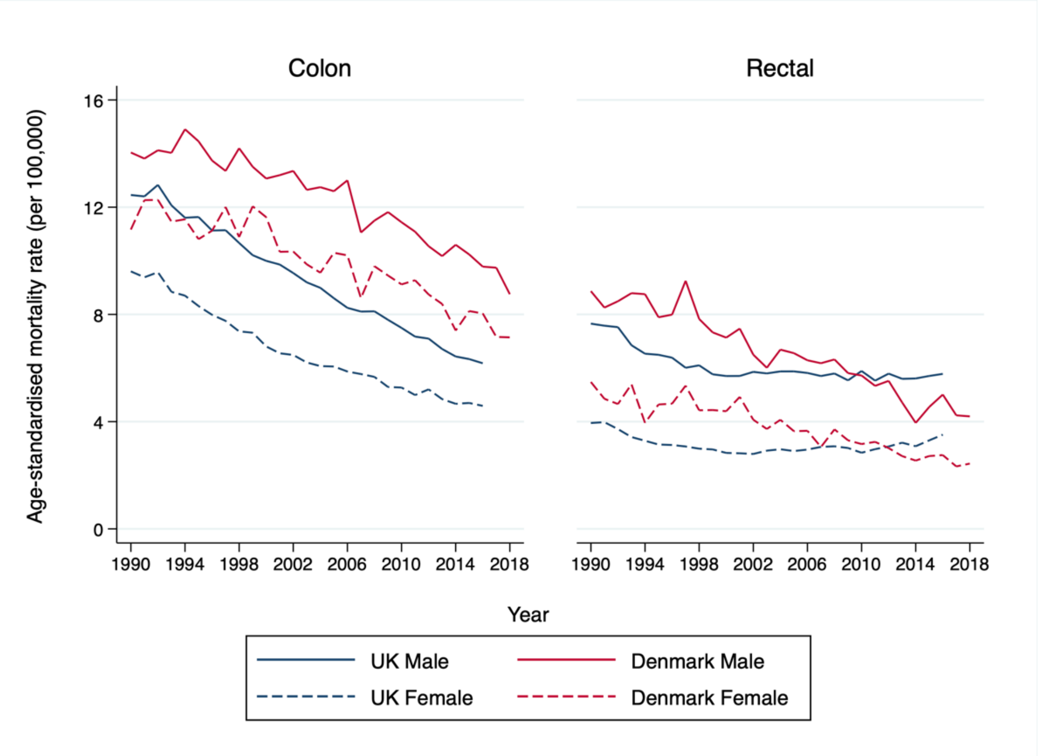

Figure 1.4 Mortality rates for colorectal cancer in the UK and Denmark. Source data[35].

1.2.3. National guidelines

The first national guidelines for the management and treatment of colorectal cancer were published in 1997 for England and 1998 for Denmark (Figure 1.5). These have been updated at various times, although Denmark now opts to publish regular updates pertaining to certain aspects of care instead of a full set of formal guidelines at one time. Alongside these, both have undergone several national cancer plans, often issuing a broad range of cancer treatment policies and targets such as waiting time guarantees. Although the timelines in both countries tend to follow a similar pattern, there are some important differences to note. For example, following the Calman-Hine report in 1995[40], national guidelines since 1997 in England recommend patients to be treated by colorectal MDTs. Establishment of MDTs in Denmark was later, coinciding with national guidelines from 2002. National TME training for rectal cancer surgery in Denmark (1996) was introduced much earlier than in England (2003).

Another noticeable area where national policies differed was in the roll out of national screening programmes. The English screening programme began roll out in July 2006 completing full national coverage by 2010[41]. Individuals aged between 60 and 69 years registered with a GP were invited to participate every two years, but from 2010 this was extended to those aged up to 74 years. Screening was initially done by a postal faecal occult blood test (FOBT) kit with further investigation by colonoscopy if they tested positive. The programme aimed to start replacing the use of the FOBT kit with a faecal immunochemical test (FIT) kit in 2019[42], as FIT has been shown to have improved participation rates, higher detection, and positive prediction values. Despite a recommendation for a national screening programme in Denmark’s National Cancer Plan in 2010, this was not introduced until early 2014[43]. The screening programme uses a postal FIT kit and has a wider age range than the English programme with those aged 50-74 years invited to participate. Individuals with a positive test result are offered a colonoscopy at their local provider.

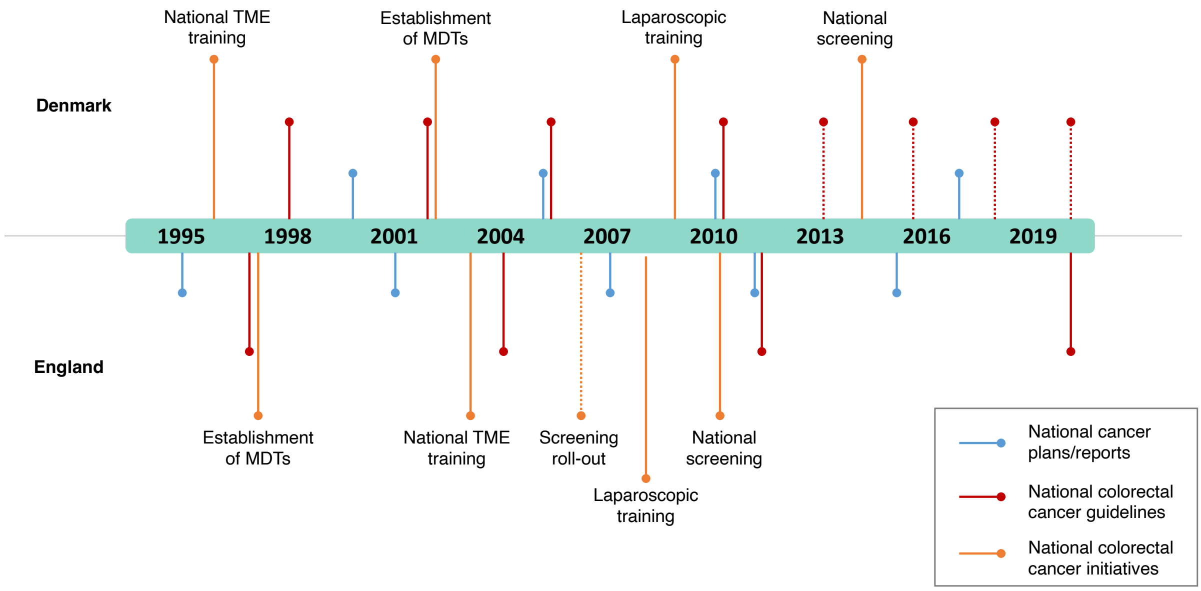

Figure 1.5 Key events in the treatment of colorectal cancer in Denmark (top) and England (bottom).

1.3. The Danish Colorectal Cancer Group

1.3.1. Overview and development

Since 1998, the Danish Colorectal Cancer Group (DCCG) have regularly updated and published evidence-based national colorectal cancer guidelines. The DCCG originated in 1994, when a subgroup of the Danish Surgical Society founded a national database with the aim to improve outcomes of patients with colorectal cancer. Initially, only patients with rectal cancer were included in the DCCG database, but since 2001 patients with colon cancer have also been included. From 2006, the DCCG expanded to include members beyond that of the surgical field (such as oncologists, radiologists and pathologists) and became a multidisciplinary group[44].

The DCCG database is integral to the group's aims, consisting largely of clinical surgical data, supplemented with some pathology and oncological data. All patients with colorectal cancer who are diagnosed or treated at a surgical department based in a Danish public hospital are included. The database has three broad aims for standardising and improving the following aspects of colorectal cancer care: 1) diagnostic workup, 2) treatment, and 3) follow-up[45]. The database enables the active monitoring and annual publication of clinical quality indicators at the hospital, regional and national levels. The quality indicators used in 2022 are given in Table 1.1.

Table 1.1 Clinical quality indicators used by the DCCG in 2022.

	Standard	
Clinical Quality Indicator	**Acceptable**	**Desirable**
1. Proportion of newly diagnosed patients with colon cancer discussed at a preoperative Multidisciplinary Team (MDT) conference. Acutely operated patients are not included.	≥95%	≥95%
2. Proportion of patients, excluding acutely operated patients, who have registered complete TNM clinical categories.	≥95%	NA
3. Proportion of patients with a local resection, where the diagnosis is confirmed by at least two specialists with expertise in gastrointestinal pathology.	≥90%	≥95%
4a. Proportion of patients with colonic resection with ileocolic anastomosis who develop anastomotic leakage requiring clinical intervention	≤2%	≤2%
4b. Proportion of patients with colonic resection with colonic anastomosis who develop anastomotic leakage requiring clinical intervention	≤4%	≤3%
4c. Proportion of patients with rectal resection who have anastomotic leakage requiring clinical intervention	≤8%	≤8%
5a. Proportion of electively operated patients with colon or rectal cancer who died within 30 days postoperatively	≤1.0% (<75 years) ≤2.5% (≥75 years)	NA
5b. Proportion of electively operated patients with colon or rectal cancer who died within 90 days postoperatively.	≤2.0% (<75 years) ≤5.0% (≥75 years)	NA
6. Proportion of elective, intended curative and macroradically operated patients with rectal cancer who have undergone a rectal resection (all types of resection) with more than 1 mm distance from the	≥97%	NA

primary tumor to the surgical resection surface and margins.		
7 Proportion of acutely operated patients with colon cancer (excluding; stenting, relief, local, exploratory) who were operated on by a specialist (certified colorectal surgeon).	≥90%	≥95%
8a. Proportion of patients under 80 years of age with pathological UICC stage III colon cancer who have a contact at an oncology department, have had a curatively intended bowel resection and have survived at least 31 days post-operatively, who have initiated oncological treatment.	80 – 90%	NA
8b. Proportion of patients under 80 years of age with rectal cancer in pathological UICC stage III, who have a contact in an oncology department, have had a curatively intended bowel resection and have survived at least 31 days post-operatively, who have started oncological treatment.	80 – 90%	NA

1.3.2. DCCG Studies

Survival

Data obtained from the DCCG database has been used in several studies to document improvements in survival in Danish patients. Overall 5-year survival in Denmark was reported to have improved from 37% to 51% from 1994 to 2006, with the greatest improvements in men and in those with stage III disease[46]. A later time period was covered by investigations from 2001 to 2012, reporting an improvement in relative 5-year survival from 58% to 63% in colon cancer and 59% to 65% in rectal cancer[24]. Around the same time-period 30-day mortality after major elective surgery decreased from 7.3% to 2.8%[25]. Central to these studies, were the authors' conclusions on the influence of the improvement initiatives taken by Denmark to improve outcomes.

Surgical technique

The granularity of the available surgical data within the DCCG has enabled a wide examination of surgical treatment in Denmark. Bertelsen et al. investigated outcomes in those undergoing CME surgery compared to those undergoing conventional colon cancer surgery[22,47]. They found a higher rate of intraoperative injury to other organs (9.1% v 3.6%), sepsis (6.6% vs 3.2%) and postoperative respiratory failure (8.1% vs 3.4%) in the CME group, but a greater 4-year disease-free survival rate (85.8% vs 75.9%). Surgical techniques in rectal cancer have also been compared: use of extralevator abdominoperineal excision (ELAPE) did not improve short-term oncological results, as it was associated with higher rates of positive CRM (16% vs 7%) compared with conventional abdominoperineal (APE), and the overall evidence of any significant benefit in oncological outcomes with ELAPE remains unclear[48-50].

Emergency surgery

A study by Iversen et al.[51] found that medical complications were the strongest risk factors for early death in patients with colon cancer undergoing emergency surgery. After adjustment for other risk factors, the odds ratio of death for those with medical complications compared to those without was 11.7. Degett et al.[52] reported that 90-day mortality in those undergoing emergency surgery decreased from 31% in 2005 to 24% in 2015 and was lower for those patients treated with a self-expanding metallic stent (18% vs 24%). Osler et al.[53] found significant variation in 30-day mortality for patients undergoing emergency surgery for colon cancer at a hospital level; a 5-fold difference was seen between the worst and best performing hospitals. However, no significant variation was observed in those undergoing elective surgery.

Postoperative complications

A severe complication of colorectal surgery is when a defect at the surgical join results in an anastomotic leak and is associated with increased short-term mortality. A study by the DCCG confirmed this association in rectal cancer patients, and not only that long-term survival decreased significantly after a leak but also there was increased risk of recurrence[54]. Risk factors associated with anastomotic leak included patients being male, smokers, having perioperative bleeding and having tumours within 10cm of the anal verge[55]. Krarup lead a series of DCCG studies investigating anastomotic leakage in patients with colon cancer[56-58]. Risk factors for leakage included patients being male, having a blood transfusion, undergoing a laparoscopic surgical approach and in those undergoing left and sigmoid colectomy procedures. Anastomotic leak was associated with increased rates of recurrence and long-term mortality.

Minimally invasive surgery

A broad range of studies comparing surgical approaches have been conducted using DCCG data. When comparing laparoscopic surgery to open surgery in patients with colon cancer, a lower incidence of incisional hernias (7.3% vs 5.2%) and small bowel obstruction (1.2% vs 1.5%) was observed in the laparoscopic group[59,60]. When assessing surgical quality, a matched analysis in colon cancer found that laparoscopic resections were of higher quality compared to open resections (CRM≥1mm 88% vs 83%)[61]. A smaller study, restricted to tumours located in the transverse colon reported higher rates of non-mesocolic resections and a lower number of harvested lymph nodes in laparoscopic resections than in open resections but similar long-term recurrence and survival[62].

As robotic-assisted surgery is becoming more frequently utilised, more recent studies have included comparisons between robotic, laparoscopic and open surgery. Resection quality was found to be significantly higher for robotic surgery compared to laparoscopic surgery in colon cancer but not in rectal cancer[63]. A higher lymph node yield and similar rates of postoperative complications were reported in patients with colon cancer undergoing robotic surgery compared to laparoscopic[64]. Long-term outcomes (including disease-free survival and all-cause survival) were similar between patients undergoing robotic and laparoscopic surgery for colon cancer[65].

Treatment in the elderly

Several DCCG studies have investigated whether age may influence treatment decisions for elderly patients. Bojer and Roikjaer considered surgical and oncological treatment in those aged ≤75 and >75 years[66]. Referral to an oncologist (59% vs 32%) and oncological treatment (90% vs 66%) were less frequent in the older group, but there was no significant difference in the receipt of surgery (90% vs 83%). Comparisons in surgical treatment for those aged ≥80 years in Denmark were made with Belgium, the Netherlands and Norway[67]. Denmark had rates of surgical treatment that were comparable with the other countries in stage 1-3 disease and lowest for stage 4 disease. Benitez Majano et al compared surgical treatment and survival in Denmark, England, Norway and Sweden in 2010 to 2012[68]. The lowest rates of survival were found in England, followed by Denmark. The proportion of those receiving surgical treatment was also lowest in England and this was most evident when considering the older age groups. Short-term mortality for patients aged ≥80 years undergoing surgery for colorectal cancer have been compared between Belgium, Denmark, the Netherlands and Sweden from 2005 to 2014[69]. Thirty-day mortality was highest in Denmark for colon cancer (Denmark 11.4%, the Netherland 10.3%, Belgium 7.8%, Sweden 5.5%) and second highest for rectal cancer (Denmark 7.3%, the Netherland 7.5%, Belgium 6.4%, Sweden 4.7%).

1.4. The Yorkshire Cancer Research Bowel Cancer Improvement Programme

1.4.1. Overview

The Yorkshire Cancer Research Bowel Cancer Improvement Programme (YCR BCIP) commenced in 2016 with the overall aim to improve outcomes for patients with bowel cancer across the region of Yorkshire[70]. The central theme of the programme is the collection and analysis of robust data to examine variation in practice and identification of where treatment can be harmonised, realised through the following objectives:

1. Quantification of the variation in demographics, management, and outcomes of the region's patients using routinely collected datasets.
2. Benchmarking regional performance against other English regions and Denmark.
3. Collection of new information on aspects of care that has not been available or quantifiable with the region.
4. Engagement with regional MDTs to present, discuss and interpret these data to develop educational initiatives to minimise variation and optimise outcomes.
5. Facilitation of implementation of colorectal cancer guidelines.

To ensure coverage of the main clinical disciplines involved with colorectal cancer care, several clinical speciality groups (workstreams) were established to provide oversight and direction. At the outset of the programme these included: surgery, pathology, oncology, radiology and specialist nursing. The need for separate gastroenterology and anaesthetics workstreams were subsequently identified and introduced later. The responsibility of each workstream and its clinical lead was to gather opinions on best practice, formulate a consensus view, ensure these were disseminated at educational events and drive agreed initiatives into routine clinical care across Yorkshire.

1.4.2. Setting, structure and methods

Patients diagnosed with colorectal cancer in the Yorkshire region are managed by 14 different MDTs, operating across the 14 NHS Trusts. The caseloads of the Trusts vary in size, ranging between approximately 120 and 390 cases a year (4%–12% of the regional workload). Patients within the geographical areas covered by each Trust exhibit a variable range of demographic features such as socioeconomic deprivation and comorbidity.

A key element of the YCR BCIP is engagement of MDTs in the understanding of the data analysis which is disseminated collectively and fed-back individually. A consensus on best practice and educational interventions can then be agreed and distributed to clinicians across the region. This is an iterative process in which the data may be reanalysed and again fed-back to MDTs at various points over the programme to assess any impact on treatment variation and patient outcomes (Figure 1.6).

While routinely collected colorectal cancer data provides a broad range of information on the aspects of care, there are elements which it does not cover. Therefore, the programme utilises data from three main sources. Firstly, routine NHS datasets are sourced primarily from the National Cancer Registration and Analysis Service (NCRAS), Hospital Episode Statistics (HES), Systemic Anti-Cancer Therapy Dataset (SACT), Radiotherapy Dataset (RTDS) to provide regional and comparative national data on patient and tumour characteristics, diagnosis pathways, treatment choices and patient outcomes.

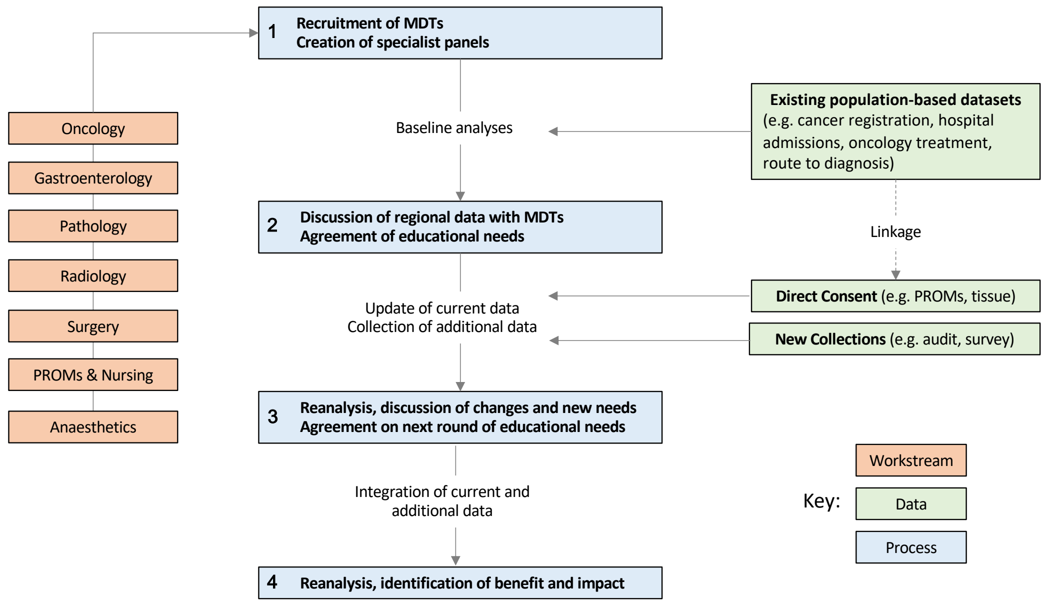

Figure 1.6 Study design and process of the Bowel Cancer Improvement Programme.

Secondly, patient reported outcomes (PROMs) and tissue collection are provided prospectively through consent of patients at regional MDTs if they are considered suitable for treatment. The PROMs data collected provides a wealth of data on the patient's quality of life via questions at the time of diagnosis and 12-months later. The collection of tissue samples removed at surgery or biopsy allows for upfront testing of novel biomarkers and molecular subtyping.

Finally, unlinked anonymised data collected by clinicians in the form of audits or surveys are identified by each workstream depending on the needs and availability of existing data (for example surgical quality using specimen photographs, the completeness of radiology reports, etc.). These additionally ensure current practice is assessed which may not always be possible using retrospective routine dataset.

1.4.3. Studies

Although much of the research from the YCR BCIP is still ongoing, several published studies have arisen as a direct result of the work conducted through the programme. Three studies relating to the surgical management of patients with colorectal cancer in comparison with Denmark are detailed in the following chapters of this thesis, a summary of other published work is given below.

The oncology workstream found large differences in the use of adjuvant chemotherapy treatment and formulated a new set of guidelines that aims to reduce the regional variation, demonstrating the key concepts of MDT engagement with data dissemination that is employed by the programme[71]. Substantial variation was also present both regionally and nationally when investigating the time interval between short-course radiotherapy (SCRT) and surgery, but there was no evidence of differences in postoperative outcomes in relation to the interval length[72].

The pathology workstream oversaw a large study into Lynch syndrome. Lynch screening was offered to all regional MDTs for patients aged ≥50 years, producing the largest study to date (over 3,000 cancers) to validate 2017 guidance on Lynch screening and confirming its achievability at scale[73]. The importance of the correct interpretation of the screening results to avoid unnecessary subsequent testing was also reported[74].

The initial work of the radiologists focussed on MRI reporting in rectal cancer. A survey of 21 radiologists and 48 other MDT clinicians found both groups commonly omitted items such as CRM and extra-mural venous invasion status in MRI reports and highlighted concerns regarding intra-radiologist consistency[75]. Further work found that using a template-style report significantly increased the inclusion of key tumour descriptors compared to non-template reports, resulting in a standardised template being made available to regional radiologists[76].

1.5. Data acquisition

1.5.1. The DCCG database

Criteria

The Danish data used for this study were acquired from the DCCG database and included all newly diagnosed patients with colorectal cancer (International Classification of Diseases for Oncology[77], C18-C20) between 1st January 2005 and 31st December 2016.

Inclusion criteria for patients registered in the DCCG database:

- are age ≥18 years,
- have a Danish social security number,
- are diagnosed with primary colorectal cancer from May 2001,
- are diagnosed and/or treated at a surgical department in a Danish public hospital,
- have a primary tumour that is adenocarcinoma, mucinous adenocarcinoma, signet ring cell carcinoma, medullary carcinoma or undifferentiated carcinoma.

Patients excluded from the DCCG database:

- have non-clinical primary colorectal cancer,
- have metachronous colorectal cancer,
- have recurrent disease,
- are treated privately or abroad,
- have cancer of the appendix C18.1 (from 2010).

Clinicians at departments responsible for the treatment of patients enter data using a proforma that covers aspects of clinical care provided. These include patient characteristics, presentation, examinations, tumour characteristics, detailed data on the surgical procedures performed and postoperative events. Pathology data and information on follow-up vital status are delivered to the database from the National Pathology Register and the Danish Civil Registration System. Those patients with a diagnosis based on a death certificate only are not captured within the DCCG database.

Data quality

Klein *et al*. performed a validation exercise on the DCCG database to assess its accuracy and completeness[78]. A random sample of 5% of patients were identified within the DCCG from 2014 to 2017. Departments were then asked to provide data from a selection of variables (covering the preoperative, intra-operative and postoperative aspects of care) using the patients' medical records. These were compared with the data held within the DCCG. There were few missing data in the DCCG, as median completeness was 96% for preoperative variables, 100% for intra-operative variables and 99% for postoperative variables. Overall, median accuracy was 95% with high agreement for intraoperative variables (93%-99%) and postoperative variables (95%-97%). Although most variables displayed high levels of agreement, particular note may be given to results for date of diagnosis. An exact match for date of diagnosis was reported in only 50% of cases. If allowing for ±7 days this rose to 81% and if allowing for ±30 days this rose to 96%. This is important to note if evaluating data on treatment management that relies on accurate date of diagnosis such as differences in timings of surgery or neoadjuvant radiotherapy.

Incident cases of cancer in Denmark have been recorded in the Danish Cancer Registry (DCR) since 1943[79]. Automatic electronic registration accounts for 80-90% of all registrations since a modernisation process in 2004-2008 using extracts from the National Patient Register (NPR), Danish Pathology Register (DPR) and Danish Register of Causes of Death, with manual registration through contact with clinical departments accounting for the remainder. Patients with all types of colorectal cancer histology are included, as are those with metachronous colorectal cancer. A study by Christensen *et al*. was undertaken to examine the agreement between patients registered in the DCCG and DCR[80]. They found that 86% of patients were included in both the DCR and DCCG, 4% in only the DCR and 10% in only the DCCG. Therefore, if one assumes any missing patients from the DCCG are registered in the DCR, then the DCCG has a case ascertainment rate of 96%. Excluding those who did not fulfil the DCCG histology inclusion criteria raises the ascertainment to 97% (Table 1.2).

Table 1.2 Details of patients found in the DCR but not in the DCCG.

Details of patients	**N**	**%**
Registered in DPR, fulfilling DCCG inclusion criteria	267	2.35%
Registered in DPR, not fulfilling DCCG histology criteria	111	0.98%
Unknown in DPR	17	0.15%
Registered in DCCG, but before DCR study period	7	0.06%
Possible Death Certificate Only	11	0.10%
Unknown	7	0.06%
Total	**420**	**3.69%**

1.5.2. The Colorectal Cancer Repository

Criteria

The UK Colorectal Cancer Intelligence Hub created a colorectal cancer research data system to combine and make available existing datasets covering different aspects of care. The system, known as the COloRECTal cancer data Repository (CORECT-R) holds a large collection of linkable data[81]. The Yorkshire data used for this study were acquired from CORECT-R and included all patients with colorectal cancer (C18-C20) newly diagnosed between 1st January 2005 and 31st December 2016.

The following inclusion criteria and adjustments were applied to match the Danish data as accurately as possible:

- age ≥18 years,
- diagnosed and/or treated at an MDT in a Yorkshire Hospital Trust,
- the primary tumour morphology must be adenocarcinoma or cancer/carcinoma,
- cancer of the appendix (C18.1) was excluded,
- patients with a diagnosis based on a death certificate only were excluded.

Data quality

The patient and tumour information for patients with colorectal cancer included in CORECT-R are comprised of extracts from the English national cancer registry dataset collated by the National Cancer Registration and Analysis Service (NCRAS). The NCRAS dataset has had national coverage since 1971 and is retrieved from multiple sources including pathology reports, hospital Patient Administration Systems and treatment records[82]. The dataset includes a subset of the Cancer Outcome and Service Dataset (COSD), the national standard for cancer reporting in England since 2013. Registrations using only a death certificate are included but this accounts for <1% of all registrations in 2016. Moller *et al*. assessed completeness of case ascertainment in English registry data, prior to formation of NCRAS when separate regional registries were responsible for reporting cases[83]. The authors compared patients in the cancer registries with HES data, where a relevant diagnosis code and surgery code were present. They reported a case ascertainment rate of 98% in colorectal cancer when compared to HES data for the period 2001-2007. The ascertainment rate for the registry responsible for patients residing in Yorkshire (then covered by the Northern and Yorkshire Cancer Registry and Information Service) was 99%.

Patient treatment information provided by CORECT-R is retrieved and largely derived from multiple routine NHS datasets, such as inpatient and outpatient activity (HES) and oncology data (RTDS and SACT). This provides researchers with streamlined key information regarding the patient’s treatment such as surgical procedures, neoadjuvant and adjuvant treatment, and allows investigation of both short- and long-term outcomes.

1.5.3. Data considerations

The DCCG database and CORECT-R datasets have different types of data collection retrieval; the DCCG is a majority clinical dataset whereas CORECT-R uses retrospective population-based data. Given this, the suitability of the variables used to compare management of patients with colorectal cancer was carefully considered.

Tumour site

In Denmark, tumours within 15cm of the anal verge are defined as rectal cancer, otherwise they are defined as colon cancer. Cancers recorded within English NCRAS (and hence CORECT-R) data are classed as either colon (C18), rectosigmoid (C19) or rectal (C20). Given that it was not possible to classify Danish tumours as rectosigmoid, Yorkshire patients with a C19 tumour we grouped with colon cancer patients (C18) as convention in recently published studies[36,68].

Tumour stage

Stage information for the Danish data was retrieved from the Union for International Cancer Control (UICC) variable which is derived from clinical stage and pathological stage TNM classification (5th edition up to 2017). Stage information for the Yorkshire data was taken from the CORECT-R summary stage variable, which is derived from pathological TNM, pretreatment TNM, Dukes' classification and information on nodes and/or metastases. Therefore, both Danish and Yorkshire patients were classified in the conventional manner: Stage 1 to 4, or unknown.

Surgical procedure

The DCCG directly records whether any surgical procedure was performed and the type of procedure. This includes different types of major surgical resections (such as right-side hemicolectomy, abdominoperineal excision, proctocolectomy and ileostomy), local resections (such as TEM), stents, relieving stoma, and exploratory intervention only.

Procedures within CORECT-R are derived from HES inpatient episodes of care. The HES dataset uses a mandatory classification coding of procedures called the Classification of Interventions and Procedures (OPCS-4). The type of surgical procedure that a patient underwent is identified through an algorithm using sets of OPCS-4 codes recorded within one month prior or up to one year after diagnosis. Each patient's surgical treatment is classified as major resection, minor resection, bypass, stoma, stent, no surgery (no OPCS-4 code found) or no linkage (patient is not present in the HES linkage dataset). The algorithm is hierarchical, so major resection is classified first, then minor resection and so on. If more than one instance of the same treatment is identified, then the one closest to the diagnosis date is used and multiple episodes within the same episode use the most radical procedure.

Given that major resections were specified and comparable in both the Danish and Yorkshire data, it was decided that it was robust to classify both sets of patients into a binary field indicating major resection for surgical treatment. An additional condition on the Danish data was imposed to include only major resections that occurred prior to one month or up to one year after diagnosis.

Additional variables

A summary of additional variables that were initially investigated for comparability are given in Table 1.3. The investigations highlighted that the most robust comparisons to be made would be around a patient's surgical treatment, short-term postoperative mortality and overall survival. An initial shortlist of areas in patient management and outcomes to compare were identified as follows:

1. use of major surgical resections,
2. use of local resections in early cancer,
3. management of patients using emergency surgery,
4. management of patients with rectal cancer; use of stomas and abdominoperineal excision (APE),
5. use of minimally invasive surgery,
6. short-term mortality after major surgical resection,
7. postoperative complications after major surgical resection.

Further investigation into the granularity of the data was performed. Detailed analysis around the use of local resections was discounted due to the amount of missing data on T-staging which is used in clinical decision making. An overview into the management of patients with rectal cancer was not progressed due to the lack of Danish data on closure of stomas and no Yorkshire data on the height of the tumour (an important consideration when investigating use of APE procedures). The possibility of classifying the OPCS-4 codes used in CORECT-R's "Return to Theatre" methodology into the DCCG's postoperative surgical complication indicators was investigated but, after consulting surgical specialists, it was decided that this could not be done robustly.

Table 1.3 Summary of initial variables investigated for comparability.

Data variable	**Yorkshire**	**Denmark**
Age (years)	Yes	Yes
Sex	Yes	Yes
Date of diagnosis	Yes	Yes
Site of tumour	Yes *C18, C19, C20*	Yes *Colon cancer or rectal cancer*
Stage of tumour	Yes *Summary stage 1-4*	*Yes* *Hybrid UICC stage 1-4*
Survival time from diagnosis	Yes	Yes
Charlson Comorbidity Index	Yes *Calculated based on comorbidities 1 year prior to cancer diagnosis*	Yes *Calculated based on comorbidities 10 years prior to cancer diagnosis*
ASA/Performance score	No	Yes
Screening Diagnosis	Yes *Available from Route to Diagnosis via NCRAS*	Yes *For patients registered in the Danish Screening Programme*
Procedure	Yes (derivable)	Yes
Surgical urgency	Yes (derivable)	Yes
Surgical approach	Yes (derivable) *Coding for laparoscopic procedures introduced from 2006*	Yes *Both laparoscopic and robotic procedures are recorded*
30 or 90-Day mortality	Yes	Yes
Postoperative complications	Partial *Derivable surgical complications only available as a “Return to Theatre”*	Yes *Indicator of complication requiring reoperation before 2014; uses the Clavien-Dindo scale post-2014*
Neoadjuvant radiotherapy	Yes (derivable) *Number of attendances and interval to surgery*	*Yes* *Any radiotherapy or chemo-radiotherapy*
Adjuvant chemotherapy	Yes (derivable) *Regimen administered and interval from surgery*	Partial *Indicator of patient referral to an oncology department*

Further investigation of the data around the remaining broad topics resulted in a more detailed analysis plan based on the following:

1. use of major resection and its impact on survival,
2. management of emergency surgery and postoperative mortality,
3. use of minimally invasive surgery including robot-assisted surgery.

Data access

Data sharing agreements were required for access to both the DCCG database and CORECT-R. Conditions of these meant that analyses must be performed "in-house" for both datasets. For Yorkshire data this was cloud-based (from the University of Leeds) via a trusted research environment. Danish data required physical presence within an approved Danish institution (the Department of Clinical Epidemiology, Aarhus University, Denmark). Therefore, datasets could not be combined and analysed together as one, so analytical techniques were considered whilst adhering to this restriction.

1.5.4. Statistical considerations

Survival analysis

Survival statistics are the most frequently used methodology to compare the prognosis of cancer patients over time and between geographical areas. However, the term *survival* or *survival analysis* in the epidemiological field is broadly applied, encapsulating several different measures. The three most commonly used measures are overall survival (also sometimes called all-cause, observed or crude survival), relative survival, and cause-specific survival[84]. For cancer patients, the *n* year survival rates for these measures can be defined as:

$$\text{Overall survival} = \frac{\text{number alive } n \text{ years after cancer diagnosis}}{\text{number of cancer patients}}$$

$$\text{Relative survival } = \frac{\text{Overall } n \text{ year survival for cancer patients}}{\text{Overall } n \text{ year survival for general population}}$$

$$\text{Cause specific survival } = \frac{\text{number not died from cancer } n \text{ years after diagnosis}}{\text{number of cancer patients}}$$

Overall survival is the simplest of these measures and can be interpreted as the percentage of cancer patients alive after *n* years. While it is often readily available, caution is needed when making comparisons across populations, as it may be influenced by deaths from other causes.

Survival measures removing the effects of competing causes of death can be considered estimators of net survival, such as relative or cause-specific survival. Use of net survival when making international comparisons is vital as background mortality differs widely between countries[85]. Relative survival is estimated from the ratio of overall survival in cancer patients to the expected survival in a comparable group from the general population. It does not require cause of death information and is estimated from life tables of the general population, which is assumed to be cancer-free. Cause specific survival is only possible when reliable information on cause of death is available. Even when cause of death information is available, such as from death certificates, it is often imprecise or lacks enough detail to determine whether cancer was the primary cause[86]. Given that cause of death information was not available for the Danish data, relative survival estimates were used for comparisons between Denmark and Yorkshire. General population survival probabilities stratified by year, sex and age (single year) were calculated from population and death tables obtained from StatBank[33] and the Office for National Statistics[32].

Multilevel modelling

Data collected in observational studies may have a hierarchical structure; for health-related research this if often the case. For example, if the response variable is the length of stay in days after a surgical procedure (*y*) and the predictor is age (*x*).

Assuming that *y_i and x_i* are independent and identically distributed, a simple regression model for this relationship would take the form:

$$y_i = \beta_0 + \beta_1 x_i + e_i$$
$$e_i \sim \mathrm{N}(0, \sigma^2)$$
$$\text{for observations } i = 1, \dots, n$$
$$\text{where } \beta_0 \text{ and } \beta_1 \text{ are the model coefficients}$$
$$e \text{ is the error term}$$
$$\sigma^2 \text{ is the variance}$$

However, if the data were collected at multiple hospitals, this model does not account for the hospital case-mix which may differ in terms of medical and social background. It would be expected that the mean length of stay differed according to hospital. So, including a hospital specific effect and assuming hospitals are randomly sampled would give (using formulation and notation by Goldstein[87]):

$$y_{ij} = \beta_0 + \beta_1 x_{ij} + \mu_{ij} + e_{ij}$$
$$\mu_j \sim \mathrm{N}(0, \sigma_\mu^2),\ e_{ij} \sim \mathrm{N}(0, \sigma_e^2)$$
$$\mathrm{cov}(\mu_j, e_{ij}) = 0,$$
$$\mathrm{cov}(y_{i1j}, y_{2j} | x_{ij}) = \sigma_\mu^2 \geq 0$$
$$\text{for hospitals } j = 1, \dots, n$$
$$\text{where } \mu_j \text{is the hospital specifc effect}$$

Then, allowing the coefficient(s) to have a random distribution gives the mixed model:

$$y_{ij} = \beta_{0ij} x_{0ij} + \beta_{1j} x_{1ij}$$
$$\beta_{0ij} = \beta_0 + \mu_{0j} + e_{0ij}$$
$$\beta_{1j} = \beta_1 + \mu_{1j}$$
$$x_{0ij} = 1$$
$$\mathrm{var}(\mu_{0j}) = \sigma_{\mu 0}^2,\ \mathrm{var}(\mu_{1j}) = \sigma_{\mu 1}^2$$
$$\mathrm{cov}(\mu_{0j}\mu_{1j}) = \sigma_{\mu 01}^2,\ \mathrm{var}(e_{0ij}) = \sigma_{e0}^2$$

Where β_0 and β_1 are referred to as fixed parameters and the variances and covariances are referred to as random parameters. Use of standard regression techniques in data with a hierarchical structure, results in underestimation of the standard errors of the coefficients, which leads to an overstatement of statistical significance. It is also beneficial to use a multilevel approach rather than including hospital as a fixed effect (as a dummy variable), as predictors defined at the hospital level (e.g. patient volume, speciality) will be confounded with the hospital dummy variables. Given that the Yorkshire and Danish data share a similar hierarchical structure, i.e. patients are nested within hospitals, the regression models used in this study have hospital fitted as a random effect.

Intrapopulation comparisons

While overall comparisons between the two populations of Denmark and Yorkshire are of great interest, any variability within each population will also be important. This is because consistency of patient care may contribute towards a difference in patient outcome, so it is of significance to identify where that variation occurs. Whilst various geographies and organisational structures exist, it is problematic to find those that are common between the two populations. For instance, regional areas often stem from historical boundaries that bear little commonalities between the two populations and the national health services have undergone organisational restructure at multiple points in the past decades. Therefore, analysis at a hospital level is the most suitable to assess intrapopulation variability.

The preferred method of making institutional comparisons (hospitals in this study) is by the use of funnel plots as outlined by Spiegelhalter[88], which avoid the spurious ranking of hospitals that may occur in league table style reporting. The funnel plot consists of 4 components[88,89]:

1. The outcome variable, sometimes referred to as the indicator. For example, postoperative mortality or hospital readmission.
2. A target value or desired expectation. For example, the average of individual estimates, the national average or a chosen rate that hospitals are expected to meet.

3. A precision parameter, to determine the statistical accuracy of the outcome estimates. This is usually the inverse variance, and an interpretable measure such as *n* (the volume of cases) is often used.
4. Control limits at given level of significance (a). These are independent of the individual estimates and depend on the target value. The chosen limits (often at a=5% and a=0.2% i.e. 2 and 3 standard deviations from the target) are drawn around the target value at each value of the precision.

The resulting plot creates a funnel shape with the wide control limits at the smaller volume hospitals gradually becoming narrower as the sample size increases (Figure 1.6). This is to allow for the greater variability in the estimates that occurs with smaller sample sizes. The hospitals with estimates lying outside the control limits are considered potential outliers and may warrant further investigation.

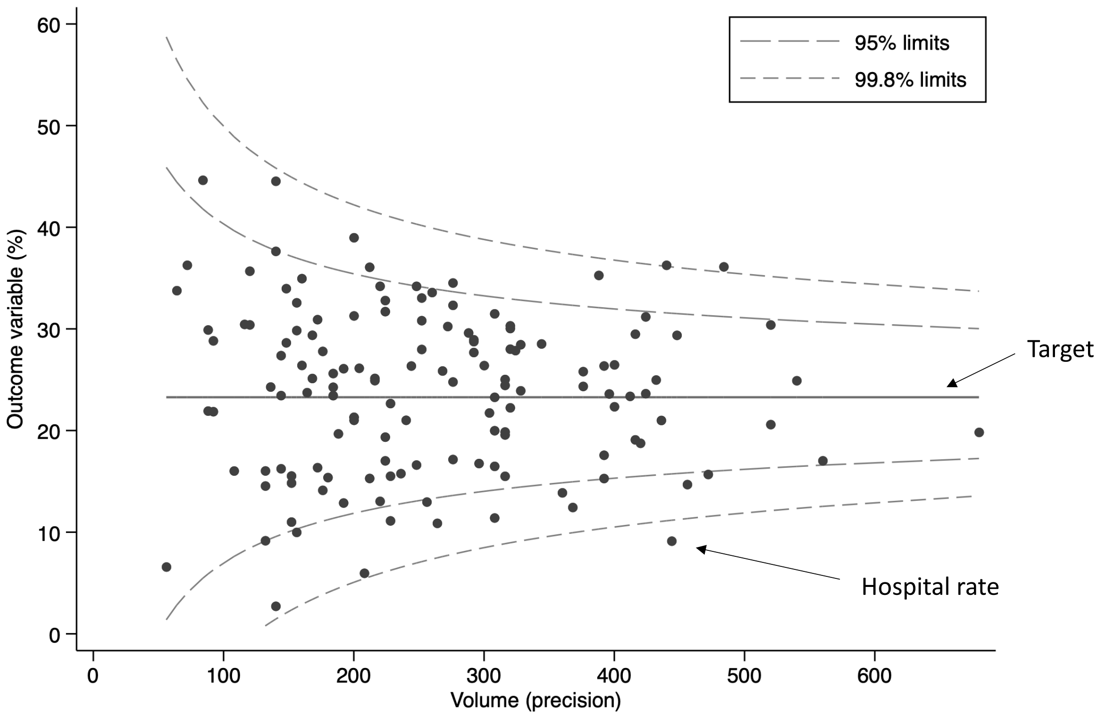

Figure 1.7 Components of a funnel plot.

Chapter 2. Influence of age on surgical treatment and postoperative outcomes of patients with colorectal cancer in Denmark and Yorkshire, England [Paper 1]

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2.1. Abstract [Paper 1]

Aim

Denmark and Yorkshire are demographically similar and both have undergone changes in their management of colorectal cancer to improve outcomes. The differential provision of surgical treatment, especially in the older age groups, may contribute to the magnitude of improved survival rates. This study aimed to identify differences in the management of colorectal cancer surgery and postoperative outcomes according to patient age between Denmark and Yorkshire.

Method

This was a retrospective population-based study of colorectal cancer patients diagnosed in Denmark and Yorkshire between 2005-2016. Proportions of patients undergoing major surgical resection, postoperative mortality and relative survival were compared between Denmark and Yorkshire across several age groups (18-59, 60-69, 70-79 and ≥80 years) and over time.

Results

The use of major surgical resection was higher in Denmark than Yorkshire, especially for patients aged ≥80 years (70.5% versus 50.5% for colon cancer, 49.3% versus 38.1% for rectal cancer). Thirty-day postoperative mortality for Danish patients aged ≥80 was significantly higher than that for Yorkshire patients with colonic cancer: OR (95% CI) = 1.22 (1.07, 1.38) but not for rectal cancer or for 1-year postoperative mortality. Relative survival significantly increased in all patients aged ≥80 years except for Yorkshire patients with colonic cancer.

Conclusion

This study suggests there are major differences between the management of elderly patients with colorectal cancer between the two populations. Improved selection for surgery and better peri- and post-operative care in these patients appears to improve long-term outcomes, but may come at the cost of a higher 30-day mortality.

What does this paper add to the literature?

Age may influence decisions to surgically treat patients with colorectal cancer and have an impact on overall survival rates. In this population-based study, we compared use of major surgical resection and how this may have impacted survival in different age-groups over a 12-year period, in two demographically similar regions of Europe.

2.2. Introduction [Paper 1]

Survival rates for patients with colorectal cancer have been shown to vary across Europe[1, 2]. In particular, it has been demonstrated that survival rates in Denmark and England were lower in the 1990s and early 2000s compared with many other countries with comparable populations and health systems[2, 3]. In response, both these countries have instigated interventions to improve colorectal cancer outcomes.

While there are common areas in which interventions have been implemented in both countries, such as the introduction of, and training in, total mesorectal excision for rectal cancer[4, 5], there have been some differences in the approaches taken. In Denmark, these interventions have included detailed reviews of readily available observational data to quantify patterns of practice, identifying areas of concern and then focussing action to improve care[6]. There is strong evidence that this has radically changed practice and has coincided with improved outcomes. For example, 30-day postoperative mortality rates have fallen dramatically and survival rates are now more comparable with neighbouring Scandinavian countries[7]. Danish 5-year net survival improved from 49% to 66% for colonic cancer and 48% to 69% for rectal cancer, compared with corresponding increases of 47% to 59% and 48% to 62% in the UK[8].

In 2016, a similar data-driven programme was implemented in Yorkshire, England. It aimed to quantify, in depth, the patterns of care and outcomes[9]. Interventions can then be developed and deployed by Yorkshire's clinical colorectal cancer community to try to eliminate any disparities in quality of care and improve outcomes. Understanding how the surgical management of patients in the region compares with that in similar demographic populations is a key element of developing these interventions. The UK and Denmark have similar populations, life expectancy, a Healthcare Access and Quality Index, smoking rates and alcohol consumption[10, 11].

Major surgical resection, to remove the tumour and surrounding tissue, i.e. bowel resection including regional lymphadenectomy, is the mainstay of treatment for colorectal cancer. It has recently been suggested that observed survival differences may stem from differences in patient selection for surgical resection, especially in older age groups[12]; and if more patients undergo a potentially curative treatment then this could lead to more patients surviving in the longer term. Although survival following surgery may be decreased in the older age groups, longer term survival may be comparable to that of younger patients[13]. It has also been demonstrated in England that older rectal cancer patients selected for surgery have comparable outcomes to their younger counterparts[14].

Given the recent substantial improvements in survival that have been observed following the clinical interventions in Denmark, comparisons of surgical practice and postoperative outcomes between Denmark and Yorkshire should help to identify areas for improvement. Therefore, this study aimed to identify any differences in the approach to colorectal cancer resection according to patient age, between Denmark and Yorkshire, and to investigate the potential impact of these on postoperative mortality and survival rates.

2.3. Materials and methods [Paper 1]

This was a retrospective population-based study, that included first-time primary colorectal cancers (ICD-10: C18-C20, excluding malignant neoplasm of the appendix C18.1), aged ≥18 years and diagnosed between 1st January 2005 and 31st December 2016 in both Denmark and Yorkshire.

Data for Denmark were obtained from the Danish Colorectal Cancer Group (DCCG) database[15]. The database captures all colorectal cancer patients who have been diagnosed and/or treated at a surgical department in a Danish public hospital. The

DCCG reports high ascertainment (95-99%) when compared with Danish National Patient Registry and the Danish Cancer Registry[15-17]. The DCCG captures the type of surgical procedure performed, if any, for all registered patients. By categorisation of these procedures, this allowed the identification of all patients who underwent a major surgical resection (Supplementary Table 2.1).

Like Denmark, the Yorkshire region has a total population of 5.7 million. The region accounts for approximately 10% of the colorectal cancer cases in England. The data for Yorkshire were sourced through the UK Colorectal Cancer Intelligence Hub's COloRECTal Repository (CORECT-R)[18]. Specifically, data from the cancer registry (National Cancer Registration and Analysis Service) were linked to hospital admission data (Hospital Episode Statistics) to identify all colorectal patients and those who underwent a major surgical resection, as described in CORECT-R's methodology[18]. The case ascertainment rate in the Yorkshire region was estimated to be 99% when compared to the Hospital Episodes Statistics dataset in the period 2001-2007[19].

Patients were deemed to have undergone a major surgical resection if the operation date occurred within one month prior, and up to one year post, the date of diagnosis. All analyses were performed separately for colon (C18-C19) and rectal cancer (C20), and further stratified by age group (18-59, 60-69, 70-79 and ≥80 years) and period of diagnosis (2005-2008, 2009-2012 and 2013-2016).

The observed percentage of patients treated with a major resection in each stratum was calculated using the total number of cases as the denominator, irrespective of treatment intent which was not available across both datasets. Odds ratios (OR) and 95% confidence intervals (CI) were then calculated comparing Denmark to Yorkshire for each stratum and also combined for the whole study period using Mantel-Haenszel weights.

To investigate the factors associated with use of major resection, we modelled Danish and Yorkshire populations separately using logistic regression with the following covariates: age group, sex, stage of disease and study period. Stage of disease was missing in 11% and 19% in Danish and Yorkshire patients respectively. Therefore, we used ordered logistic imputation to impute missing values and estimated model coefficient and standard errors according to the Rubin's combination rules (via the *mi impute* and *mi estimate* commands in Stata version 16).

To investigate the postoperative outcome following major resection, the proportion of deaths within 30 days of resection (30-day postoperative mortality) and within 1-year of resection (one-year postoperative mortality) were compared using odds ratios, with the same strata as before.

To investigate whether differences in the use of major resection may have an effect on overall outcome of colorectal patients in the two populations, we calculated 1-year survival estimates. We used relative survival using the *strs*[20] function in Stata to estimate survival and to control for any differences in background mortality between Denmark and Yorkshire. The background mortality of the general populations was estimated using life tables by sex, single year of age and calendar year. These were estimated over the three periods of diagnosis for all patients, and both resected and non-resected patients.

2.4. Results [Paper 1]

Colorectal populations

A total of 51,021 Danish and 39,456 Yorkshire patients with colorectal cancer were included. The age distribution of patients was broadly similar in the two populations at the beginning of the study, however a higher proportion of patients in Yorkshire were aged ≥80 years during the most recent period for both colonic (30.9% v 23.0%) and rectal (20.6% v 16.5%) cancer (Table 2.1). An increase in the occurrence of stage 1 colon cancers over time was observed in both populations, but comparisons between stage groups was difficult due to a differential rate of missing stage over the study period.

Table 2.1 Characteristics for patients diagnosed with colorectal cancer in Denmark and Yorkshire between 2005 and 2016.

	Denmark N (%)			Yorkshire N (%)		
	2005 - 08	2009 - 12	2013 - 2016	2005 - 08	2009 - 12	2013 - 2016
			Colon Cancer			
Total	10,186 (100.0)	10,634 (100.0)	13,321 (100.0)	8,784 (100.0)	9,628 (100.0)	9,393 (100.0)
Age (years)						
18-59	1,560 (15.3)	1,486 (14.0)	1,777 (13.3)	1,241 (14.1)	1,266 (13.1)	1,325 (14.1)
60-69	2,580 (25.3)	2,909 (27.4)	3,605 (27.1)	2,020 (23.0)	2,452 (25.5)	2,215 (23.6)
70-79	3,379 (33.2)	3,545 (33.3)	4,874 (36.6)	2,994 (34.1)	3,121 (32.4)	2,947 (31.4)
≥80	2,667 (26.2)	2,694 (25.3)	3,065 (23.0)	2,529 (28.8)	2,789 (29.0)	2,906 (30.9)
Sex						
Male	4,976 (48.9)	5,229 (49.2)	6,914 (51.9)	4,737 (53.9)	5,279 (54.8)	5,144 (54.8)
Female	5,210 (51.1)	5,405 (50.8)	6,407 (48.1)	4,047 (46.1)	4,349 (45.2)	4,249 (45.2)
Stage						
Stage 1	965 (9.5)	1,095 (10.3)	1,859 (14.0)	748 (8.5)	999 (10.4)	1,307 (13.9)
Stage 2	3,173 (31.2)	3,394 (31.9)	3,737 (28.1)	2,441 (27.8)	2,503 (26.0)	2,534 (27.0)
Stage 3	2,567 (25.2)	2,486 (23.4)	3,013 (22.6)	2,180 (24.8)	2,490 (25.9)	2,379 (25.3)
Stage 4	2,974 (29.2)	3,054 (28.7)	3,012 (22.6)	1,692 (19.3)	1,809 (18.8)	2,409 (25.6)
Unknown	507 (5.0)	605 (5.7)	1,700 (12.8)	1,723 (19.6)	1,827 (19.0)	764 (8.1)
			Rectal Cancer			
Total	5,254 (100.0)	5,449 (100.0)	6,177 (100.0)	3,732 (100.0)	4,014 (100.0)	3,905 (100.0)
Age						
18-59	1,110 (21.1)	1,050 (19.3)	1,139 (18.4)	732 (19.6)	764 (19.0)	843 (21.6)
60-69	1,583 (30.1)	1,782 (32.7)	1,920 (31.1)	1,024 (27.4)	1,135 (28.3)	1,063 (27.2)
70-79	1,525 (29.0)	1,611 (29.6)	2,099 (34.0)	1,167 (31.3)	1,257 (31.3)	1,196 (30.6)
≥80	1,036 (19.7)	1,006 (18.5)	1,019 (16.5)	809 (21.7)	858 (21.4)	803 (20.6)
Sex						
Male	3,115 (59.3)	3,343 (61.4)	3,845 (62.2)	2,379 (63.7)	2,648 (66.0)	2,550 (65.3)
Female	2,139 (40.7)	2,106 (38.6)	2,332 (37.8)	1,353 (36.3)	1,366 (34.0)	1,355 (34.7)
Stage						
Stage 1	963 (18.3)	1,129 (20.7)	1,181 (19.1)	453 (12.1)	728 (18.1)	911 (23.3)
Stage 2	1,232 (23.4)	1,248 (22.9)	944 (15.3)	436 (11.7)	627 (15.6)	684 (17.5)
Stage 3	1,237 (23.5)	1,180 (21.7)	1,146 (18.6)	504 (13.5)	897 (22.3)	1,343 (34.4)
Stage 4	1,326 (25.2)	1,367 (25.1)	1,200 (19.4)	513 (13.7)	529 (13.2)	722 (18.5)
Unknown	496 (9.4)	525 (9.6)	1,706 (27.6)	1,826 (48.9)	1,233 (30.7)	245 (6.3)

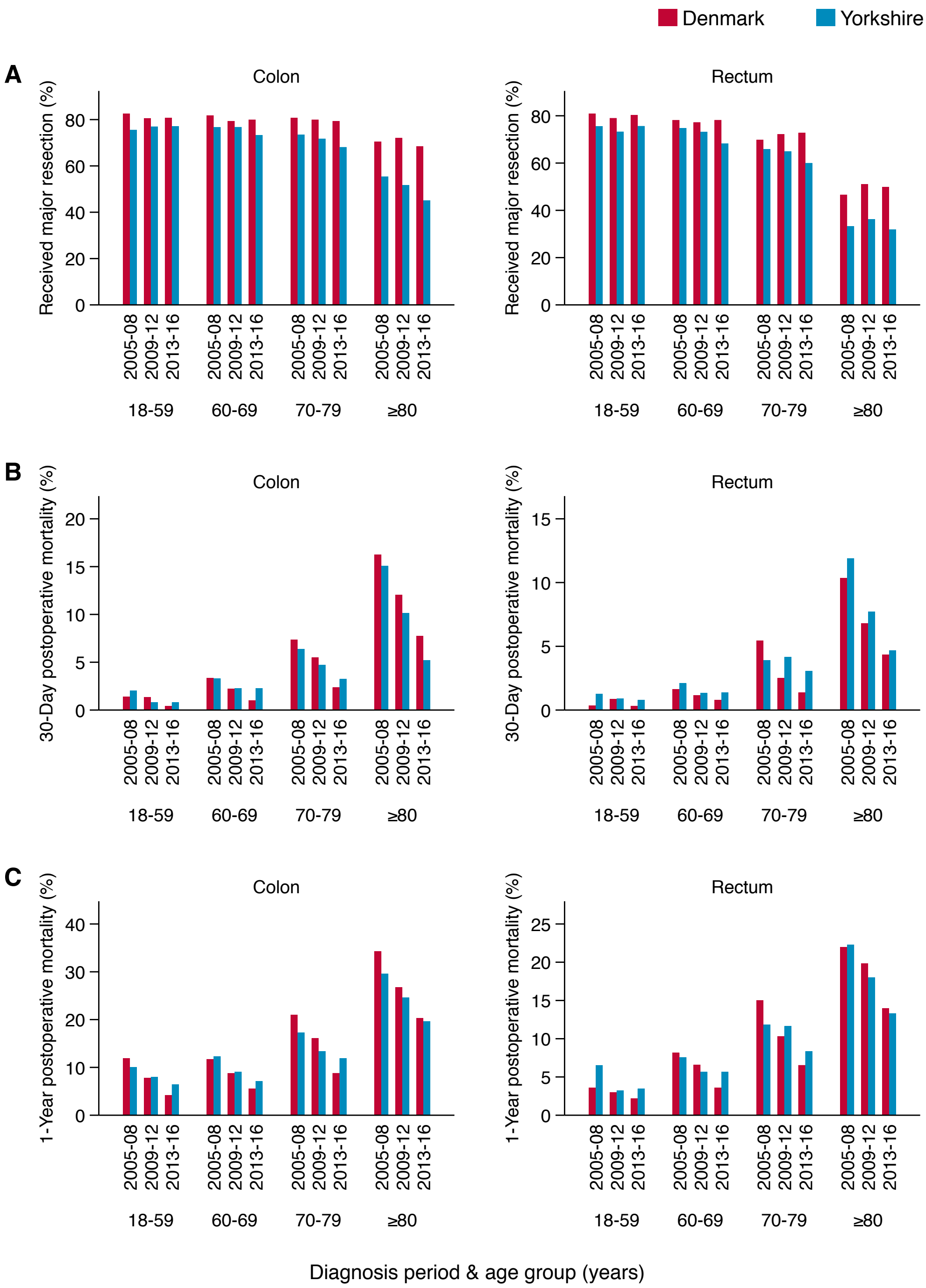

Figure 2.1 Observed percentage of patients receiving major surgical resection, irrespective of intent (A), death within 30-days of resection (B) and death within 1-year of resection (C) for patients diagnosed with colorectal cancer in Denmark and Yorkshire between 2005 and 2016.

Colon cancer resections and outcomes

Overall, the proportion of colon cancer patients treated with major resection was higher in Denmark compared to Yorkshire (77.3% v 63.5%). This was consistent across all the periods of study and the difference in the use of major resections increased with age (70.5% v 50.5% for the ≥80 age group). After adjustment for covariates, the odds of resection for those aged ≥80 compared to 60-69 years in Yorkshire was OR (95% CI) =0.26 (0.23, 0.28), which was lower than the corresponding odds in Denmark, OR (95% CI) =0.54 (0.50, 0.59) (Table 2.2). Odds of resection was also lower in Stage 3 patients compared to Stage 2 patients in Yorkshire, OR (95% CI) =0.54 (0.49,0.60) but not in Denmark, OR (95% CI) =0.97 (0.82, 1.16). Additionally, a significant decrease in the use of resection was observed over the study period for both populations (Table 2.2).

Within patients aged ≥80 years, the use of resection decreased from 55.4% to 45.1% in Yorkshire. The corresponding decrease in Denmark was much smaller, from 70.9% to 68.5% (Figure 2.1A). Figure 2.2A shows the use of major resection in Denmark compared to Yorkshire was significantly higher over all ages and study periods. Within the ≥80 age group, the use of major resection in Denmark, compared to Yorkshire, also significantly increased over time from OR (95% CI) =1.92 (1.71,2.16) in 2005-08 to 2.63 (2.36,2.93) in 2013-16.

To investigate whether the differences in the use of resection across age groups had an effect on short-term outcomes, we compared 30-day postoperative mortality between the populations (Figure 2.1B and Supplementary Table 2.3). A decrease in mortality was observed over time in all groups for both populations. Mortality was significantly higher in Denmark compared to Yorkshire in the ≥80 age group over the whole study period, OR (95% CI) =1.22 (1.07,1.38). When stratified by study period, Denmark had lower mortality than Yorkshire in 2013-16 for all except the ≥80 age group, significantly so for those aged 60-69.

To investigate differences longer-term, we compared one-year postoperative mortality between the populations (Figure 2.1C and 2.2C). By the latest study period, there was no difference in the odds of death for Danish as compared with Yorkshire patients in the

≥80 age group. Additionally, the odds of death were significantly lower in Denmark than Yorkshire in all the other age groups in 2013-16.

Table 2.2 Adjusted odds ratios (OR) and 95% confidence intervals (95% CI) for the use of major resection for patients diagnosed with colorectal cancer in Denmark and Yorkshire between 2005 and 2016.

	Denmark N (%)			**Yorkshire N (%)**		
	OR	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
			Colon Cancer			
Age (years)						
18-59	1.23	1.10 – 1.37	<0.001	1.36	1.21 – 1.53	<0.001
60-69	reference			reference		
70-79	0.92	0.84 – 1.00	0.046	0.72	0.66 – 0.79	<0.001
≥80	0.54	0.50 – 0.59	<0.001	0.26	0.23 – 0.28	<0.001
Sex						
Male	reference			reference		
Female	1.20	1.13 -1.29	<0.001	1.11	1.04 – 1.18	0.002
Stage						
Stage 1	0.27	0.23 – 0.33	<0.001	0.26	0.23 – 0.30	<0.001
Stage 2	reference			reference		
Stage 3	0.97	0.82 – 1.16	0.77	0.54	0.49 – 0.60	<0.001
Stage 4	0.03	0.02 – 0.03	<0.001	0.03	0.03 – 0.04	<0.001
Period						
2005 - 2008	reference			reference		
2009 - 2012	0.92	0.84 – 1.00	0.039	0.89	0.81 – 0.96	0.004
2013 - 2016	0.70	0.65 – 0.76	<0.001	0.74	0.68 – 0.80	<0.001
			Rectal Cancer			
Age						
18-59	1.25	1.09 – 1.43	0.001	1.31	1.13 – 1.51	<0.001
60-69	reference			reference		
70-79	0.70	0.62 – 0.78	<0.001	0.65	0.57 – 0.73	<0.001
≥80	0.25	0.22 – 0.29	<0.001	0.16	0.14 – 0.19	<0.001
Sex						
Male	reference			reference		
Female	0.97	0.88 – 1.06	0.50	1.02	0.93 – 1.12	0.67
Stage						
Stage 1	0.48	0.39 – 0.58	<0.001	0.40	0.33 – 0.48	<0.001
Stage 2	reference			reference		
Stage 3	1.04	0.85 – 1.28	0.71	0.80	0.68 – 0.93	0.005
Stage 4	0.03	0.03 – 0.04	<0.01	0.06	0.05 – 0.07	<0.001
Period						
2005 - 2008	reference			reference		
2009 - 2012	1.09	0.98 – 1.22	0.12	0.85	0.76 – 0.95	0.006
2013 - 2016	1.02	0.92 – 1.14	0.72	0.67	0.60 – 0.76	<0.001

Rectal cancer resections and outcomes

Overall, the proportion treated with major resection, was higher in Denmark than in Yorkshire (71.2% v 61.9%), this difference increased with age (Figure 2.1A and Supplementary Table 2.2), with the largest difference in the ≥80 age group (49.3% v 38.1%, over the whole study period). Adjusted models showed similar results to colonic cancer, but with a stronger influence of age in both populations and no significant decrease over time in Danish patients (Table 2.2). Odds of resection was lower in Stage 3 patients compared to Stage 2 patients in Yorkshire, OR (95% CI) =0.80 (0.68,0.93) but not in Denmark, OR (95% CI) =1.04 (0.85, 1.28). However, unlike colon cancer, there was no large decrease over time in the observed proportion of resections for Yorkshire patients aged ≥80 years (33.3% to 31.9%, Figure 1A).

The difference in use of major resection was significant in all age groups, with an increase in odds of major resection in Denmark compared to Yorkshire with increasing age group (Figure 2.3A). Within the ≥80 age group, the odds of resection in Denmark compared to Yorkshire increased, but not significantly, over time from OR (95% CI) =1.75 (1.44,2.13) to 2.12 (1.74,2.59).

Thirty-day mortality was similar across the majority of age groups (Figure 2.1B and Supplementary Table 2.2) including in the ≥80 age group; OR (95% CI) =0.87 (0.64,1.20) over the whole study period. The only significant difference was observed in the 70-79 age group during the last study period, with lower odds of death in Denmark compared to Yorkshire. When comparing 1-year postoperative mortality, Denmark had significantly lower mortality than Yorkshire for the youngest age group in 2005-08 and those aged 60-69 in 2013-16 (Figure 2.1C and 2.3C).

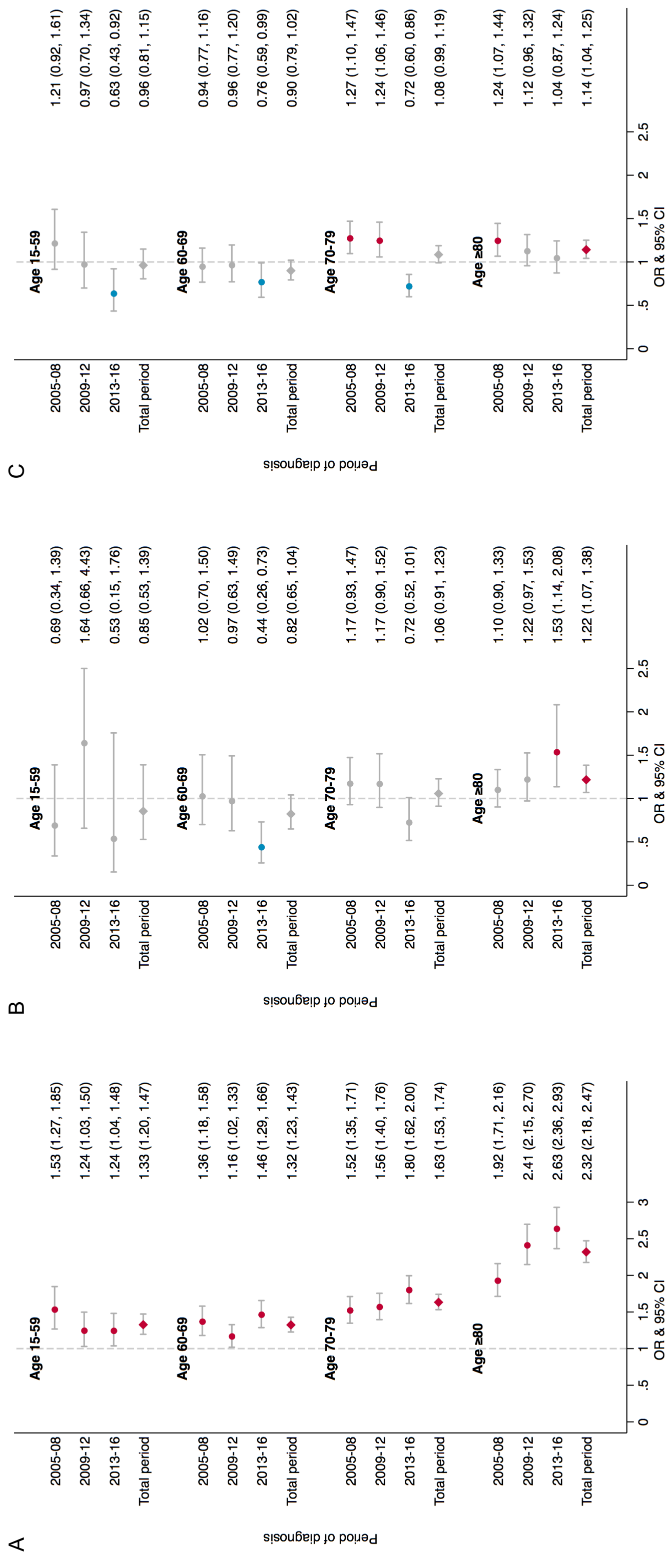

Figure 2.2 Odds ratios and 95% confidence intervals for major surgical resection (A), death within 30-days of resection (B), and death within 1-year of resection (C) in Denmark compared to Yorkshire, by age and period of diagnosis in colonic cancer. Significant results are indicated in red (increased odds in Denmark) and blue (increased odds in Yorkshire).

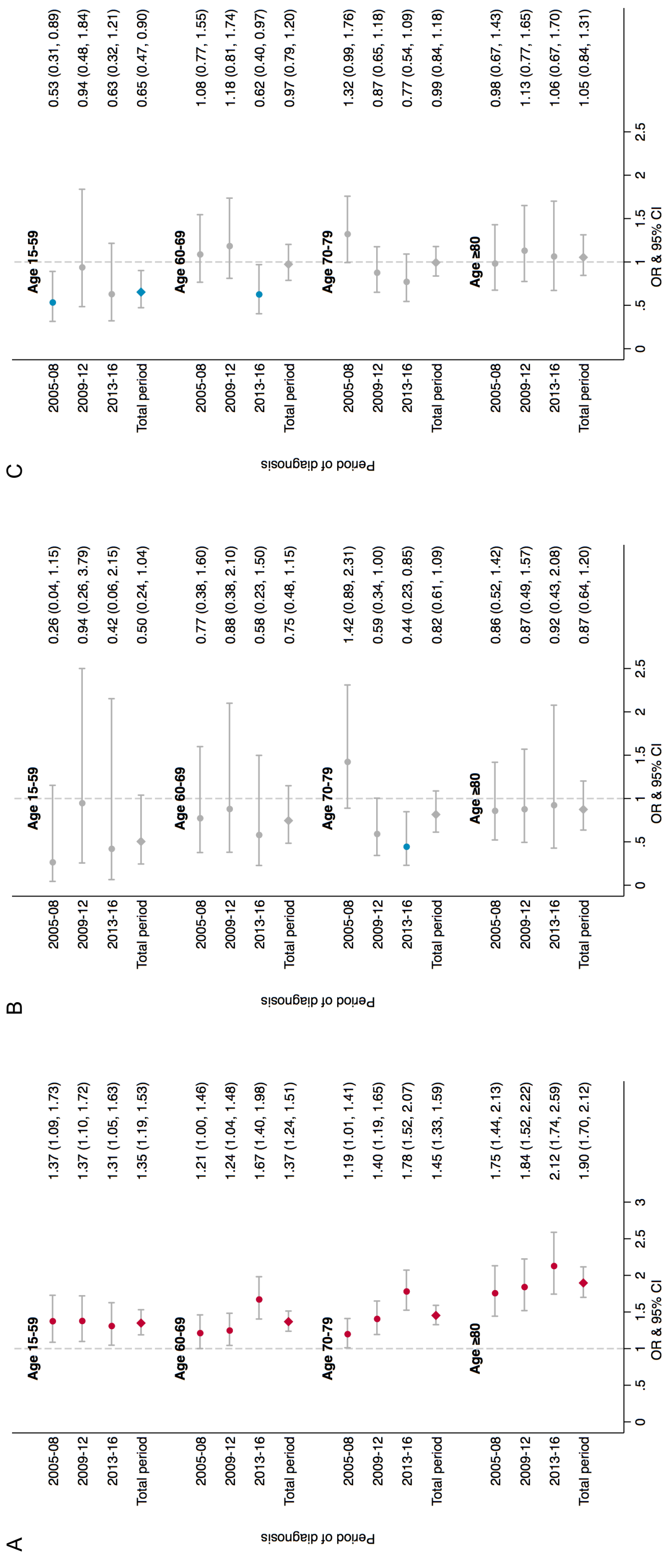

Figure 2.3 Odds ratios and 95% confidence intervals for major surgical resection (A), death within 30-days of resection (B), and death within 1-year of resection (C) in Denmark compared to Yorkshire, by age and period of diagnosis in rectal cancer. Significant results are indicated in red (increased odds in Denmark) and blue (increased odds in Yorkshire).

Impact on 1-year relative survival over time

For the entire cohort of patients with colonic cancer, relative survival in Denmark significantly improved over the study period for all patient age groups, including those aged ≥80 years (Figure 2.4A). Survival for patients with colonic cancer in Yorkshire showed a non-significant increase in all age groups. In non-resected patients, significant increases in relative survival were observed for all age groups ≥60 years in Denmark, and in Yorkshire for those aged ≥80 years.

For the entire cohort of patients with rectal cancer, relative survival in Denmark displayed a consistent significant improvement over time in all ages (Figure 2.4B). Relative survival In Yorkshire did not significantly improve in patients <80 years, but a large significant improvement was observed in those aged ≥80 years. Also of note, was a particularly large increase in survival for non-resected patients for those aged 70-79 years in Denmark and those aged ≥80 years in Yorkshire.

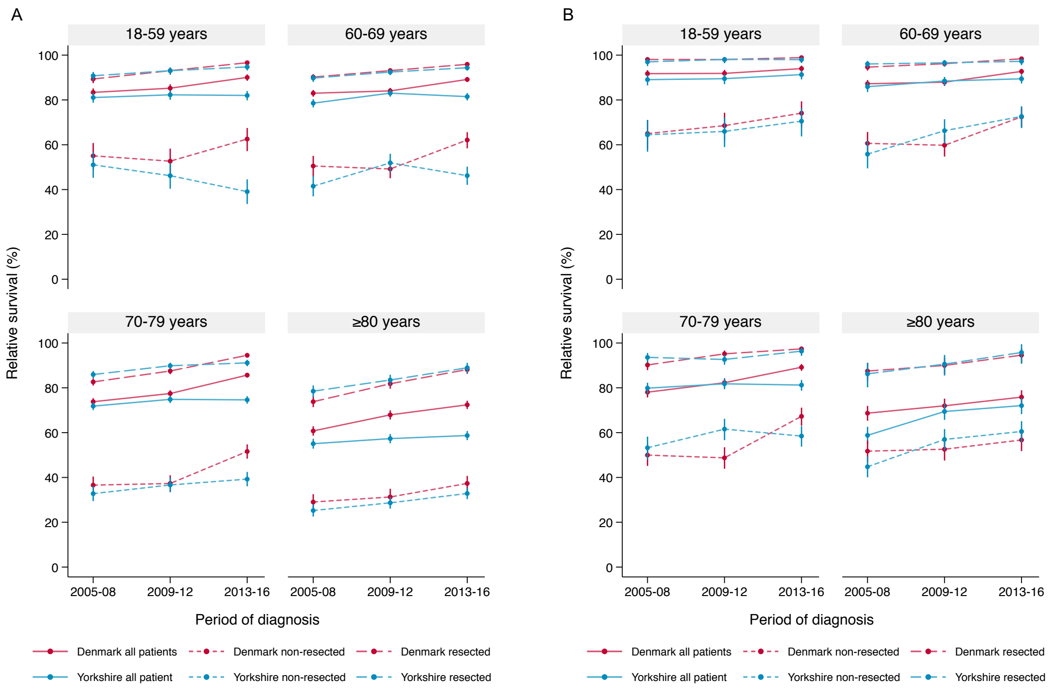

Figure 2.4 One-year relative survival and 95% confidence intervals stratified by age and period of diagnosis for all patients with colon cancer (A) and rectal cancer (B) in Denmark and Yorkshire, and by resection status.

2.5. Discussion [Paper 1]

This retrospective population-based study has shown a differing approach to surgical management of patients with colorectal cancer between Denmark and Yorkshire, especially in older age groups. A higher proportion of all patients underwent major surgical resection in Denmark and, of these patients, long-term postoperative mortality was as low as that in Yorkshire. High use of major resection in those aged ≥80 years in Denmark has been maintained while still increasing overall rates of survival, whereas decreasing use of resection in Yorkshire patients with colon cancer of the same age, has coincided with period of unchanging survival.

Although differences in the rates of use of resection for colonic cancer were found across all age groups, the most pronounced difference was found in those aged ≥80 years, but also with noticeable differences in those aged 70-79 years. There is a concern that increased use of resection in older age groups will lead to a higher postoperative mortality as they are more likely to have existing comorbidity and frailty[13]. Some evidence for this was observed here, as there was an increased odds of death within 30-days for Danish patients with colonic cancer cases aged ≥80 years. However, 1-year postoperative mortality in this age group in Denmark was equivalent to that observed in Yorkshire patients, and was actually lower for the latest study period in patients aged 70-79 years. The potential for a trade-off between increased short-term risk and longer-term benefit has been suggested previously when considering treatment of the older population[13]. It is also worth noting that 30-day postoperative mortality decreased sharply over time in both populations (16.2% to 7.7% in Denmark, 15.1% to 5.2% in Yorkshire), which suggests patient care in the ≥80 age group has improved considerably and needs to be considered in patient selection for surgery.

Given that relative survival for resected patients aged ≥80 years with colonic cancer in Yorkshire improved over the study period, but not for all patients aged ≥80, it is possible that this could be because of a tendency to select fewer elderly patients for major resection. Whereas use of a major resection in Yorkshire decreased over the study period, the Danish maintained relatively high use whilst still increasing 1-year relative survival. As more of the Danish patients aged ≥80 years received surgical resection, this could explain the substantial difference in relative survival between the two cohorts of patients in this age group.

Use of major resection was lower for rectal cancer in both countries. This is to be expected since a number of patients will have alternative treatments including radiotherapy[21] and local surgical resection[22]. However, use of major resection was again higher in the Danish population. Unlike in colon cancer, the higher rate of resections did not coincide with a higher 30-day mortality for Danish patients aged ≥80 years compared to Yorkshire and the mortality was significantly lower when comparing Danish and Yorkshire patients aged 70-79 years.

Whereas, use of a major resection in Yorkshire for colonic cancer in patients aged ≥80 years decreased over time, the same was not true for the equivalent rectal cancer population. This coincided with an improvement in 1-year relative survival for Yorkshire patients of this age and was, in fact, the only age group in Yorkshire to exhibit a significant improvement. As with colon cancer, relative survival steadily increased for the older age groups in both populations suggesting an improvement in patient care. Interestingly, relative survival in the non-resected Danish patients aged <80 years improved dramatically from 2009-12 to 2013-16, which could possibly be due to increased survival for patients with metastatic disease.

Older patients are more likely to suffer from existing comorbidities and frailty. Therefore, it is an important issue to establish why the Danes appears more likely to operate in the older age groups than their counterparts in Yorkshire. Centralisation of colorectal surgical treatment was implemented in Denmark during the 2000s[4, 23], but the resulting number of centres is similar to that found in Yorkshire[9] with an equivalent size population. The increased number of Danish cases shown in the last period of this study is almost certainly due to the later introduction of screening[24]. The impact of screening and centralisation will have resulted in a higher number of cases per centre and, possibly, a higher per surgeon workload. Increased hospital and surgeon workload have shown associations with better outcomes in colorectal cancer[25, 26]. Preoperative and postoperative initiatives may also differ, for example, enhanced recovery after surgery (ERAS) has been adopted widely in Denmark[7], but not region-wide within

Yorkshire. Since ERAS has been shown to lower the risk of postoperative complications and reduce recovery time[27], having such a policy in place may increase the willingness to operate. Additionally, Denmark is known to have a high uptake of laparoscopic surgery[6], which has been associated with reduced length of hospital stay and 30-day mortality compared to those having open surgery[28] and could be a contributing factor when considering patient recovery.

There are limitations in this study and the implications of comparing the two datasets needs to be considered. Potential disparities in case ascertainment may have a marginal effect on estimates of ORs when comparing proportions of resections between the two populations. However, we calculated that over 60% of colon cancer and over 40% of rectal cancer cases in Denmark would need to be missing in the ≥80 age group in 2013-16 for differences in ORs to be non-significant.

There are likely to be additional differences between the two datasets that may have an impact when investigating surgical management. The DCCG records the surgical procedure used at the time of operation, whereas the CORECT-R methodology uses an algorithm to retrospectively search hospital admission records and identify those patients who underwent a major resection. In addition, it is important to take into consideration the possibility that international comparison of survival estimates may be impacted by differences in cancer registration practices[29]. This includes the completeness of the registration source[19, 30, 31] or errors in registration such as in the date of diagnosis[32]. However, it is unlikely to impact the survival estimates to the extent that it explains the observed differences[33].

The increased number of unknown stages in Denmark over time was largely due to revised TNM guidelines in 2014, as some who were to receive neoadjuvant radio-(chemo-)therapy may not have been given an initial stage due to the possibility of down-staging and thus classified as ‘stage unknown’. Conversely, staging information for Yorkshire patients improved over time. Thus, stratifying by stage groups may have resulted in spurious associations. Our stage-imputed models suggested a difference in the use of resection according to stage. Stage 3 patients were less likely to have a major resection than Stage 2 patients in Yorkshire, but not in Denmark. Further work investigating this using additional treatment information, or detailed TNM information would improve stratification, allowing the impact of neoadjuvant radiotherapy in Stage 3 patients and use of local resections in Stage 1 patients to be assessed. Additionally, detailed comorbidity, performance status and lifestyle factors would all allow more detailed investigation of the differences shown in this study.

This study shows greater use of major resection in the older age groups for the Danish colorectal cancer population when compared with Yorkshire, corresponding to an increased short-term risk in colon cancer patients aged over 80 years, but no increased risk in the longer-term or in rectal cancer. If this is confirmed through further study we should be able to identify more patients from Yorkshire who, with appropriate improvement of selection and improved peri- and post-operative care, are suitable for potentially curative surgery, thus improving long-term outcomes. It is important to appropriately communicate the risks of surgery, but it is also possible that many older patients in Yorkshire would benefit from consideration of a major resection.

2.6. Acknowledgements [Paper 1]

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The study was granted ethical approval (17/WM/0374) by the West Midlands - Solihull Research Ethics Committee in December 2017. The study was approved by the Health Research Authority and granted approval for inclusion in the National Institute for Health Research's portfolio of studies in December 2017 (Project ID 227673)

The UK Colorectal Intelligence Hub played a vital role in collating and quality assuring the Yorkshire data assisted by Health Data Insight CiC. We thank the Danish Colorectal Cancer Group (DCCG) for the provision of Danish data presented in this study.

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The data used for this study are available from the National Cancer Registration and Analysis Service via application to the Public Health England Office for Data Release and CORECT-R, and application to the DCCG, subject to relevant approvals.

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2.8. Supplementary information [Paper 1]

Supplementary Table 2.1 Categorisation of Danish Colorectal Cancer Group (DCCG) database operation codes into the major surgical resection grouping.

DCCG code	DCCG Operation	Major resection category (Y/N)
1	Ileocecal resection	Yes
2	Right hemicolectomy	Yes
3	Extended right hemicolectomy	Yes
4	Resection of traverse colon	Yes
5	Left hemicolectomy	Yes
6	Resection of sigmoid colon	Yes
7	Resection of sigmoid colon with colostomy	Yes
8	Other combined resection of small intestine and colon	Yes
9	Other colonic resection without colostomy	Yes
10	Other colectomy with colostomy and distal closure	Yes
11	Colectomy and ileorectostomy (anastomosis)	Yes
12	Colectomy and ileostomy	Yes
13	Rectal resection (TME and PME)	Yes
14	Rectal resection + colostomy (=Hartmann's)	Yes
15	APE, ischioanal	Yes
16	APE, extralevator (ELAPE)	Yes
17	APE, conventional	Yes
18	APE, intersphincteric	Yes
19	Proctocolectomy and ileostomy	Yes
20	Alleviating only (bypass, stoma)	No
21	Exploration only	No
22	Transanal endoscopic microsurgery (TEM)	No
23	Other local procedures incl. polypectomy-EMR	No
24	Stent in rectum	No
25	Stent in colon	No

Supplementary Table 2.2 Observed percentage of patients receiving major surgical resection, irrespective of intent, for patients diagnosed with colorectal cancer in Denmark and Yorkshire between 2005 and 2016.

	Denmark N (%)			**Yorkshire N (%)**		
	2005 - 08	**2009 - 12**	**2013 - 2016**	**2005 - 08**	**2009 - 12**	**2013 - 2016**
			Colon Cancer			
Total	8,067 (79.2)	8,319 (78.2)	10,301 (77.3)	6,089 (69.3)	6,539 (67.9)	5,964 (63.5)
Age (years)						
18-59	1,296 (83.1)	1,204 (81.0)	1,436 (80.8)	938 (75.6)	975 (77.0)	1,022 (77.1)
60-69	2,127 (82.4)	2,323 (79.9)	2,889 (80.1)	1,550 (76.7)	1,883 (76.8)	1,622 (73.2)
70-79	2,753 (81.5)	2,844 (80.2)	3,877 (79.5)	2,199 (73.4)	2,240 (71.8)	2,008 (68.1)
≥80	1,891 (70.9)	1,948 (72.3)	2,099 (68.5)	1,402 (55.4)	1,441 (51.7)	1,312 (45.1)
Sex						
Male	3,923 (78.8)	4,036 (77.2)	5,239 (75.8)	3,277 (69.2)	3,622 (68.6)	3,292 (64.0)
Female	4,144 (79.5)	4,283 (79.2)	5,062 (79.0)	2,812 (69.5)	2,917 (67.1)	2,672 (62.9)
Stage						
Stage 1	874 (90.6)	1,031 (94.2)	1,841 (99.0)	666 (89.0)	854 (85.5)	880 (67.3)
Stage 2	3,091 (97.4)	3,368 (99.2)	3,735 (99.9)	2,360 (96.7)	2,392 (95.6)	2,269 (89.5)
Stage 3	2,483 (96.7)	2,460 (99.0)	2,987 (99.1)	2,090 (95.9)	2,377 (95.5)	2,029 (85.3)
Stage 4	1,586 (53.3)	1,389 (45.5)	1,194 (39.6)	599 (35.4)	590 (32.6)	749 (31.1)
Unknown	33 (6.5)	71 (11.7)	544 (32.0)	374 (21.7)	326 (17.8)	37 (4.8)
			Rectal Cancer			
Total	3,712 (70.7)	3,904 (71.6)	4,466 (72.3)	2,357 (63.2)	2,519 (62.8)	2,338 (59.9)
Age						
18-59	905 (81.5)	837 (79.7)	918 (80.6)	553 (75.5)	560 (73.3)	638 (75.7)
60-69	1,248 (78.8)	1,385 (77.7)	1,505 (78.4)	766 (74.8)	831 (73.2)	726 (68.3)
70-79	1,075 (70.5)	1,167 (72.4)	1,533 (73.0)	769 (65.9)	817 (65.0)	718 (60.0)
≥80	484 (46.7)	515 (51.2)	510 (50.0)	269 (33.3)	311 (36.2)	256 (31.9)
Sex						
Male	2,243 (72.0)	2,418 (72.3)	2,813 (73.2)	1,531 (64.4)	1,694 (64.0)	1,537 (60.3)
Female	1,469 (68.7)	1,486 (70.6)	1,653 (70.9)	826 (61.0)	825 (60.4)	801 (59.1)
Stage						
Stage 1	868 (90.1)	1,066 (94.4)	1,145 (97.0)	358 (79.0)	555 (76.2)	507 (55.7)
Stage 2	1,195 (97.0)	1,210 (97.0)	932 (98.7)	386 (88.5)	568 (90.6)	533 (77.9)
Stage 3	1,162 (93.9)	1,142 (96.8)	1,115 (97.3)	448 (88.9)	789 (88.0)	1,091 (81.2)
Stage 4	445 (33.6)	462 (33.8)	442 (36.8)	140 (27.3)	132 (25.0)	185 (25.6)
Unknown	42 (8.5)	24 (4.6)	832 (48.8)	1,025 (56.1)	475 (38.5)	22 (9.0)

Supplementary Table 2.3 Observed percentage of patient deaths within 30-days of major surgical resection for patients diagnosed with colorectal cancer in Denmark and Yorkshire between 2005 and 2016.

	Denmark N (%)			**Yorkshire N (%)**		
	2005 - 08	**2009 - 12**	**2013 - 2016**	**2005 - 08**	**2009 - 12**	**2013 - 2016**
Colon Cancer						
Total	7.4	5.5	2.8	6.9	4.6	3.0
Age (years)						
18-59	1.4	1.3	<1.0	2.1	<1.0	<1.0
60-69	3.4	2.2	<1.0	3.3	2.3	2.3
70-79	7.3	5.5	2.3	6.4	4.7	3.2
≥80	16.2	12.1	7.7	15.1	10.1	5.2
Rectal Cancer						
Total	3.5	2.2	1.3	3.6	2.9	2.1
Age (years)						
18-59	<1.0	<1.0	<1.0	1.3	0.9	<1.0
60-69	1.6	1.2	<1.0	2.1	1.3	1.4
70-79	5.4	2.5	1.4	3.9	4.2	3.1
≥80	10.4	6.8	4.3	11.9	7.7	4.7

Supplementary Table 2.4 Observed percentage of patient deaths within 1-year of major surgical resection for patients diagnosed with colorectal cancer in Denmark and Yorkshire between 2005 and 2016.

	Denmark N (%)			Yorkshire N (%)		
	2005 - 08	**2009 - 12**	**2013 - 2016**	**2005 - 08**	**2009 - 12**	**2013 - 2016**
			Colon Cancer			
Total	20.2	15.3	9.6	17.7	13.8	11.4
Age (years)						
18-59	11.9	7.8	4.2	10.0	8.0	6.5
60-69	11.7	8.7	5.5	12.3	9.1	7.1
70-79	21.0	16.1	8.8	17.3	13.3	11.9
≥80	34.3	26.8	20.3	29.6	24.6	19.7
			Rectal Cancer			
Total	10.8	8.7	5.5	10.4	8.6	6.7
Age (years)						
18-59	3.6	3.0	2.2	6.5	3.2	3.4
60-69	8.2	6.6	3.6	7.6	5.7	5.6
70-79	15.0	10.3	6.5	11.8	11.6	8.4
≥80	21.9	19.8	14.0	22.3	18.0	13.3

2.9. Additional unpublished material [Paper 1]

Excluding patients with advanced disease

To account for any influence of advanced disease on surgical management, a subset analysis was performed by restricting to patients with disease stage 1-3. The percentage of those receiving major surgical resection, 30-day postoperative mortality and 1-year postoperative mortality we calculated as previously described by study diagnosis period and age group.

The percentage of stage 1-3 patients with colon cancer receiving a major resection was >95% in Denmark, regardless of diagnosis period or age (Figure 2.5). The percentage in Yorkshire was similar to that in Denmark for each age group in 2005-08 but had decreased by 2013-16. Nearly all colon cancer patients aged ≥80 years in Denmark received a major resection (99.8%) in 2013-16 compared to just over two thirds of patients in Yorkshire (68.9%). In rectal cancer, percentages were lower but similar trends were observed to that in colon cancer. In Denmark, 94.5% of rectal cancer patients aged ≥80 years received a major resection in 2013-16 compared to 44.5% in Yorkshire.

For 30-day postoperative mortality, the results when restricting to stage 1-3 show similar trends to the results when considering all patients.

Denmark saw a decrease in 1-year postoperative mortality for stage 1-3 rectal cancer patients aged ≥80 (19.7% in 2005-08 to 13.7% in 2013-16), whereas those in Yorkshire observed a slight increase (16.3% in 2005-08 to 17.3% in 2013-16). This is different to the results when considering all patients, which saw a decrease in both populations. It should, however, be noted that patients with unknown stage were also excluded here, which may impact the results.

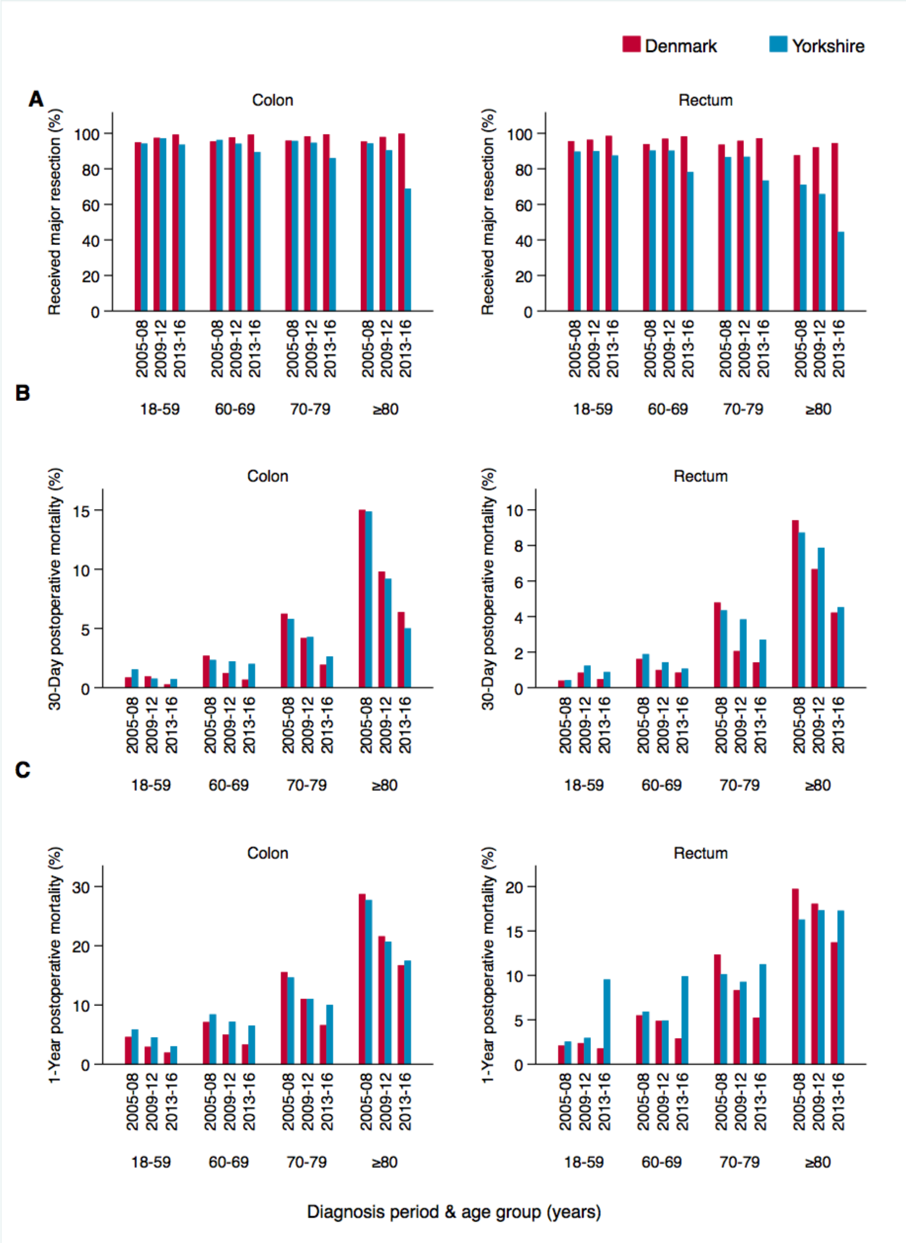

Figure 2.5 Observed percentage of stage 1-3 patients receiving major surgical resection, irrespective of intent (A), death within 30-days of resection (B) and death within 1-year of resection (C) for patients diagnosed with colorectal cancer in Denmark and Yorkshire between 2005 and 2016.

Use of minor resections

The percentage of minor (or local) surgical resections were estimated to assess whether this could explain some of the differences in the rates of major resections between Denmark and Yorkshire. The Danish data were retrieved from the surgical procedure field and those who underwent ‘transanal endoscopic microsurgery’ or ‘other local resections including polyp removal/EMR’ were categorised as undergoing a minor surgical resection. The Yorkshire data were categorised as undergoing a minor resection using CORECT-R’s methodology which uses HES admission codes analogous to the methodology used to assign major resections. However, unlike the major resection methodology, data using the minor resection categorisation have not been verified and published so care should be taken when interpreting results.

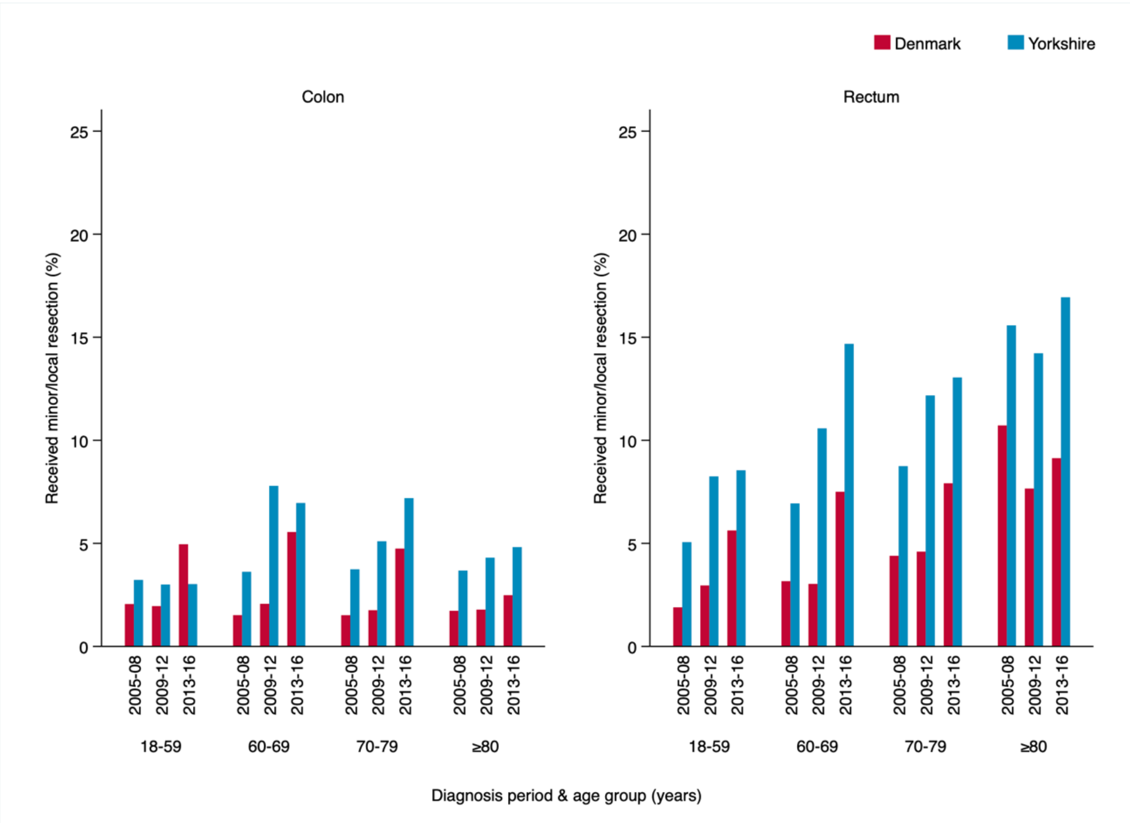

Figure 2.6 Observed percentage of patients receiving minor surgical resection for patients diagnosed with colorectal cancer in Denmark and Yorkshire between 2005 and 2016.

A general increase in use of minor resections was observed over time for both Denmark and Yorkshire, with increases most prominent in rectal cancer rather than colon cancer. Overall, a higher percentage of patients in Yorkshire received a minor resection than those in Denmark for colon cancer (2013-16: Yorkshire 5.8% vs Denmark 4.5%) and rectal cancer (2013-16: Yorkshire 13.3% vs 7.8%). For rectal cancer only, use of minor resection increased with age in both populations (Figure 2.6); for those age ≥80 years in 2013-16 use in Yorkshire was higher than that in Denmark (16.9% vs 9.1%).

Additional time-points for outcomes

The published results present relatively short-term outcomes (30-day postoperative mortality, 1-year postoperative mortality and 1-year relative survival). Therefore additional time-points were added to investigate longer-term outcomes: 2-year postoperative mortality and 2-year relative survival.

The results for 2-year postoperative mortality were similar to that for 1-year postoperative mortality in both colon cancer (Figure 2.7A) and in rectal cancer (Figure 2.7B). The main difference being there was a significant higher risk of death in Yorkshire compared to Denmark for those aged 70-79 with colon cancer OR (95% CI) = 0.63 (0.49, 0.82).

As observed for 1-year relative survival, two-year relative survival was significantly higher in Denmark than Yorkshire for all age groups by 2013-2016. This was also the case for rectal cancer, including those aged ≥80 years (Figure 2.8).

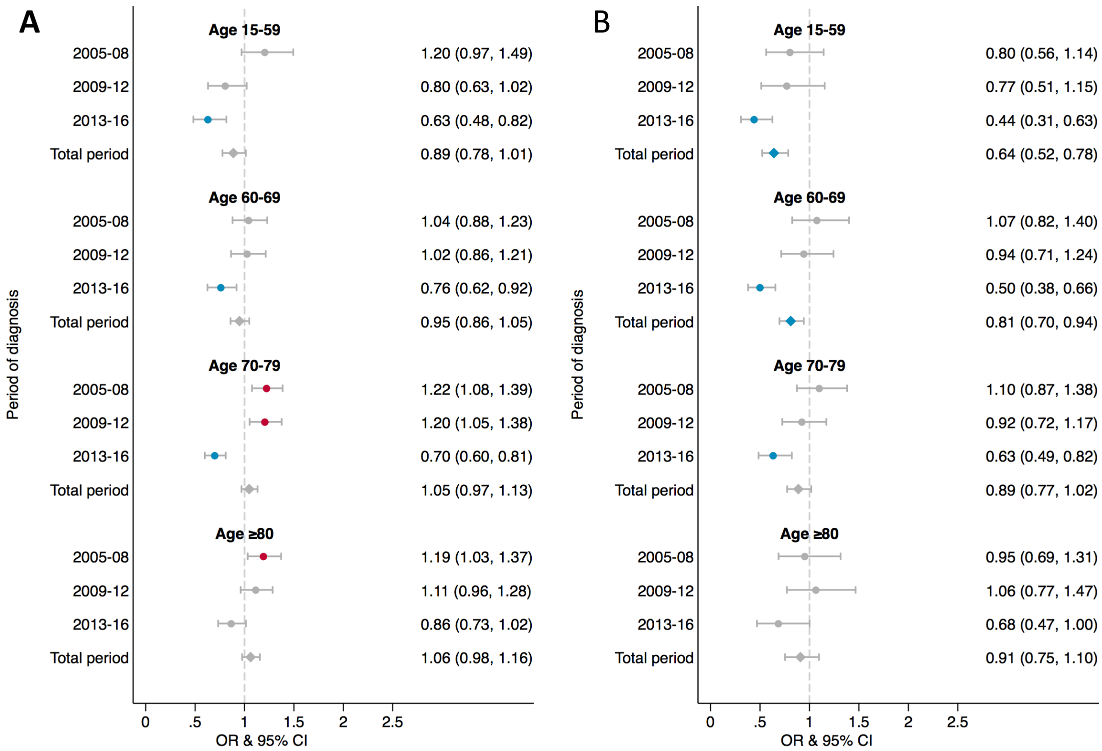

Figure 2.7 Odds ratios and 95% confidence intervals for death within 1-year of resection in Denmark compared to Yorkshire, by age and period of diagnosis in colonic cancer (A) and rectal cancer (B). Significant results are indicated in red (increased odds in Denmark) and blue (increased odds in Yorkshire).

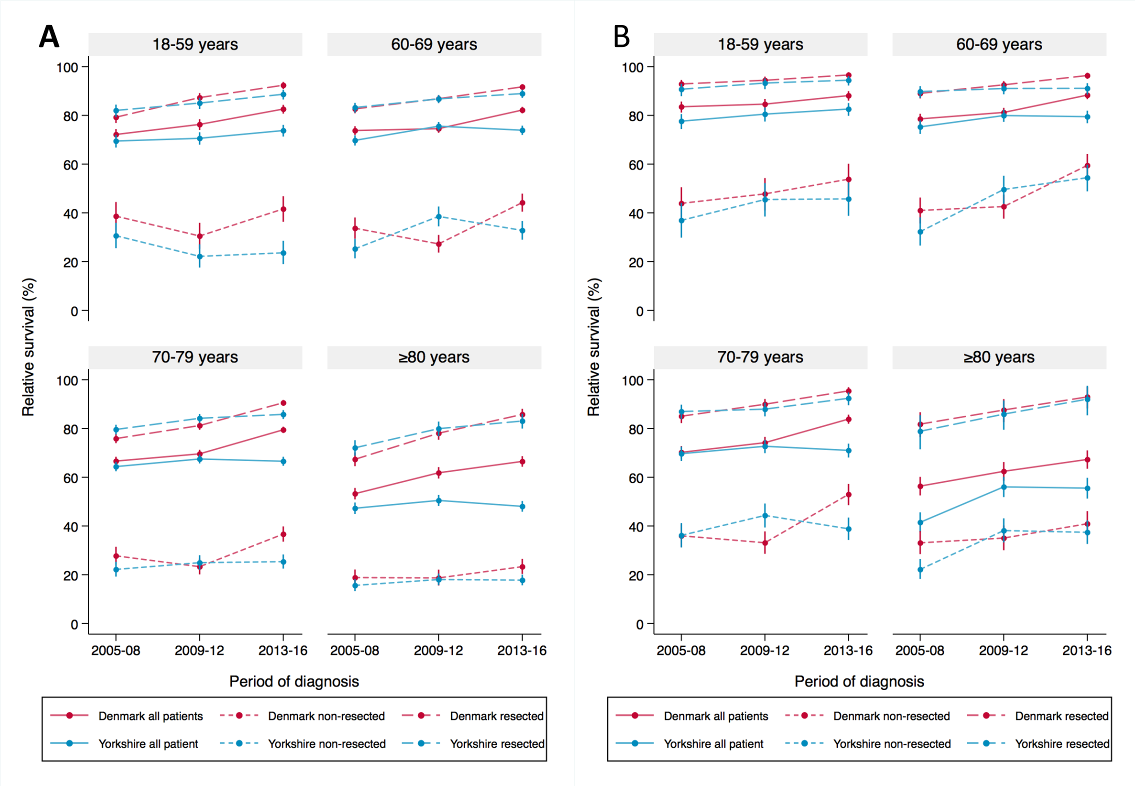

Figure 2.8 Two-year relative survival and 95% confidence intervals stratified by age and period of diagnosis for all patients with colon cancer (A) and rectal cancer (B) in Denmark and Yorkshire, and by resection status.

Sensitivity analyses

Any potential disparities in case ascertainment may have an effect on estimated ORs when comparing proportions of resection between the two populations. Therefore sensitivity analyses were conducted by assuming a percentage of cases were missing in the Denmark dataset. We recalculated ORs and 95% CIs for differing missing rates of 5% upwards in those aged ≥80 years in the 2013-16 diagnosis period (Table 2.3). A missing rate of 0% corresponds to the raw data used in the publication. A reasonable assumption of 5% or 10% missing data had little influence on the significant result of higher major resection rates in Denmark. Even assuming extreme levels of missing data (50% in colon cancer, 40% in rectal cancer) still gave significant results.

Table 2.3 Recalculated odds ratios (OR) and 95% confidence intervals (CI) for major surgical resection in Denmark compared to Yorkshire for patients ≥80 years in 2013-16, assuming differing rates of missing Danish data.

Assumed missing Denmark cases	Colon Cancer OR (95% CI)	Significant	Rectal Cancer OR (95% CI)	Significant
0%	2.63 (2.36, 2.93)	Yes	2.12 (1.74, 2.59)	Yes
5%	2.50 (2.25, 2.78)	Yes	2.02 (1.66, 2.46)	Yes
10%	2.37 (2.13, 2.63)	Yes	1.91 (1.57, 2.32)	Yes
20%	2.11 (1.90, 2.33)	Yes	1.70 (1.40, 2.06)	Yes
30%	1.84 (1.67, 2.04)	Yes	1.49 (1.23, 1.80)	Yes
40%	1.58 (1.43, 1.74)	Yes	1.27 (1.05, 1.54)	Yes
50%	1.32 (1.19, 1.45)	Yes	1.06 (0.88, 1.28)	No
60%	1.05 (0.96, 1.16)	No	0.85 (0.71, 1.02)	No

Modelling major resection

To investigate whether the association between major resection and age remained consistent over time, a multilevel logistic regression stratified by diagnosis period was fitted with the following covariates: age group, sex, stage of disease and tumour site, and hospital as a random effect. As described previously in the methods, ordered logistic imputation was used to impute missing values of disease stage via the *mi impute* and *mi estimate* commands in Stata.

The reference group for age was 60-69 years. When compared to the reference, the OR for major resection in Yorkshire patients aged ≥80 remained consistent (approximately

0.20) over each study period. This was not the case in Danish patients, where the OR increased from 0.35 in 2005-08 to 0.49 in 2013-16 (Table 2.4).

Table 2.4 Adjusted odds ratios (OR) and 95% confidence intervals (95% CI) for the use of major resection for patients diagnosed with colorectal cancer in Denmark and Yorkshire between 2005 and 2016, stratified by diagnosis period.

	2005 – 2008 **OR (95% CI)**	**P-value**	**2009 – 2012** **OR (95% CI)**	**P-value**	**2013 – 2016** **OR (95% CI)**	**P-value**
			Denmark			
Age (years)						
18-59	1.26 (1.09, 1.46)	0.002	1.15 (0.98, 1.34)	0.077	1.27 (1.09, 1.46)	0.001
60-69	reference		reference		reference	
70-79	0.73 (0.64, 0.82)	<0.001	0.83 (0.73, 0.94)	0.003	0.91 (0.81, 1.01)	0.075
≥80	0.35 (0.31, 0.40)	<0.001	0.41 (0.36, 0.47)	<0.001	0.49 (0.44, 0.56)	<0.001
Sex						
Male	reference		reference		reference	
Female	1.08 (0.98, 1.19)	0.12	1.13 (1.02, 1.24)	0.015	1.14 (1.04, 1.24)	0.005
Stage						
Stage 1	0.34 (0.27, 0.42)	<0.001	0.31 (0.24, 0.40)	<0.001	0.39 (0.30, 0.50)	<0.001
Stage 2	reference		reference		reference	
Stage 3	0.75 (0.60, 0.93)	0.011	0.93 (0.71, 1.23)	0.61	1.29 (1.04, 1.59)	0.020
Stage 4	0.03 (0.03, 0.04)	<0.001	0.02 (0.02, 0.02)	<0.001	0.03 (0.03, 0.04)	<0.001
Site						
Colon	reference		reference		reference	
Rectal	0.45 (0.41, 0.50)	<0.001	0.52 (0.47, 0.58)	<0.001	0.64 (0.58, 0.71)	<0.001
			Yorkshire			
Age (years)						
18-59	1.18 (0.99, 1.40)	0.058	1.28 (1.09, 1.50)	0.003	1.57 (1.35, 1.82)	<0.001
60-69	reference		reference		reference	
70-79	0.68 (0.58, 0.79)	0.003	0.70 (0.62, 0.80)	<0.001	0.67 (0.59, 0.75)	<0.001
≥80	0.23 (0.20, 0.27)	<0.001	0.24 (0.21, 0.27)	<0.001	0.19 (0.17, 0.22)	<0.001
Sex						
Male	reference		reference		reference	
Female	1.12 (1.01, 1.25)	0.032	1.06 (0.96, 1.16)	0.23	1.04 (0.95, 1.13)	0.43
Stage						
Stage 1	0.37 (0.30, 0.45)	<0.001	0.34 (0.29, 0.40)	<0.001	0.24 (0.20, 0.27)	<0.001
Stage 2	reference		reference		reference	
Stage 3	0.54 (0.45, 0.64)	<0.001	0.66 (0.55, 0.80)	<0.001	0.63 (0.56, 0.72)	<0.001
Stage 4	0.03 (0.03, 0.04)	<0.001	0.03 (0.03, 0.04)	<0.001	0.05 (0.04, 0.05)	<0.001
Site						
Colon	reference		reference		reference	
Rectal	0.58 (0.52, 0.65)	<0.001	0.54 (0.49, 0.61)	<0.001	0.56 (0.51, 0.62)	<0.001

Chapter 3. Differences in the management of patients requiring an emergency resection for colon cancer in two European populations [Paper 2]

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3.1. Abstract [Paper 2]

Background

Patients with colon cancer who require emergency colon cancer surgery often experience poorer outcomes compared to their elective counterparts. The aim of this study was to compare the use of elective and emergency resections for colon cancer and postoperative mortality in two similar demographic populations.

Methods

All patients who underwent a major resection for colon cancer, between 2005 and 2016 in Denmark and Yorkshire (England), were identified. The proportion undergoing emergency surgery, the proportion receiving a stent procedure before their resection and 30-day postoperative mortality were compared between the populations. Logistic regression was used to determine changes in the proportion of those undergoing emergency surgery and 30-day postoperative mortality.

Results

Out of 45,397 patients treated during the study period, 41,880 were selected. Emergency surgery decreased in Denmark from 16.6% in 2005-07 to 12.9% in 2014-16, but increased in Yorkshire (13.5% to 16.8%). Danish patients with left-sided tumours were less likely to undergo emergency surgery (RR 0.90, 95% CI 0.82 to 0.99) and an increase in stent use coincided with a statistically significant decrease in emergency surgery in these patients. Thirty-day postoperative mortality in all resections (elective and emergency) decreased in both populations, but a larger decrease was observed in Denmark (7.7% to 3.0% in Denmark, 7.1% to 3.3 in Yorkshire).

Conclusion

Patients in Denmark experienced a reduction in the use of emergency resection and increase in stenting procedures, following a policy of converting potential emergency resections into elective resections implemented in some departments.

3.2. Introduction [Paper 2]

Approximately 15-30% of patients with colorectal cancer present as an emergency[1]. Those who require an emergency surgical resection tend to have worse short-term outcomes than those who receive elective care, and these include increased rates of postoperative mortality, postoperative complications and length of hospital stay[2-5]. Poorer survival and recurrence rates have also been reported in some, but not all studies[6-8]. The introduction of alternative treatments for suitable patients, such as self-expanding metallic stents (SEMS) as a bridge to surgery, may reduce the number of patients undergoing an emergency resection[9]. However, because of the expertise required and the lack of consensus in published guidelines, the utilization of treatment options such as SEMS are likely to vary both within and across populations[10, 11].

Comparisons in the management of patients with colorectal cancer between similar demographic populations, can help to identify differences in practices which may have an impact on outcomes[12, 13], but few studies have been undertaken. The Yorkshire Cancer Research Bowel Cancer Improvement Programme (YCR BCIP) is using this philosophy by attempting to identify areas of improvement in the management of patients with colorectal cancer in Yorkshire[14]. Denmark and the UK both have healthcare provision that is largely free at the point of care and financed through taxation, with a similar disease burden and adult life expectancy[15, 16]. This, and given that Denmark has a similar population size to Yorkshire (both 5.7 million), presents the opportunity to use Denmark as a suitable comparator in the management of patients with colorectal cancer.

In 2009, guidelines were issued in Denmark recommending treatment with SEMs for obstruction in left-sided tumours as a bridge to surgery[17]. Given the demanding technical skill, however, it was emphasized that the use of stents in an emergency situation should only be performed in departments with the necessary expertise.

The present study was undertaken to compare the use of elective and emergency resections for colon cancer and postoperative mortality between Denmark and the region of Yorkshire, England.

3.3. Materials and methods [Paper 2]

This is a retrospective population-based study of patients with a first primary colon cancer diagnosed in Denmark and the region of Yorkshire, England. All patients aged ≥18 years were diagnosed between 1st January 2005 and 31st December 2016 (ICD-10 C18 and C19) and had undergone a major surgical resection at a Danish or an English NHS hospital, up to one year post diagnosis. Patients with a malignant neoplasm of the appendix (ICD-10 C18.1) were excluded as these were not recorded in Denmark from 2014.

Danish patients were obtained from the Danish Colorectal Cancer Group (DCCG) database[18], which captures all colorectal cancer patients who have been diagnosed and/or treated at a public hospital. The main surgical procedure, and urgency of that procedure, is recorded in the DCCG and those patients recorded as undergoing a major resection procedure were identified and categorized as either an elective or emergency resection. Major resection was defined as receiving certain selected radical procedures (Supplementary Table 3.1) occurring within 1 month prior to, and up to 1 year after, the date of diagnosis. No formal definition of emergency surgery is given in the DCCG, except that the indication for emergency surgery (ileus, perforation, bleeding or otherwise) should be reported. The majority of those classed as an emergency are operated on within 36 hours of admission. Surgical procedures, and other interventions, prior to the main surgery are also recorded and those who had a stent inserted before their main surgical procedure were identified.

Patients in Yorkshire were identified using the UK Colorectal Cancer intelligence Hub's COloRECTal Repository (CORECT-R) by linkage of the data from the national cancer registry (National Cancer Registration and Analysis Service) and inpatient hospital admissions (Hospital Episode Statistics, HES)[19]. Major surgical resection is defined in CORECT-R using a methodology that matches procedure codes within HES to identify all operations used to surgically treat colorectal cancer. The nature of the patients' admission for the procedure is also recorded. A resection is categorised as an emergency resection if the procedure was undertaken within two days of an emergency admission, and an elective resection otherwise. Those who had a recorded HES procedure with OPSC4 codes pertaining to the insertion of a stent (H214, H243, H244, H273, H274, H314 and Y141 to Y149) up to 30-days prior or with the same date as the major surgical resection, were identified as having a stent inserted.

Outcomes of interest

The primary outcome of interest was the rate of emergency resection in the two populations over time. Secondary outcomes included the rate of stent procedures, hospital variation in the use of emergency resection and 30-day postoperative mortality following elective and emergency resections by study period, and defined as death of the patient within 30-days of the resection date.

Statistics

The proportion of emergency resections was calculated as a percentage of all resections over the study period and by grouped year of diagnosis (2005-07, 2008-10, 2011-2013 and 2014-2016). To investigate the factors associated with use of emergency resection and to test the statistical significance of changes over time, Danish and Yorkshire populations were modelled separately using multilevel mixed effects. Poisson regression with a robust error variance to estimate the risk ratio (RR), as is recommended for binary outcomes where the probability of the outcome is common[20]. The binary dependent variable was emergency resection or not, independent fixed effects were age group (18-59, 60-69, 70-79 and ≥80 years), sex, tumour site (right, left, unspecified), stage of disease (1 to 4) and study period, and hospital where the operation was conducted was fitted as a random effect. Tumours located in the caecum, ascending colon, hepatic flexure and transverse colon were categorized as right-sided tumours, whereas those in the splenic flexure, descending colon, sigmoid colon and rectosigmoid junction were categorized as left sided tumours. Stage of disease was missing in 2.4% and 4.0% of Danish and Yorkshire patients respectively. Therefore, an ordered logistic regression was used to impute missing values and estimated model coefficients and standard errors according to Rubin's combination rules.

Variation in the use of emergency resection by hospital was assessed by the median odds ratio (MOR), calculated from the estimated variance of the distribution of random effects following fitting of multilevel logistic models with the same covariates described above and stratified by study period. The MOR quantifies the variation in areas between the second-level variation (hospitals in the models) and allows comparisons with the fixed effects covariates on the odds ratio scale[21, 22]. A MOR equal to one would indicate no variation in the use of emergency surgery between hospitals, whereas a MOR >1 would indicate variation. Bootstrapping was performed to calculate bias-corrected 95% confidence intervals for the variance estimate from the multilevel logistic models using 200 replications, which were then used to create confidence intervals for the MORs[23].

To moderate the effect of colorectal screening programmes on changes in the emergency resection proportion, for all analyses, Danish patients who were registered as being diagnosed based on the Danish Screening Programme and Yorkshire patients who had a screening diagnosis as defined by the Routes to Diagnosis methodology[24] were excluded.

The risk ratio for deaths following emergency resection were calculated and compared to elective resection by fitting a multilevel mixed effects regression model, with hospital as a random effect. The binary dependent variable was 30-day postoperative mortality, and independent fixed effects were age, sex, tumour site, stage of disease and surgical urgency (elective or emergency resection), while stratifying by study period. Adjustments were performed for these covariates, as they have been previously associated with both postoperative mortality[25] and use of emergency surgery[3] so are assumed to be confounders of the relationship between them. The missing stage information were imputed as described above.

Statistical analyses were performed using Stata version 16, (StataCorp, College Station, Texas, USA). Statistical significance was set at $P<0.05$.

3.4. Results [Paper 2]

Emergency resections

Out of 45,397 patients treated, a total of 24,828 and 17,052 major resections were included for patients diagnosed with colon cancer between 2005 and 2016 in Denmark and Yorkshire respectively (Table 3.1). Exclusions consisted of 1,742 patients in Denmark (1,733 elective and 9 emergency) and 1,775 patients in Yorkshire (1,752 elective and 23 emergency) with diagnoses derived from the respective screening programmes. Emergency resections accounted for 15.2% of all resections in Denmark and 15.0% in Yorkshire.

The use of emergency resections increased with increasing age and stage of disease in both Denmark and Yorkshire (Table 3.2). Patients with a left-sided tumour were significantly less likely to have received an emergency resection than those with a right-sided tumour in Denmark (adjusted RR 0.90, 95% CI 0.82 to 0.99, p-value=0.024) but not in Yorkshire (RR 1.11, 0.99 to 1.24, p=0.062). Use of emergency resections decreased over time in Denmark from 16.6% in 2005-07 to 12.9% in 2014-16, but significantly increased in Yorkshire from 13.5% to 16.8% (p<0.001)

Table 3.1 Characteristics for patients with colon cancer undergoing an elective and emergency resection in Denmark and Yorkshire between 2005 and 2016.

		Denmark				**Yorkshire**			
		Elective		**Emergency**		**Elective**		**Emergency**	
		N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Total		21,053	100	3,775	100	14,500	100	2,552	100
Age (years)	18-59	3,131	14.9	523	13.9	2,492	17.2	495	19.4
	60-69	5,717	27.2	909	24.1	3,336	23.0	587	23.0
	70-79	7,464	35.5	1166	30.9	5,165	35.6	786	30.8
	≥80	4,741	22.5	1177	31.2	3,507	24.2	684	26.8
Sex	Male	10,422	49.5	1757	46.5	7,757	53.5	1,389	54.4
	Female	1,0631	50.5	2018	53.5	6,743	46.5	1,163	45.6
Tumour site	Right	10,460	49.7	2,076	55.0	7,118	49.1	1,208	47.3
	Left	10,584	50.3	1,695	44.9	7,024	48.4	1,258	49.3
	Unspecified	<10	<1	<10	<1	358	2.5	86	3.4
Stage	1	3,060	14.5	76	2.4	1,898	13.1	58	2.3
	2	8,485	40.3	1,169	31.0	5,614	38.7	887	34.8
	3	6,273	29.8	1,173	31.1	5,004	34.5	1022	40.0
	4	2,820	13.4	1,228	32.5	1,363	9.4	523	20.5
	Unknown	415	2.0	129	3.4	621	4.3	62	2.4
Study period	2005 – 07	5,046	24.0	1003	26.6	3,892	26.8	607	23.8
	2008 – 10	5,029	23.9	955	25.3	3,808	26.3	626	24.5
	2011 – 13	5,414	25.7	993	26.3	3,523	24.3	656	25.7
	2014 – 16	5,564	26.4	824	21.8	3,277	22.6	663	26.0

Table 3.2 Adjusted risk ratios and 95% confidence intervals for use of emergency resection in patients with colon cancer in Denmark and Yorkshire between 2005 and 2016.

	Denmark			**Yorkshire**		
	Emergency (%)	**RR (95% CI)**	**p-value**	**Emergency (%)**	**RR (95% CI)**	**p-value**
Total	15.2			15.0		
Age (years)						
18-59	14.3	0.99 (0.90, 1.10)	0.872	16.6	1.06 (0.93, 1.20)	0.393
60-69	13.7	1.00 (reference)		15.0	1.00 (reference)	
70-79	13.5	1.02 (0.92, 1.11)	0.805	13.2	0.94 (0.83, 1.05)	0.248
≥80	19.9	1.49 (1.36, 1.64)	<0.001	16.3	1.16 (1.03, 1.31)	0.014
Sex						
Male	14.4	1.00 (reference)		15.2	1.00 (reference)	
Female	16.0	1.05 (0.96, 1.14)	0.276	14.7	0.97 (0.92, 1.02)	0.240
Tumour site						
Right	16.6	1.00 (reference)		14.5	1.00 (reference)	
Left	13.8	0.90 (0.82, 0.99)	0.024	15.2	1.11 (0.99, 1.24)	0.062
Unspecified	NA	NA		19.4	1.39 (1.09, 1.77)	0.007
Stage						
1	2.4	0.22 (0.18, 0.28)	<0.001	3.0	0.23 (0.18, 0.29)	<0.001
2	12.1	1.00 (reference)		13.6	1.00 (reference)	
3	15.8	1.34 (1.28, 1.40)	<0.001	17.0	1.25 (1.15, 1.37)	<0.001
4	30.3	2.58 (2.35, 2.83)	<0.001	27.7	2.02 (1.84, 2.22)	<0.001
Study period						
2005 – 07	16.6	1.00 (reference)		13.5	1.00 (reference)	
2008 – 10	16.0	0.98 (0.89, 1.08)	0.674	14.1	1.04 (0.92, 1.18)	0.54
2011 – 13	15.5	0.99 (0.87, 1.13)	0.926	15.7	1.16 (1.00, 1.34)	0.051
2014 – 16	12.9	0.86 (0.71, 1.03)	0.106	16.8	1.24 (1.10, 1.39)	<0.001

Tumour site and use of stents

Use of emergency resection decreased in both patients with right- and left-sided tumours in Denmark, however the decrease was significant only in the left-sided (p=0.520 and p=0.007 respectively, Table 3.3, Figure 3.1). In Yorkshire, no significant change in use of emergency resection was observed in patients with left-sided tumours (p=0.327), but an increase was seen in those with right-sided tumours (p<0.001).

The observed proportion of patients receiving a stent procedure increased for patients with a left-sided tumour in Denmark from 6.1% in 2005-07 to 10.5% in 2014-16, while remaining <2% for patients with a right-sided tumour (Figure 3.1). A small increase in the proportion of patients receiving a stent procedure was observed for left-sided Yorkshire patients (0.7% to 1.4%).

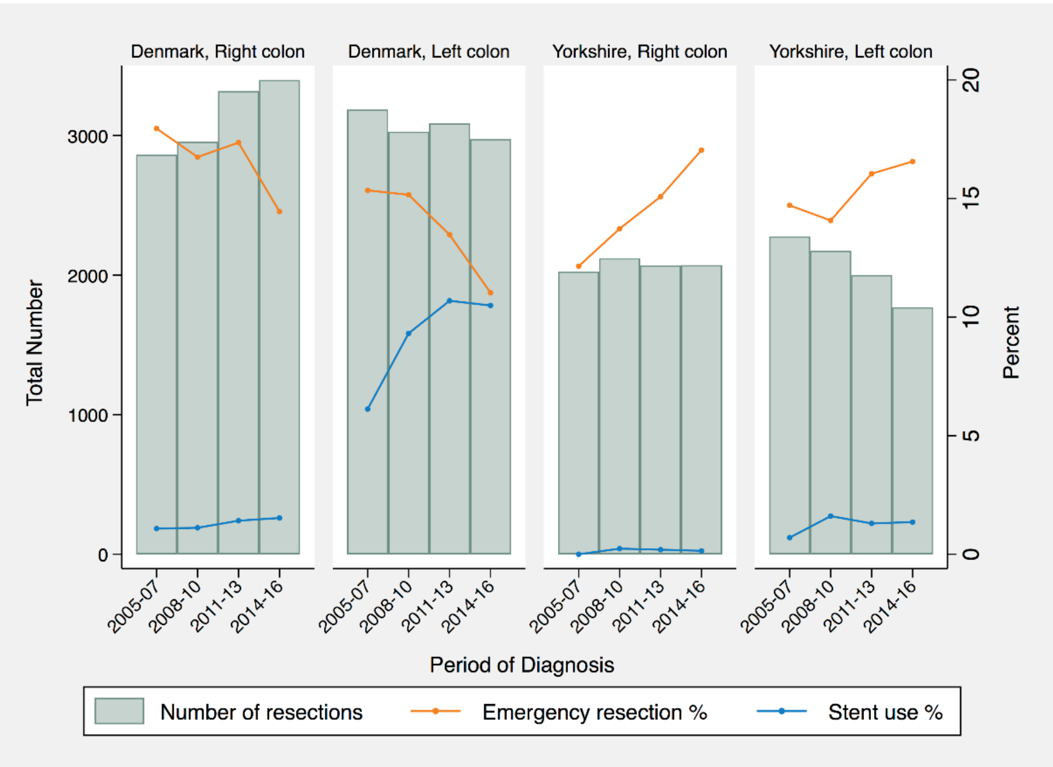

Figure 3.1 Number of resections, proportion of resections classified as an emergency and proportion of resections that were preceded by a stent procedure for patients with left- and right- sided colon cancer in Denmark and Yorkshire by study period.

Hospital variation

The median odds ratio (MOR) for the use of emergency resection across Danish hospitals increased from 1.18 (confidence interval 1.08 to 1.24) in 2005-2007 to 1.52 (1.42 to 1.59) in 2014-2016. There was no increase in the MOR across Yorkshire hospitals; 1.19 (1.06 to 1.24) in 2005-07, and 1.24 (1.14 to 1.32) in 2015-17.

Postoperative mortality

Thirty-day postoperative mortality for all patients undergoing an elective or emergency resection decreased over time in both Denmark (7.7% to 3.0%) and Yorkshire (7.1% to 3.3%). For patients who underwent an emergency resection, a larger decrease in 30-day mortality was observed over the study period in Yorkshire (16.2% to 7.7%) than that for Denmark (18.0% to 11.5%). However, a larger decrease in 30-day mortality was observed in Denmark (5.7% to 1.8%) than Yorkshire (5.7% to 2.4%) for patients who underwent an elective resection (Figure 3.1).

The adjusted risk ratios for 30-day mortality in patients who underwent an emergency resection compared with elective resection, stratified by study period are reported in Table 3.4. In Denmark, patients undergoing an emergency resection were more likely to have died than those undergoing an elective resection in 2005-07, RR 2.55 (2.09 to 3.10), and this had increased by 2014-16 to RR 4.67 (3.44 to 6.33). In Yorkshire, the corresponding change was not to the same extent: RR 2.60 (1.96 to 3.46) in 2005-07, to RR 3.13 (2.36 to 4.14) in 2014-16.

Table 3.3 Adjusted risk ratios and 95% confidence intervals for emergency resection in patients with right- and left-sided colon cancer in Denmark and Yorkshire between 2005 and 2016.

		Elective	Emergency		RR (95% CI)	P
Tumour site	**Study period**	**N**	**N**	**% of all resections**		
			Denmark			
Right-sided	2005 – 07	2,349	514	18.0	1.00 (reference)	
	2008 – 10	2,460	495	16.8	0.97 (0.84, 1.11)	0.659
	2011 – 13	2,743	576	17.4	1.06 (0.90, 1.24)	0.481
	2014 – 16	2,908	491	14.4	0.93 (0.74, 1.16)	0.520
Left-sided	2005 – 07	2,697	489	15.3	1.00 (reference)	
	2008 – 10	2,569	460	15.2	0.98 (0.88, 1.11)	0.780
	2011 – 13	2,671	417	13.5	0.93 (0.81, 1.05)	0.237
	2014 – 16	2,647	329	11.1	0.77 (0.64, 0.93)	0.007
			Yorkshire			
Right-sided	2005 – 07	1,779	246	12.1	1.00 (reference)	
	2008 – 10	1,829	291	13.7	1.12 (0.91, 1.39)	0.285
	2011 – 13	1,757	312	15.1	1.25 (1.02, 1.53)	0.029
	2014 – 16	1,718	353	17.0	1.40 (1.18, 1.66)	<0.001
Left-sided	2005 – 07	1,942	335	14.7	1.00 (reference)	
	2008 – 10	1,868	306	14.1	0.96 (0.83, 1.10)	0.518
	2011 – 13	1,679	321	16.1	1.08 (0.88, 1.33)	0.451
	2014 – 16	1,476	293	16.6	1.09 (0.91, 1.31)	0.327

Table 3.4 Observed 30-day mortality rates for elective and emergency resections, and risk ratios and 95% confidence intervals for 30-day mortality in emergency resections compared to elective resection in patients with colon cancer in Denmark and Yorkshire by study period.

	Observed 30-day mortality (%)			Emergency v Elective	
Study Period	**Elective**	**Emergency**	**All**	**RR (95% CI)**	**P**
		Denmark			
2005 – 07	5.7	18.0	7.7	2.55 (2.09, 3.10)	<0.001
2008 – 10	4.1	18.1	6.4	3.63 (2.96, 4.44)	<0.001
2011 – 13	2.7	14.5	4.5	4.30 (3.48, 5.31)	<0.001
2014 – 16	1.8	11.5	3.0	4.67 (3.44, 6.33)	<0.001
		Yorkshire			
2005 – 07	5.7	16.2	7.1	2.60 (1.96, 3.46)	<0.001
2008 – 10	4.9	12.8	6.0	2.48 (1.99, 3.08)	<0.001
2011 – 13	3.2	11.7	4.6	3.36 (2.82, 4.01)	<0.001
2014 – 16	2.4	7.7	3.3	3.13 (2.36, 4.14)	<0.001

3.5. Discussion [Paper 2]

This study has identified differences in the use of emergency resection for patients with colon cancer between Denmark and Yorkshire. Postoperative mortality in the earliest period of the study for all patients was higher in Denmark than in Yorkshire. The substantial reduction in use of emergency resections in Denmark over the study period coincided with a decrease in the overall 30-day mortality rate that was subsequently lower than that in Yorkshire by the most recent period of the study.

The high 30-day mortality in Danish patients undergoing emergency resection compared to those in Yorkshire, indicates that only the patients with a higher morbidity are undergoing an emergency resection. When the models were stratified by study period, the risk of postoperative mortality increased over time for Danish patients undergoing an emergency resection compared to those undergoing an elective resection. This provides some evidence in the shifting of Danish patients who would have undergone emergency resection to an elective resection, for those with potentially curable disease. However, further work to investigate whether this is indeed the case is required.

Differential use of SEMs as a bridge to surgery may explain the large decrease observed in the proportion of emergency resection performed in Denmark but not in Yorkshire. Danish guidelines in 2009/10 recommended treatment with SEMS for obstruction in left-sided tumours without suspicion of perforation where possible, as a bridge to surgery[17]. Some evidence of this were observed in the present study, as patients with left-sided tumours were less likely to undergo an emergency resection than those with a right-sided tumor and we observed an increase in the use of stents after 2005-07. However, the guidelines also highlight the demanding technical skill and set-up for this technique needed in the emergency situation and that stenting should only be performed in departments with the necessary expertise. As a result, the use of SEMS increased from the early 2010s, but is likely to vary by surgical department. This, and different interpretation of the existing literature may explain the wide variation of emergency surgery by treating hospital observed in the later period of this study.

Colonic stents were also considered as a bridge to surgery in the English 2011 NICE guidelines[26]. This was updated in 2014 to state that it should be explained to patients (or family members) that the obstruction can be managed initially either by emergency surgery or colonic stent with no clear evidence that one is better than the other, and/or patients be given the chance to participate in a randomized controlled trial comparing the two treatments[27]. The observed variation in emergency surgery between Yorkshire hospitals seen in this study is also likely to reflect this. Although current evidence may indicate bridge to surgery as the preferred treatment in some cases[28-30], the differences between the Danish and English guidelines and the timing of their releases, together with the evidence available at the time of study may explain the differences observed here. In this study, an increase in the use of stents in Yorkshire was not observed, and patients with a left-sided tumour were no less likely to receive an emergency resection. However, further investigation on the uptake of SEMS in both populations is required to determine the contribution to the probability of performing emergency surgery.

While the total number of emergency resections in Yorkshire remained relatively stable the number of elective resections decreased, resulting in a statistically significant increase in the emergency resection proportion. The English screening programme began in July 2006 but by October 2008 not all of the Yorkshire region had achieved complete roll out[31]. National coverage across all English regions was achieved in 2010. Excluding screened patients here could have impacted the number of elective cases in later periods, as the population 'at-risk' of diagnosis (and hence resection) will have reduced if diagnosed earlier through screening. The Danish screening programme was introduced at a later time, in March 2014[32]. Additionally, Denmark had a higher resection rate than Yorkshire over the same study time period[33]. This, in addition to a higher incidence rate in Denmark[34], may also explain why the overall number of resected patients in this study was much higher in Denmark when the overall populations are of equal size.

Comparative data on patient morbidity were not available in this study. Factors such as socioeconomic deprivation, comorbidities, ASA grade and histopathological profile have been reported to be associated with emergency patients[1, 7, 35]. Data on these characteristics would have allowed us to account for their influence on the differences in the use of emergency surgery reported in this study. The potential for these factors to contribute to the differences in practice observed here, should be considered in studies that look to confirm these results.

It is important to consider the limitations of the data used here when considering the findings of this study. The main weakness of the study concerns the definition of emergency resection and how directly comparable the proportions calculated in the two populations are. Emergency resection in Denmark is recorded by surgeons using a surgical proforma to indicate the urgency of the procedure. Although there is no formal definition of what constitutes an emergency procedure, guidance states emergency patients are those where indication for surgery is suspected due to either ileus, perforation, bleeding or otherwise and usually occurs within 36 hours of admission. This information was not directly available in the Yorkshire data, so we used surgery within 2 days following an emergency admission. We believe this to be an acceptable way to define an emergency resection, as we compared the estimated proportion in England using our definition, with results from the National Bowel Cancer Audit (NBOCA) over the same time period[36]. The NBOCA used the National Confidential Enquiry into Patient Outcomes and Death (NCEPOD) to classify resections in urgent and emergency procedures[37]. For the period April 2014 – March 2016, the proportion of

English resections we estimated to be an emergency resection was 16.0%, and the proportion of resections in NBOCA classified as urgent and emergency resections was also estimated to be 16.0%. Although the definitions of emergency surgery differ between Denmark and Yorkshire, they are defined in a way that are robust to changes over time, and therefore the observed trend observed in this study should remain valid within both populations.

This study has shown that both Denmark and Yorkshire have substantially reduced mortality postoperatively in both elective and emergency resections. The larger decrease in overall postoperative mortality in Denmark has coincided with a reduction in the use of emergency resection and increase in stenting procedures, following a policy of converting potential emergency resections into elective resections implemented in some departments. Identifying and addressing the reasons for an increase in emergency surgery in Yorkshire could contribute to a further lowering of postoperative mortality.

3.6. Acknowledgements [Paper 2]

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The study was granted ethical approval (17/WM/0374) by the West Midlands - Solihull Research Ethics Committee in December 2017. The study was approved by the Health Research Authority and granted approval for inclusion in the National Institute for Health Research's portfolio of studies in December 2017 (Project ID 227673) and the Scientific Committee of the Danish Colorectal Cancer Group (DCCG.dk).

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3.8. Supplementary information [Paper 2]

Supplementary Table 3.1 Operations used to define major resection from the Danish Colorectal Cancer Group (DCCG) database procedure field.

DCCG code	DCCG Operation	Major resection
1	Ileocecal resection	Yes
2	Right hemicolectomy	Yes
3	Extended right hemicolectomy	Yes
4	Resection of traverse colon	Yes
5	Left hemicolectomy	Yes
6	Resection of sigmoid colon	Yes
7	Resection of sigmoid colon with colostomy	Yes
8	Other combined resection of small intestine and colon	Yes
9	Other colonic resection without colostomy	Yes
10	Other colectomy with colostomy and distal closure	Yes
11	Colectomy and ileorectostomy (anastomosis)	Yes
12	Colectomy and ileostomy	Yes
13	Rectal resection (TME and PME)	Yes
14	Rectal resection + colostomy (=Hartmann's)	Yes
15	APE, ischioanal	Yes
16	APE, extralevator (ELAPE)	Yes
17	APE, conventional	Yes
18	APE, intersphincteric	Yes
19	Proctocolectomy and ileostomy	Yes
20	Alleviating only (bypass, stoma)	No
21	Exploration only	No
22	Transanal endoscopic microsurgery (TEM)	No
23	Other local procedures incl. polypectomy-EMR	No
24	Stent in rectum	No
25	Stent in colon	No

3.9. Additional unpublished material [Paper 2]

Coding in the Yorkshire data

In the Yorkshire data, the procedure was defined as an emergency resection if it was undertaken within two days of an emergency admission, and an elective resection otherwise (Figure 3.2).

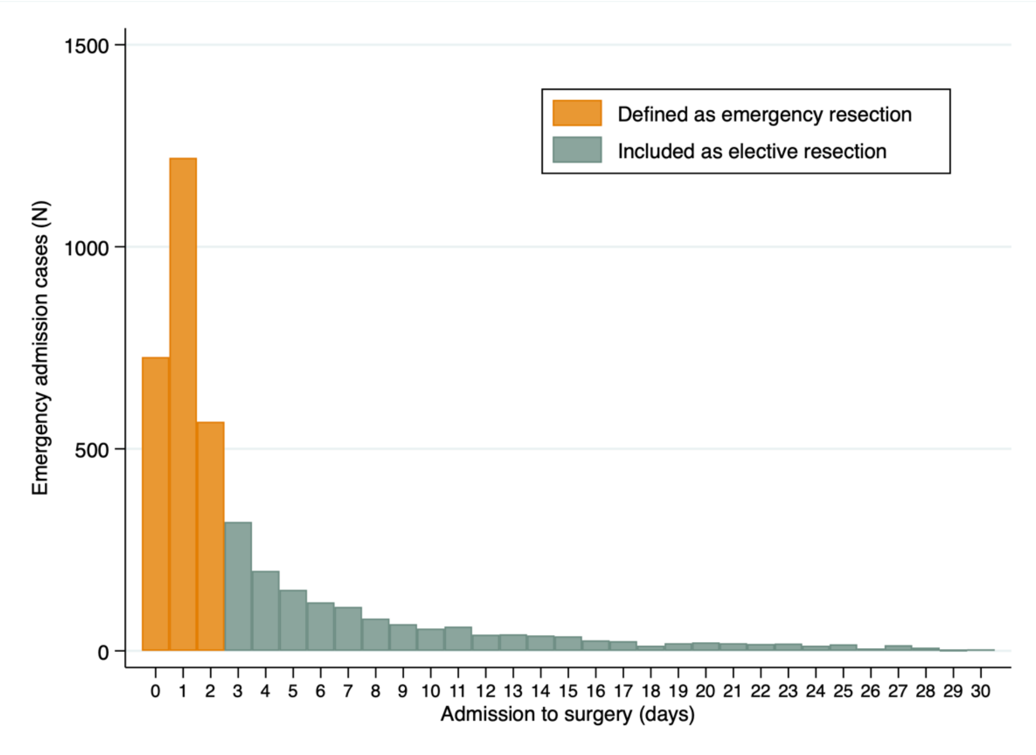

Figure 3.2 Number of resections occurring within 30-days of an emergency admission in Yorkshire.

A sensitivity analysis was performed to see how the proportions of emergency resections changed when varying the definition to include procedures within one or three days of an emergency admission (Figure 3.3). The percentage categorised as an emergency using one, two or three days was 7.7%, 15.0% and 16.9% and had little impact on the adjusted risk-ratios for use of emergency surgery over time period; a significant increase in use was observed over time for right-sided but not for left-sided tumours (Table 3.5).

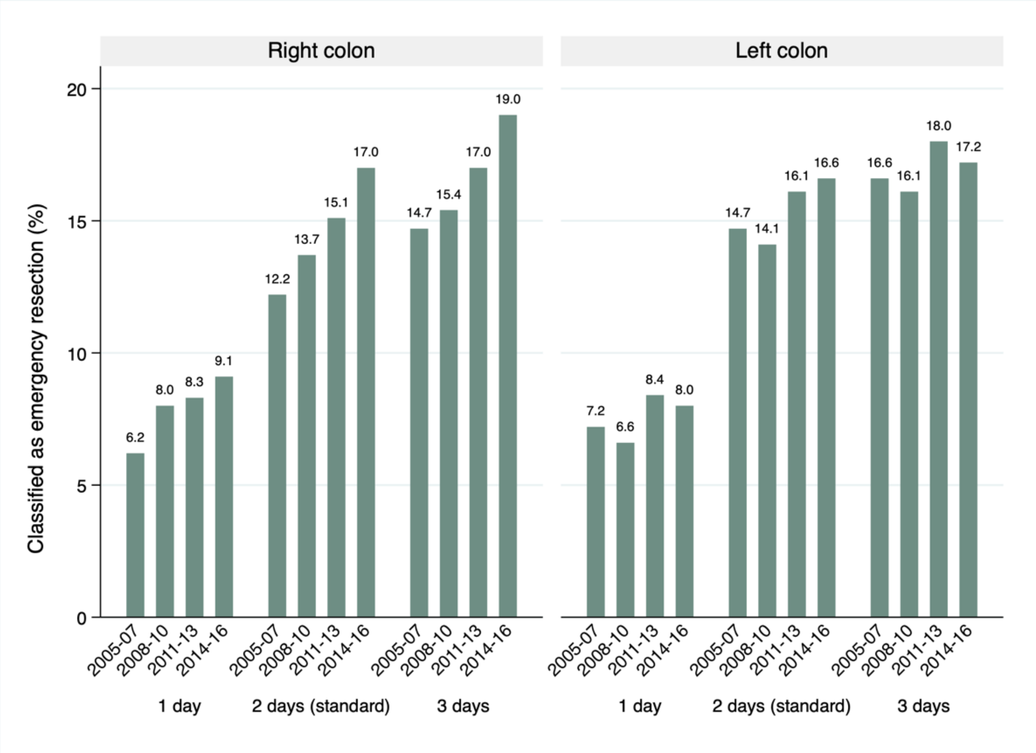

Figure 3.3 Proportion of resection classified as an emergency when considering differing intervals from emergency admission to surgery.

Table 3.5 Adjusted risk ratios (RR) and 95% confidence intervals (CI) for emergency resection in Yorkshire patients when considering differing intervals from emergency admission to surgery to classify emergency resections.

		RR (95% CI) for emergency resection		
Tumour site	**Study Period**	**1 day**	**2 days (standard)**	**3 days**
Right-sided	2005 – 07	1.00 (reference)	1.00 (reference)	1.00 (reference)
	2008 – 10	1.31 (1.03, 1.67)	1.12 (0.91, 1.39)	1.05 (0.88, 1.25)
	2011 – 13	1.37 (1.07, 1.74)	1.25 (1.02, 1.53)	1.18 (1.00, 1.41)
	2014 – 16	1.50 (1.19, 1.91)	1.40 (1.18, 1.66)	1.35 (1.14, 1.60)
Left-sided	2005 – 07	1.00 (reference)	1.00 (reference)	1.00 (reference)
	2008 – 10	0.91 (0.72, 1.15)	0.96 (0.83, 1.10)	0.97 (0.83, 1.15)
	2011 – 13	1.14 (0.91, 1.43)	1.08 (0.88, 1.33)	1.07 (0.91, 1.26)
	2014 – 16	1.06 (0.83, 1.34)	1.09 (0.91, 1.31)	1.03 (0.87, 1.22)

The HES admission codes used to define a stent procedure in the Yorkshire data are given in Table 3.6. The majority of stent procedures (89%) were coded as either H214, H243, H244 or H314.

Table 3.6 Codes used to define stent procedures in the Yorkshire dataset and their frequency.

OPCS4 Code	Code Description	Frequency
H214	Fibreoptic endoscopic insertion of expanding metal stent into colon	20%
H243	Endoscopic insertion of tubal prosthesis into lower bowel using fibreoptic sigmoidoscope	26%
H244	Endoscopic insertion of expanding metal stent into lower bowel using fibreoptic sigmoidoscope	26%
H273	Endoscopic insertion of tubal prosthesis into sigmoid colon using rigid sigmoidoscope	3%
H274	Endoscopic insertion of expanding metal stent into sigmoid colon using rigid sigmoidoscope	2%
H314	Image guided insertion of colorectal stent	17%
Y141	Insertion of expanding covered metal stent into organ NOC	1%
Y142	Insertion of expanding metal stent into organ NOC	2%
Y143	Insertion of metal stent into organ NOC	4%
Y144	Insertion of plastic stent into organ NOC	<1%
Y145	Insertion of stent graft into organ NOC	<1%
Y148	Placement of stent in organ other specified NOC	<1%
Y149	Placement of stent in organ unspecified NOC	<1%

Effect of excluding screening patients

The English screening programme was introduced earlier (roll-out in 2008 and national coverage by 2010) than the Danish screening programme (nationwide roll-out in 2014). This would likely influence the rates of emergency surgery over the course of the study period. Therefore, the proportion of resections classified as an emergency were compared in all cases and when excluding those identified as having a diagnosis through the screening programmes (as in the published paper).

As expected, when including all cases, the percentage receiving emergency resections was lower than when excluding screened patients in both Denmark (2014-16: 10.3% vs

12.9%, difference = 2.6%) and Yorkshire (2014-16: 14.8% vs 16.8% = 2.0%). This was particularly the case for tumours located in the left-side of the colon (Figure 3.4).

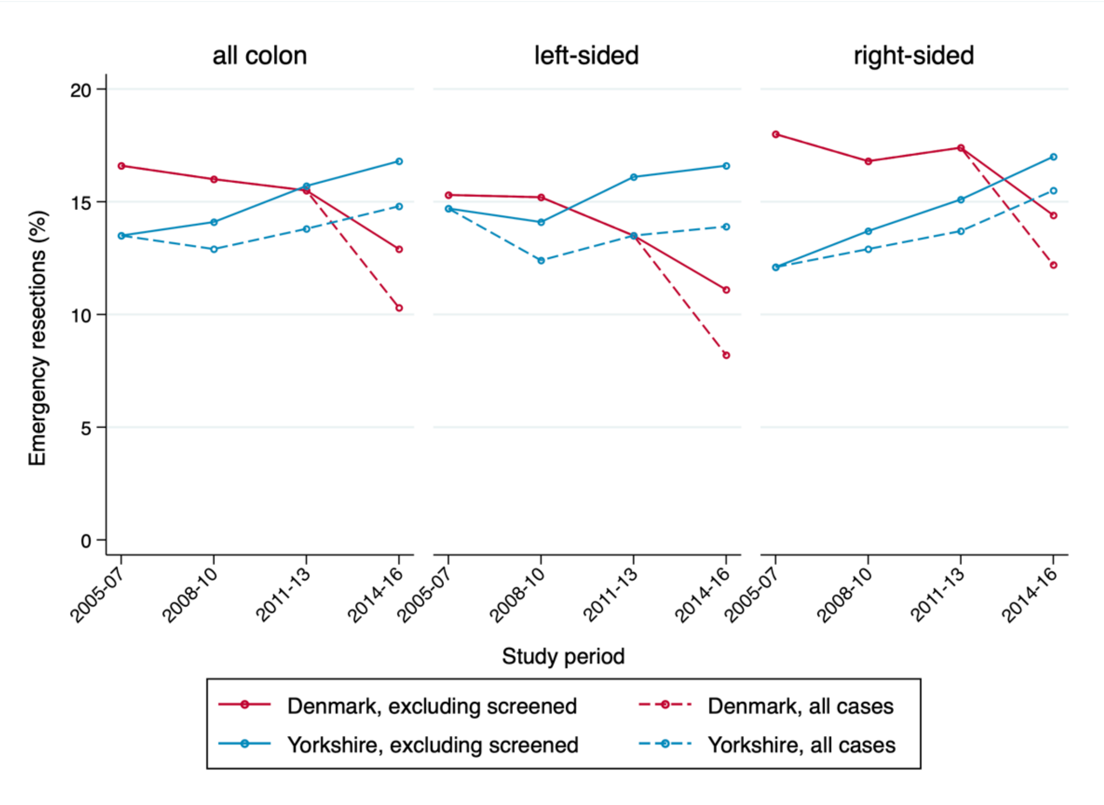

Figure 3.4 Proportion of resections classified as an emergency for patients with left- and right- sided colon cancer in Denmark and Yorkshire by study period.

Use of stents across Danish hospitals

Given the comparatively higher use of stents in left-sided colon cancer for Denmark compared to Yorkshire, the proportion of resections that were preceded by a stent procedure for patients with left-sided colon cancer was calculated across individual Danish hospitals (Figure 3.5).

The majority of Danish hospitals observed an increase in the use of stents over the study period which was consistent with the national figures. Over half the 16 hospitals (n=9) had a rate ≥10% by 2014-16, with the remaining having a rate of 5-10%. In 2014-

16, the highest rate of stent use in Danish hospitals was 15.7% and the lowest was 6.2%. In comparison, the range for Yorkshire hospitals was 0% to 4.0%.

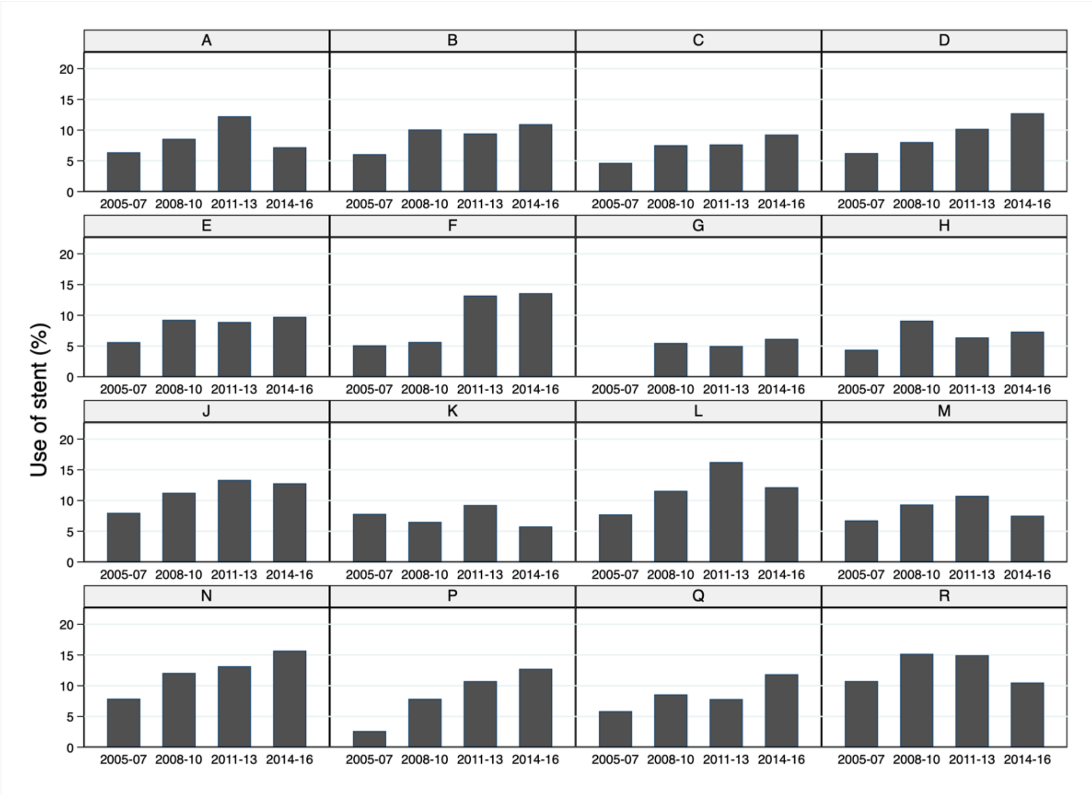

Figure 3.5 Proportion of resections that were preceded by a stent procedure for patients with left-sided colon cancer at Danish hospitals (A-R).

Modelling use of stents

Multilevel mixed effects models with stent use as the outcome (stent procedure before major resection vs no stent procedure before major resection) were run separately in the Danish and Yorkshire populations. For methodological consistency with the publication analyses, Poisson regression with a robust error variance to estimate the risk ratio was used with the same covariates that were used in the models for emergency resection: age group (18-59, 60-69, 70-79 and ≥80 years), sex, tumour site (right, left, unspecified), stage of disease (1 to 4) and study period. Hospital where the operation was conducted was fitted as a random effect and the same imputation methodology was implemented to impute missing stage.

Table 3.7 Adjusted risk ratios and 95% confidence intervals for use of stents before major resection in patients with colon cancer in Denmark and Yorkshire between 2005 and 2016.

	Denmark			Yorkshire		
	Stent (%)	RR (95% CI)	p-value	Stent (%)	RR (95% CI)	p-value
Total	5.2			0.7		
Age (years)						
18-59	6.2	1.04 (0.89, 1.22)	0.600	0.6	0.54 (0.28, 1.05)	0.070
60-69	5.4	1.00 (reference)		0.9	1.00 (reference)	
70-79	4.5	0.95 (0.80, 1.14)	0.600	0.5	0.68 (0.41, 1.11)	0.414
≥80	5.2	1.21 (1.08, 1.35)	<0.001	0.8	1.10 (0.73, 1.67)	0.646
Sex						
Male	5.7	1.00 (reference)		0.8	1.00 (reference)	
Female	4.7	0.99 (0.88, 1.10)	0.797	0.6	0.92 (0.69, 1.22)	0.562
Tumour site						
Right	1.3	1.00 (reference)		0.1	1.00 (reference)	
Left	9.1	7.53 (5.92, 9.58)	<0.001	1.2	9.30 (4.69, 18.5)	<0.001
Unspecified	7.7	NA		0.5	NA	
Stage						
1	0.5	0.10 (0.06, 0.16)	<0.001	0.1	0.13 (0.03, 0.51)	0.004
2	4.8	1.00 (reference)		0.7	1.00 (reference)	
3	6.6	1.36 (1.19, 1.55)	<0.001	0.8	1.16 (0.79, 1.71)	0.444
4	7.2	1.56 (1.33, 1.82)	<0.001	1.1	1.75 (1.25, 2.45)	<0.001
Study period						
2005 – 07	3.7	1.00 (reference)		0.4	1.00 (reference)	
2008 – 10	5.3	1.45 (1.25, 1.67)	<0.001	0.9	2.66 (1.38, 5.11)	0.003
2011 – 13	5.9	1.73 (1.49, 2.00)	<0.001	0.8	2.19 (1.26, 3.81)	0.005
2014 – 16	5.7	1.75 (1.40, 2.20)	<0.001	0.7	2.27 (0.98, 5.28)	0.057

Results of the models for use of stents in Denmark and Yorkshire are found in Table 3.7. Danish patients age ≥80 years were more likely to receive a stent procedure than those aged 60-69 years, RR 1.21 (1.08 to 1.35), p-value <0.001. There were no significant differences between age groups for patients in Yorkshire. Patients with a left-sided tumour were significantly more likely to undergo a stent procedure than those with a right-sided tumour in both Denmark, RR 7.53 (5.93 to 9.58), p-value <0.001 and Yorkshire, RR 9.30 (4.69 to 18.5), p-value <0.001. A more advanced stage of disease was association with increased use of stent procedures in both Denmark and Yorkshire. Use of stent procedures significantly increased over time in both Denmark and Yorkshire.

Chapter 4. Minimally invasive surgery for colorectal cancer: Benchmarking uptake for a regional improvement programme [Paper 3]

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4.1. Abstract [Paper 3]

Use of minimally invasive surgery can benefit recovery in patients treated for colorectal cancer. We investigated its uptake in England between 2007 and 2021. As expected, use of laparoscopic and robotic surgery increased but we observed wide variation at the hospital level. Our data-driven approach identified potential outlying hospitals for further investigation through a regional cancer improvement programme.

Background

The uptake of minimally invasive surgery (MIS) for patients with colorectal cancer has progressed at differing rates, both across countries, and within countries. This study aimed to investigate uptake for a regional colorectal cancer improvement programme in England.

Method

We calculated the proportion of patients receiving elective laparoscopic and robot-assisted surgery amongst those diagnosed with colorectal cancer over 3 time periods (2007-2011, 2012-2016 and 2017-2021) in hospitals participating in the Yorkshire Cancer Research Bowel Cancer Improvement Programme (YCR BCIP). These were benchmarked against national rates. Regression analysis and funnel plots were used to develop a data driven approach for analysing trends in the use of MIS at hospitals in the programme.

Results

In England, resections performed by MIS increased from 34.9% to 72.9% for colon cancer and from 28.8% to 72.5% for rectal cancer. Robot-assisted surgery increased from 0.1% to 2.7% for colon cancer and from 0.2% to 7.9% for rectal cancer. Wide variation in the uptake of MIS was observed at a hospital level. Detailed analysis of the YCR BCIP region identified a decreasing number of surgical departments, since the start of the programme, as potential outliers for MIS when compared to the English national average.

Conclusion

Wide variation in use of MIS for colorectal cancer exists within the English National Health Service and a data-driven approach can help identify outlying hospitals. Addressing some of the challenges behind the uptake of MIS, such as ensuring adequate provision of surgical training and equipment, could help increase its use.

4.2. Introduction [Paper 3]

In the 1990s, minimally invasive surgery (MIS), such as laparoscopic surgery, emerged as an alternative to traditional open surgery for the treatment of colorectal cancer[1]. Subsequently, a number of randomised controlled trials demonstrated laparoscopic surgery was as effective as open surgery in terms of recurrence and survival rates, but with a potential to reduce hospital stay and improve recovery[2-4]. Following these studies, English guidance issued by The National Institute for Health and Care Excellence (NICE) was updated in 2006 to recommend laparoscopic surgery as an alternative to open resection for some patients, by suitably trained surgeons and after informed discussion between surgeon and patient[5]. Subsequent retrospective studies have demonstrated the safety of laparoscopic techniques in colorectal cancer with outcomes at least equivalent to open surgery[6-10].

It has previously been shown that the uptake of MIS varies widely both between and within European countries[7,11] with some adopting the techniques much more readily than others. For example, the percentage of patients undergoing MIS in Denmark increased from <10% in 2004 to 80% in 2016[12]. The Yorkshire Cancer Research Bowel Cancer Improvement Programme (YCR BCIP) which commenced in 2016, benchmarks surgical metrics (including MIS) of multidisciplinary teams (MDTs) or Hospital Trusts responsible for patient care in Yorkshire, against other regions and English national figures[13]. The results of these are fed back to the regional MDTs, with the aim of reducing the variation in treatment experienced by patients in the region.

The purpose of this population-based study was to compare MIS uptake for patients with colorectal cancer in England, and to develop data driven methodology for identifying trends in MIS for a regional improvement programme.

4.3. Patients and methods [Paper 3]

The study population consisted of all patients who had undergone an elective major surgical resection for colorectal cancer (ICD C18-C20) in an English National Health Service (NHS) hospital between 1 January 2007 and 30 June 2021, obtained from the UK Colorectal Cancer Intelligence Hub's colorectal cancer data repository (CORECT-R)[14]. This included patients diagnosed between 1 January 2007 and 31 December 2019 provided by the National Cancer Registry and Analysis Service (NCRAS), and those diagnosed between 1 January 2020 and 30 June 2021 extracted from the Rapid Cancer Registrations Dataset (RCRD). The RCRD enables a near-real time analysis of cancer data but less quality assurance is feasible than is adhered to in the gold-standard NCRAS dataset due to the rapidity of the reporting resulting in lower case ascertainment and should therefore be used with caution.

Those treated at one of 14 YCR BCIP Hospital Trusts were identified as described previously[15]. In the English NHS, MDTs consist of a team of specialists who are responsible for the treatment plan of patients and include surgeons, oncologists, pathologists, radiologists and nurse specialist, amongst others. Within the YCR BCIP region, one MDT covers the care at each hospital Trust, so for the purpose of this paper we have used the term "hospital" in place of MDT or Hospital Trust.

Benchmarking uptake of minimally invasive surgery

Firstly, we compared the uptake of MIS across all hospitals in the YCR BCIP region. Linked cancer registry and inpatient hospital records (Hospital Episode Statistics) were used to classify major resections for colorectal cancer as laparoscopic (OPCS procedure codes Y751, Y752, Y754, Y755, Y758 and Y759 on the same day of the major resection), robotic (OPCS code Y753 on the same day of major resection) or open (absence of laparoscopic or robotic OPCS codes)[14]. The proportion of attempted elective MIS resections were compared in the YCR BCIP region to National figures for colon and rectal cancer over 3 time periods (2007-2011, 2012-2016 and 2017-2021). Similarly, the proportion of MIS resections that were performed as robotic (or robot-assisted) surgery were compared.

A key strategy of YCR BCIP is to benchmark regional care and outcomes in colorectal cancer with that of Denmark, which is of a similar size to the Yorkshire region, has previously implemented a MIS training strategy and also has healthcare provision mainly financed through taxation. Therefore, we obtained the number of elective major resections that were classified as open, laparoscopic, and robotic in patients with colorectal cancer that were reported by the Danish Colorectal Cancer Group (DCCG) for patients diagnosed between 2008 and 2021[16] and used these a benchmark rates in comparison with YCR BCIP figures.

Identifying regional outliers and trends

We investigated the presence of potential outlying hospitals in their use of MIS within the YCR BCIP region. To do this, a multilevel mixed effects logistic regression for MIS use was constructed for 3 time periods (2007-2011, 2012-2016 and 2017-2021) and funnel plots[17] were created from the hospital-specific treatment rates. The three periods of time were chosen to cover a time before and after the start of the programme in 2016. Hospital was fitted as a random effect and the model was adjusted for age at diagnosis, sex, deprivation (categorized using quintiles of the income domain of the Index of Multiple Deprivation, IMD), Charlson Comorbidity Index (CCI, categorized as a score of 0, 1, 2 and ≥3), stage of disease and tumour site.

In addition, we developed a new approach (described as ‘tunnel plots’) to display the information from several funnel plots over an extended time period, which enabled identification of outliers while taking into account trends over time. Tunnel plots were constructed by splitting the study period into 10 equal time frames and constructing a funnel plot for each of these. The MIS rate, national rate and control limits (at P=0.05 and P=0.002) were then taken for each of the 14-regional hospitals at each of the 10 time points and plotted over time (Figure 4.1). The results were fed back via face-to-face and online meetings between representatives from the YCR BCIP team and the regional surgical teams.

Since the majority of hospitals were found to be not performing any robotic surgery, the use of funnel and tunnel plots would not be suitable. Therefore, to assess regional variation in use of robotic surgery, we reported the observed percentage of MIS performed using robotic surgery by hospital. We classified hospitals as performing robotic surgery if the hospital had at least two instances of robotic surgery recorded, and the percentage of robotic surgery accounted for at least 1% of all MIS in the period 2017-2021.

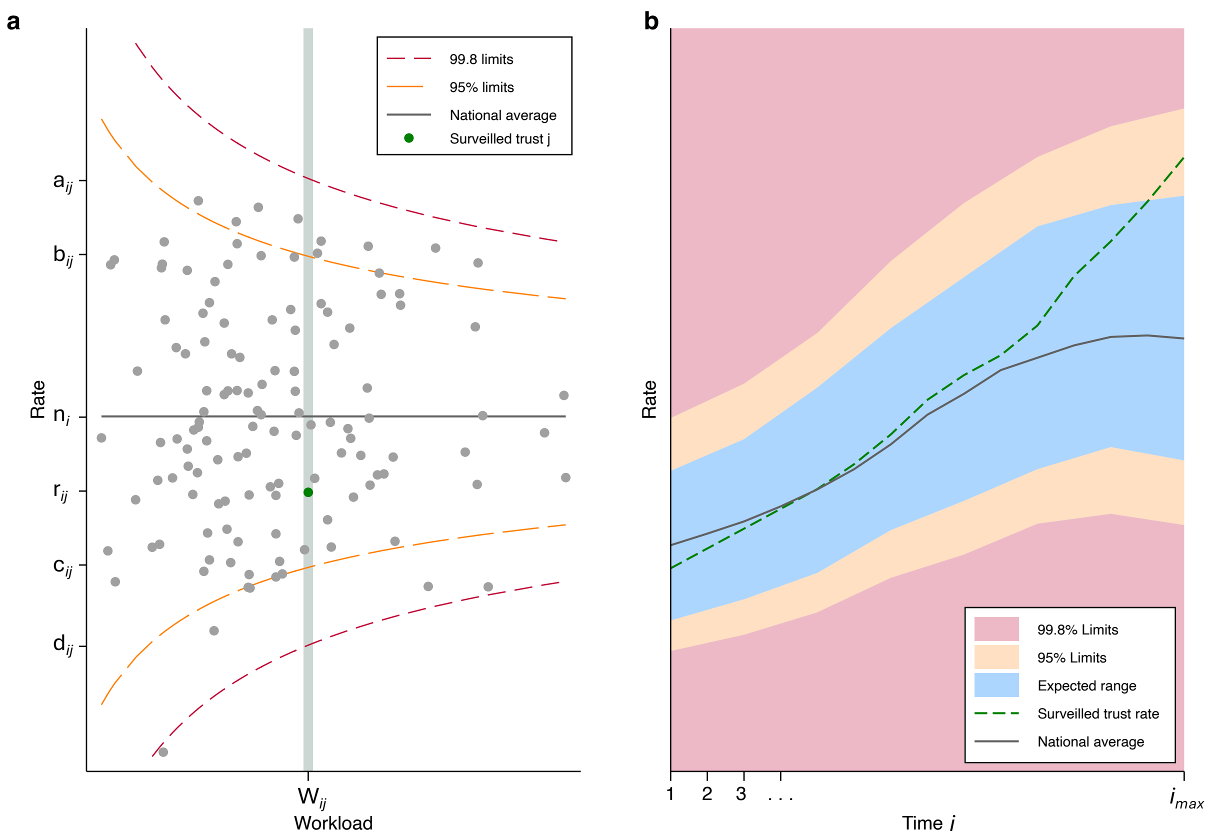

Figure 4.1 Funnel plots are constructed for each time period *i* and the surveilled trust *j* is identified (a). The corresponding trust rate r_{ij}, 99.8% limits a_{ij} and d_{ij}, 95% limits b_{ij} and c_{ij} at the given trust workload W_{ij} are then plotted with the national rate n_i at each time period to form the tunnel plot (b).

4.4. Results [Paper 3]

Benchmarking uptake

A total 185,017 elective resections for colon cancer and 68,890 elective resections for rectal cancer were included in the analysis. The YCR BCIP region accounted for 27,834 (11%) of these. In England, 100,348 (54.2%) colon cancer resection and 34,330 (49.8%) for rectal cancer resection were performed using MIS. Patients characteristics are given in Table 4.1 (colon cancer) and Table 4.2 (rectal cancer).

Table 4.1 Characteristics for patients with colon cancer undergoing open, laparoscopic and robotic surgery in England diagnosed between 2007 and 2021.

	Open		**Laparoscopic**		**Robotic**		**Total**
	N	%	N	%	N	%	
Total	84,669		98,513		1,835		185,017
Age (years)							
18-59	13,935	*16.5*	15,625	*15.9*	402	*21.9*	29,962
60-69	21,864	*25.8*	28,338	*28.8*	576	*31.4*	50,778
70-79	28,957	*34.2*	34,640	*35.2*	619	*33.7*	64,216
≥80	19,913	*23.5*	19,910	*20.2*	238	*13.0*	40,061
Sex							
Male	44,395	*52.4*	53,171	*54.0*	1,044	*56.9*	98,610
Female	40,274	*47.6*	45,342	*46.0*	791	*43.1*	86,407
IMD							
1 – Least deprived	17,636	*20.8*	22,093	*20.8*	372	*20.3*	40,101
2	19,043	*22.5*	22,808	*22.5*	381	*20.8*	42,232
3	17,566	*20.8*	20,569	*20.9*	379	*20.7*	38,514
4	15,939	*18.8*	18,101	*18.4*	372	*20.3*	34,412
5 – Most deprived	14,485	*17.1*	14,942	*15.2*	331	*18.0*	29,758
CCI score							
0	61,605	*72.8*	76,814	*78.0*	1,526	*83.2*	139,945
1	14,384	*17.0*	14,014	*14.2*	211	*11.5*	28,609
2	5,061	*6.0*	4,670	*4.7*	53	*2.9*	9,784
≥3	3,619	*4.3*	3,015	*3.1*	45	*2.5*	6,679
Stage							
1	9,235	*10.9*	18,915	*19.2*	379	*20.7*	28,529
2	31,658	*37.4*	36,785	*37.3*	566	*30.8*	69,009
3	28,999	*34.3*	31,967	*32.5*	648	*35.3*	61,614
4	9,494	*11.2*	6,049	*6.1*	108	*5.9*	15,651
Unknown	5,283	*6.2*	4,797	*4.9*	134	*7.3*	10,214
Study period							
2007-2011	42,482	*50.2*	22,507	*22.9*	63	*3.4*	65,052
2012-2016	26,794	*31.7*	36,927	*37.5*	306	*16.7*	64,027
2017-2021	15,393	*18.2*	39,079	*39.7*	1,466	*79.9*	55,938
YCR BCIP region							
No	74,750	*88.3*	88,787	*90.1*	1,653	*90.1*	165,190
Yes	9,919	*11.7*	9,726	*9.9*	182	*9.9*	19,827

Table 4.2 Characteristics for patients with rectal cancer undergoing open, laparoscopic and robotic surgery in England diagnosed between 2007 and 2021.

	Open		**Laparoscopic**		**Robotic**		**Total**
	N	%	N	%	N	%	
Total	34,560		32,317		2,013		68,890
Age (years)							
18-59	8,227	*23.8*	7,839	*24.3*	528	*26.2*	16,594
60-69	11,263	*32.6*	10,541	*32.6*	698	*34.7*	22,502
70-79	10,811	*31.3*	10,092	*31.2*	601	*29.9*	21,504
≥80	4,259	*12.3*	3,845	*11.9*	186	*9.2*	8,290
Sex							
Male	22,818	*66.0*	20,772	*64.3*	1,355	*67.3*	44,945
Female	11,742	*34.0*	11,545	*35.7*	658	*32.7*	23,945
IMD							
1 – Least deprived	7,248	*21.0*	6,966	*21.6*	493	*24.5*	14,707
2	7,901	*22.9*	7,386	*22.9*	424	*21.1*	15,711
3	7,221	*20.9*	7,000	*21.7*	402	*20.0*	14,623
4	6,565	*19.0*	5,918	*18.3*	356	*17.7*	12,839
5 – Most deprived	5,625	*16.3*	5,047	*15.6*	338	*16.8*	11,010
CCI score							
0	29,641	*85.8*	28,044	*86.8*	1,764	*87.6*	59,449
1	3,482	*10.1*	2,998	*9.3*	184	*9.1*	6,664
2	926	*2.7*	825	*2.6*	43	*2.1*	1,794
≥3	511	*1.5*	450	*1.4*	22	*1.1*	983
Stage							
1	7,285	*21.1*	8,276	*25.6*	550	*27.3*	16,111
2	8,310	*24.1*	7,815	*24.2*	445	*22.1*	16,570
3	12,646	*36.6*	12,585	*38.9*	839	*41.7*	26,070
4	2,102	*6.1*	1,524	*4.7*	83	*4.1*	3,709
Unknown	4,217	*12.2*	2,117	*6.6*	96	*4.8*	6,430
Study period							
2007-2011	18,172	*52.6*	7,391	*22.9*	64	*3.2*	25,627
2012-2016	11,151	*32.3*	12,897	*39.9*	537	*26.7*	24,585
2017-2021	5,237	*15.2*	12,029	*37.2*	1,412	*70.1*	18,678
YCR BCIP region							
No	30,302	*87.7*	28,759	*89.0*	1,822	*90.5*	60,883
Yes	4,258	*12.3*	3,558	*11.0*	191	*9.5*	8,007

The annual proportion of resections performed using MIS for England, YCR BCIP and Denmark are shown in Figure 4.2. Slower uptake in MIS was observed for YCR BCIP when compared to overall English rates in both colon and rectal cancer, but this difference reduced by the latest study period (Supplementary Table 4.1). In 2017-2021, the percentage of MIS for colon cancer was 69.1% for YCR BCIP compared with the overall English percentage of 72.9%. In rectal cancer the corresponding figures were 67.3% for YCR BCIP and 72.5% for England.

When benchmarking MIS against Danish national figures, uptake in England and YCR BCIP was slower than in Denmark. In 2017-2021 the Danish MIS percentage had reached 87.6% in colon cancer and 92.3% in rectal cancer.

In 2017-2021, the percentage of all resections done by robotic surgery in colon cancer was 2.1% for YCR BCIP compared with the overall English percentage of 2.7% (Supplementary Table 4.1). In rectal cancer the corresponding figures were 4.7% for YCR BCIP and 7.9% for England. Over the same time period, in Denmark, the percentage of all resections performed using robotic surgery was 13.1% in colon cancer and 47.4% in rectal cancer.

The annual proportion of MIS resections that were performed using robotic surgery for England, YCR BCIP and Denmark are shown in Figure 4.3. Uptake of robotic surgery in YCR BCIP was slower than in England for rectal cancer, while Denmark had a much quicker uptake than England. Figure 4.3 shows that by 2021, robotic surgery accounted for over 60% of all Danish rectal cancer resections performed using a MIS technique, compared to <20% in England.

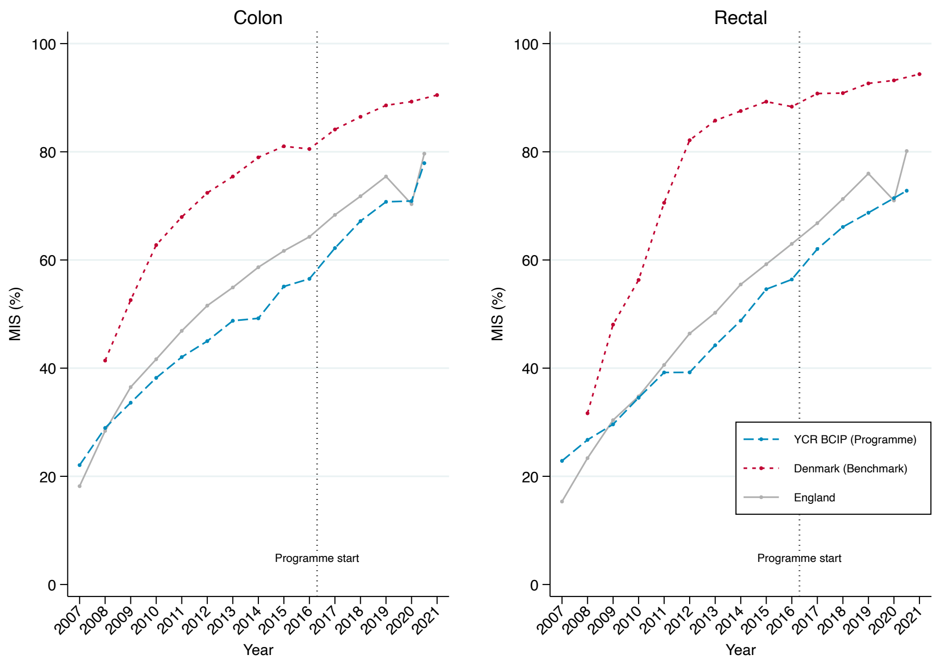

Figure 4.2 Percentage of major resections performed using minimally invasive surgery (MIS) for patients with colon and rectal cancer in YCR BCIP hospitals compared to the Danish benchmark.

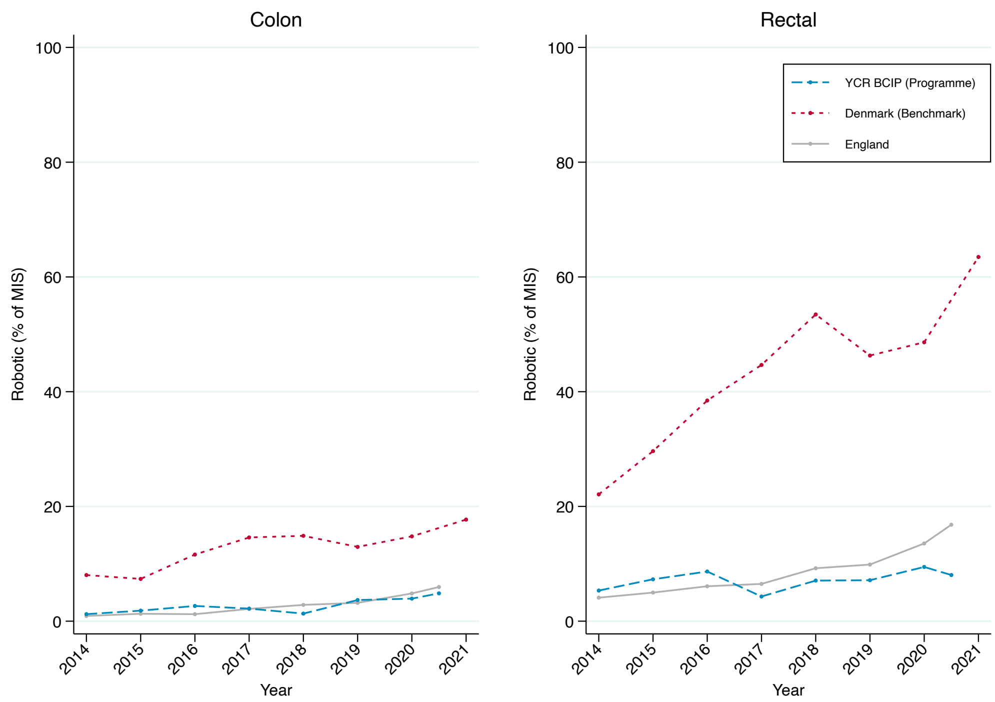

Figure 4.3 Percentage of minimally invasive surgery (MIS) performed using robotic surgery for patients with colon and rectal cancer in YCR BCIP hospitals compared to the Danish benchmark.

Identifying regional outliers and trends

The multilevel logistic regression models revealed higher use of MIS within England across all study periods was associated in those aged 60-69 years, residing in the least deprived areas, a CCI score of zero, an early stage tumour and a tumour located in the colon.

YCR BCIP hospitals were identified upon construction of the Funnel plots (Figure 4.4). In the period before the start of the programme (2012-2016), seven regional hospitals were found to be potential outlying units for low use of MIS at the 95% confidence limit. In the period after the start of the programme (2017-2021) the number of potential outliers for low use of MIS had reduced to two hospitals.

Splitting of the study period into 10 equal time-frames, approximately 18 months (530 days) apart was performed for construction of the tunnel plot. This enabled identification of trends in MIS use for each hospital while maintaining the use of control limits (Figure 4.5). The following observations were noted for feedback to the regional hospitals: A number of hospital showed a decrease in use of MIS to become low outliers (A and E); the majority of hospitals observed an increase in use or maintained use above the national average; one longstanding low outlier experienced a sharp increase to no longer being an outlier (B).

Out of the 122 hospitals in England, 41 were observed to be performing robotic surgery in patients with colon cancer, and 46 were observed to performing robotic surgery in patients with rectal cancer. The highest percentage of MIS performed using robotic surgery in hospitals was 28.5% in colon cancer and 75.9% in rectal cancer (Supplementary Figure 4.1). Out of the 14 YCR BCIP hospitals, 4 hospitals were observed to be performing robotic surgery for colon cancer, and 5 hospitals were observed to be performing robotic surgery for rectal cancer.

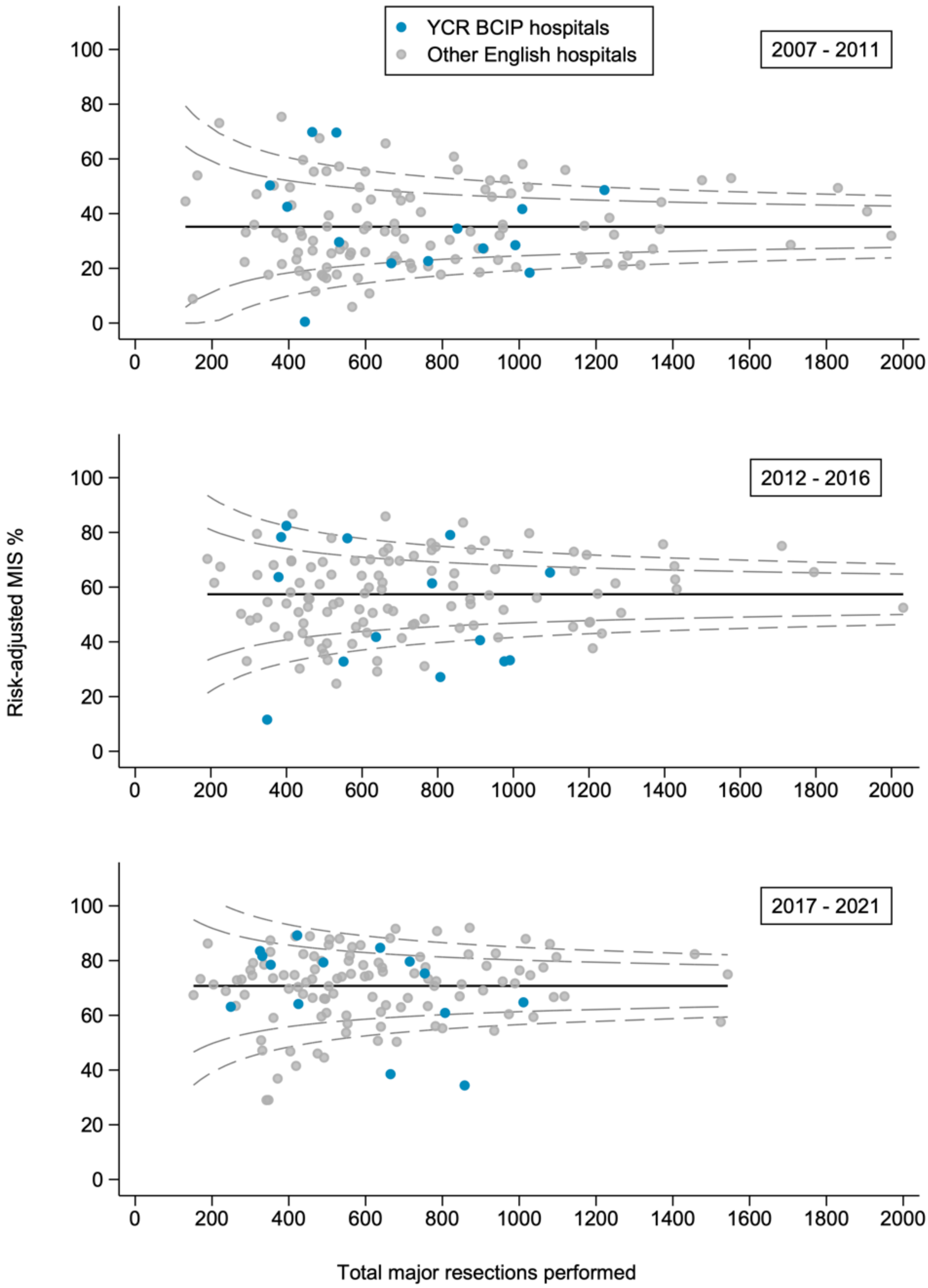

Figure 4.4 Funnel plots for adjusted minimally invasive surgery (MIS) percentage for patients with colorectal cancer in the English NHS.

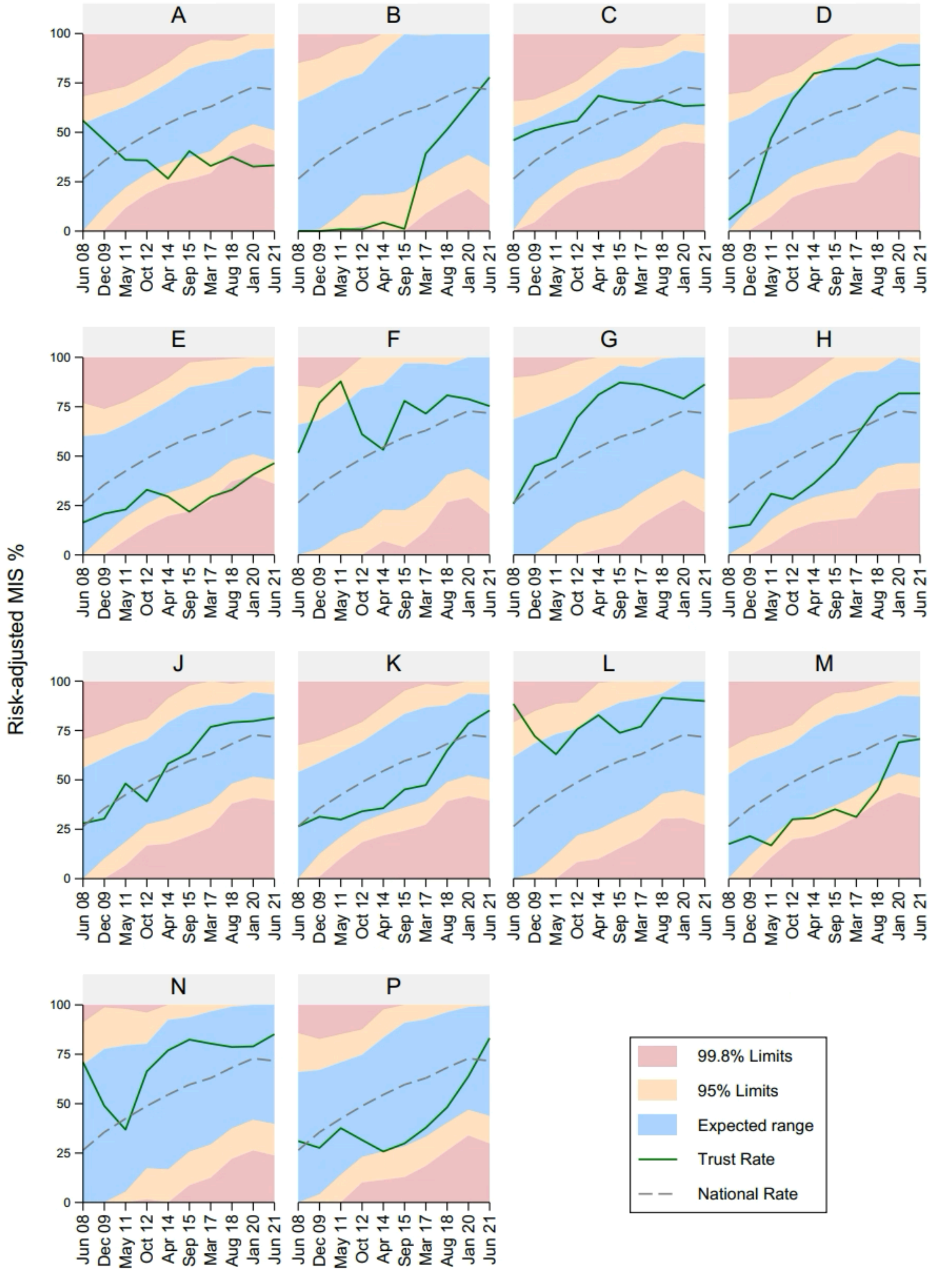

Figure 4.5 Tunnel plots for adjusted minimally invasive surgery (MIS) percentage for patients with colorectal cancer diagnosed between 2007 and 2021 at each hospital (A to P) in the Yorkshire (YCR BCIP) region.

4.5. Discussion [Paper 3]

This study has shown a steady increase in the use of MIS for colorectal cancer patients undergoing an elective major resection in England, but with substantial variation across providers. Differences in the rate of uptake of MIS within England may be attributed to interpretation of national guidelines, the provision of surgical training and the availability of capital investment for relevant equipment. The national training plan (Programme for Laparoscopic Colorectal Cancer Surgery, LAPCO) was run at 11 national centres from 2006 to 2013[18], providing one-to-one training by laparoscopic experts. The LAPCO Training the Trainer (LAPCO-TT) commenced in 2010 to improve the effectiveness of clinical training[19]. The number of surgeons attending these over the course of the study period and obtaining the necessary skills to provide laparoscopic surgery, will have impacted greatly on the uptake of MIS rates observed here. NICE guidelines will have influenced the uptake of MIS, and the need for a national training plan. Prior to the period covered by this study, guidelines in 2000 stated that open surgery should be the preferred procedure[20]. The guidelines were updated in 2006 to recommend laparoscopic surgery as an alternative to open resection for some patients by suitably trained surgeons and by those performing the procedure often enough to maintain competence.

Given the improvement in outcomes reported in Denmark[21,22], a strategic approach of YCR BCIP was to compare management of Yorkshire's colorectal cancer population and benchmark that with those in Denmark. This study has shown MIS in Yorkshire now appears to be representative of MIS in England. However, by 2021, 80% of patients were receiving MIS in every England, still behind the Danish benchmark figure of greater than 90%. While Denmark did not employ a formal national laparoscopic-only training plan, several surgeons from three Danish regions attended individual and supervision by international experts in the UK. Subsequent training of surgeons was then conducted in Denmark. Danish guidelines initially issued the same conservative approach to the introduction of laparoscopic surgery; guidelines in 2009 recommend it should only be performed by surgeons with sufficient experience and volume. However, in 2014, laparoscopic surgery was recommended as the standard treatment for non-advanced colon cancer and recommended for non-advanced rectal cancer[23]. The DCCG have also monitored the approach to surgery across the five Danish regions. Similar to England, annual reports observed regional differences in MIS uptake. This was most prominent in patients with colon cancer, in which one region had a much lower rate of MIS (50%) compared to other regions (range 75% to 98%) in 2016[12].

For interrogating data at set periods of time, the funnel plot methodology used in this study identified a number of potential outliers for use of laparoscopic surgery. However, we wished to identify trends for all hospitals (MDTs) within the YCRBCIP region, so extended the methodology to create ‘tunnel plots’. This has the benefit of being a simple graphical presentation comparing patterns across multiple time periods, and helped show how hospitals are performing over that time. The data relating to MIS were presented and discussed with regional MDTs at programme events, annual reports and through individual meetings between the programme’s surgical lead and a MDT representative as part of a wider data feedback schedule. While it was acknowledged that our analyses could not account for the all the differences experienced across the regional population, we aimed to identify potential sources of variation. Following feedback, a number of reasons for low rate of MIS were given: too few adequately trained surgeons, time pressures on available operating sessions (i.e. quicker to perform open surgery), patient selection in need of refinement and issues with regard to provision of modern laparoscopic equipment. Conversely, sharp upturns in rates of MIS coincided with recent appointments of laparoscopically trained surgeons. Following the start of the programme and regular feedback of data to surgical teams, the number of outlying hospitals in the region has reduced. Further work and monitoring will be needed to assess any potential influence the programme has had on MIS uptake in the region. This will also need to consider the impact of the COVID-19 pandemic and the debate around the safety of aerosol generating procedure and increased risk of viral transmission in healthcare workers[24]. The proportion of resections performed laparoscopically in England fell to 25% in the first wave of the pandemic under guideline issued at the time[25].

In 2020, NICE guidelines included recommendations that robotic surgery in England should only be considered within established programmes that have appropriate audited outcomes. This was based on the reasoning that while clinical evidence suggested that there was no difference in effectiveness between laparoscopic and robotic techniques, robotic surgery was not found to be cost-effective at this time. This may impact on the uptake of robotic surgery equipment and training, as surgical departments not already in possession of such equipment may have delayed investment until more evidence on its cost-effectiveness was gathered. A few years earlier, but with a similar conclusion, the DCCG formulated provisional guidelines in 2014 on robotic surgery for rectal cancer, stating that robot-assisted rectal surgery is equivalent to similar laparoscopic procedures in terms on short-term outcomes, with ongoing auditing and evaluation of short-term and long-term outcomes. While several studies from countries across the world have concluded robotic surgery for colorectal cancer resections is safe and outcomes are as at least equivalent of laparoscopic techniques, larger studies are needed to confirm its cost-effectiveness and long-term outcomes[26-29].

Both regional and national variation in the uptake of robotic surgery may be driven by access to appropriate training programs. Around the time of this study, these have been predominantly provided by industry with the exception of a few and calls for a train-the-trainer curriculum were identified[30]. The successful introduction of robotic surgery may also depend upon sufficient support at a hospital and operation level, through provision of adequate funding, operating time and staffing[31].

There are some limitations to this study that need to be considered when interpreting the results. Coding for MIS procedures in the hospital admission data used in the study was only introduced in 2006, so although rates are likely to be low for these years, it was not possible to confirm this. The years included rely on accurate data submission for MIS procedures and it is not possible to assess any changes in coding accuracy over that time. Several trials have reported noninferiority of single-port laparoscopic surgery when compared to multiport laparoscopic surgery in selected patients with colorectal cancer[32-34]. However, a further limitation of the coding meant that we could not investigate if there had been any uptake in single-port laparoscopic surgery. While use of the RCRD dataset provides more timely analysis of cancer data and enabled us to calculate rates of MIS more relevant to discussion with MDTs, this comes at a cost in data quality. When compared to diagnoses used for the gold-standard cancer registry, the RCRD had a false negative rate of near to 10% and a false positive rate <5%[35]. Completeness of tumour staging is also lower in the RCRD than in the cancer registry (22% v 9% unknown stage), but agreement of those who are staged is 85-93%. While only one year of overlap was available for our study, the annual MIS rate in the RCRD was slightly higher (1.3%) than in the NCRAS dataset.

A direct comparison on the patient characteristics between England, Yorkshire and Denmark, would give more insight into the populations undergoing MIS and whether the higher rates observed in Denmark could be attributed to a greater suitability of those selected for MIS. Previous studies have shown similarities between the basic patient characteristics, disease burden and life expectancies[36-38], but it should be noted that both per capita healthcare spending and the relative number of doctors and nurses per person are both higher in Denmark than the UK[39].

This study has found wide variation in the use of MIS exists in the English NHS and a data-driven approach has helped identify outlying hospitals (MDTs) for a regional improvement programme, and further monitoring of the results presented here over the following years will help to assess the impact of the programme. Addressing some of the challenges behind the provision of MIS, such as ensuring adequate provision of surgical training, and provision of modern state-of-the-art equipment, could help increase the number of suitable patients selected for elective MIS and the associated benefit of improved postoperative recovery.

Clinical Practice Points

- Minimally invasive surgery for colorectal cancer is as effective as open surgery but has the potential to improve recovery time, but its uptake varies between countries.
- We found uptake of laparoscopic and robotic surgery in England was slower than that in Denmark and found significant variation in rates of minimally invasive surgery at the hospital level.
- The reasons identified for low uptake of minimally invasive surgery included too few adequately trained surgeons and lack of modern laparoscopic equipment.

- Through a quality improvement programme we have demonstrated a reproducible methodology to identify outlying hospitals and the areas to focus on for improving provision of minimally invasive surgery.

4.6. Acknowledgements [Paper 3]

This work was funded by Yorkshire Cancer Research (Award reference number L394). Prof Quirke holds an NIHR Senior Investigator award. The UK Colorectal Cancer Intelligence Hub is supported by the Bobby Moore Fund/Cancer Research UK (C23434/A23706).

The data used for this study are available from the National Cancer Registration and Analysis Service via application to NHS England or CORECT-R.

The study was granted ethical approval (17/WM/0374) by the West Midlands - Solihull Research Ethics Committee in December 2017. The study was approved by the Health Research Authority and granted approval for inclusion in the National Institute for Health Research's portfolio of studies in December 2017 (Project ID 227673).

This work uses data that has been provided by patients and collected by the NHS as part of their care and support. This work uses data that has been provided by patients and collected by the NHS as part of their care and support. The data are collated, maintained and quality assured by the National Cancer Registration and Analysis Service. Access to the data was facilitated by the Office for Data Release and the Cancer Research UK funded UK Colorectal Cancer Intelligence Hub (C23434/A23706). We thank the Danish Colorectal Cancer Group (DCCG) the provision of published Danish data presented in this study.

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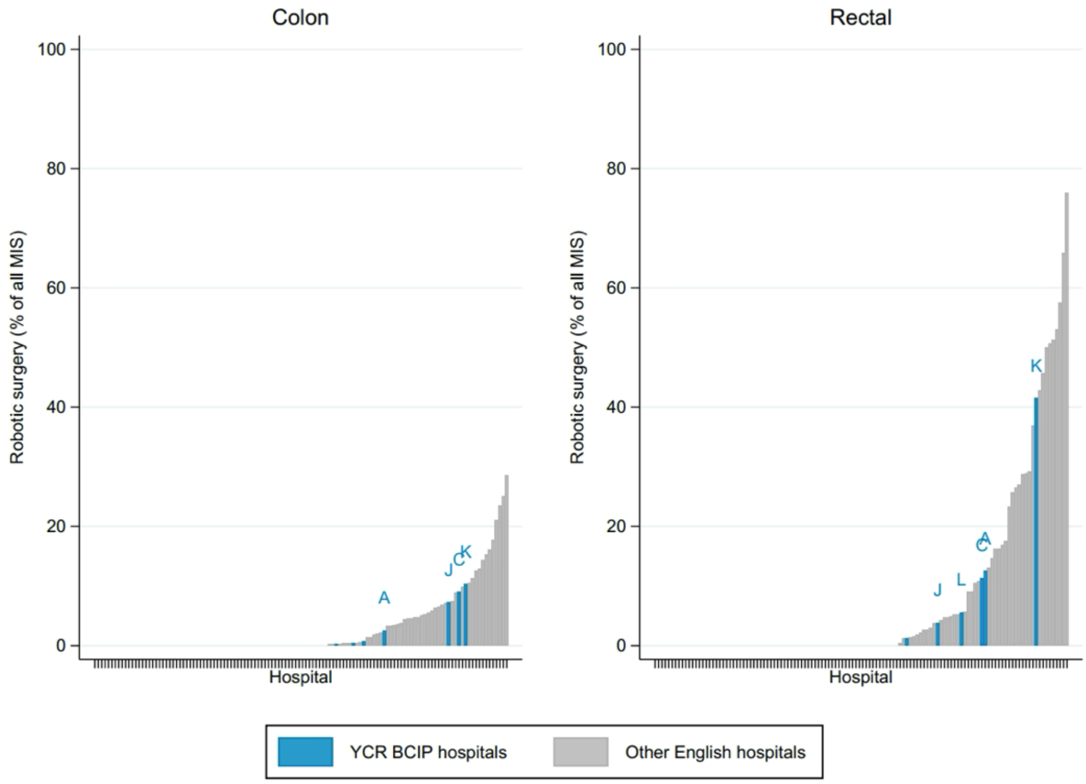
4.8. Supplementary information [Paper 3]

Supplementary Table 4.1. Percentage of resection preformed using open, laparoscopic and robotic surgery in YCR BCIP and England for patients with colorectal cancer diagnosed between 2007 and 2021.

	Colon			Rectal		
	Open	Laparoscopic	Robotic	Open	Laparoscopic	Robotic
YCR BCIP						
2007–2011	66.9	33.0	0.2	69.0	30.4	0.6
2012–2016	49.2	50.2	0.6	51.4	46.1	2.5
2017–2021	30.9	66.9	2.1	32.7	62.6	4.7
England						
2007–2011	65.1	34.8	0.1	71.2	28.6	0.2
2012–2016	41.0	58.6	0.5	44.5	53.3	2.1
2017–2021	27.1	70.2	2.7	27.5	64.6	7.9
Difference						
2007–2011	+1.7	-1.8	+0.1	-2.2	+1.8	+0.4
2012–2016	+8.2	-8.4	+0.2	+6.9	-7.3	+0.4
2017–2021	+3.8	-3.3	-0.5	+5.2	-2.0	-3.2

Supplementary Figure 4.1. Hospital variation in percentage of minimally invasive surgery performed robotically in patients with colorectal cancer diagnosed between 2017 and 2021. Hospitals within the YCR BCIP region and performing robotic surgery are labelled A to P.



4.9. Additional unpublished material [Paper 3]

Comparison of models for laparoscopic surgery

The risk ratios from multilevel mixed effects Poisson regression models for use of MIS in elective major resections were compared when fitted for the Danish and English data. Data were available for patients diagnosed between 2010 and 2017, from the DCCG and CORECT-R databases described in the previous two chapters. Independent fixed effects common to both models were age group (18-59, 60-69, 70-79 and ≥80 years), sex, tumour site (right colon, left colon, colon unspecified and rectal), stage of disease (1 to 4) and diagnosis year. Independent fixed effects unique to the English model were Charlson Comorbidity Index (CCI, categorized as a score of 0, 1, 2 and ≥3) and Index of Multiple Deprivation, IMD). The CCI and IMD were not available in the Danish data, so American Society of Anaesthesiologists' physical status (ASA grade) was included instead. Hospital was fitted as a random effect and imputation of stage and ASA was performed as described previously in the paper methods.

Results of the models for Denmark and England are given in Table 4.3. In both populations, higher use of MIS was significantly associated with non-metastatic disease and lower patient comorbidity (ASA grade in Denmark, CCI in England). Lower use of MIS was associated with older age in England, particularly those aged ≥80 years compared to those age 60-69, but not in Denmark. When compared to right-sided colon tumours, increased use of MIS was associated with left-sided colon and rectal tumours in Denmark. In England, decreased use of MIS was associated with rectal tumours compared to right-sided tumours.

Table 4.3 Adjusted risk ratios and 95% confidence intervals for use of minimally invasive surgery in patients with colorectal cancer in Denmark and Yorkshire between 2010 and 2017.

	Denmark		**England**	
	RR (95% CI)	**p-value**	**RR (95% CI)**	**p-value**
Age (years)				
18-59	0.98 (0.96, 0.99)	0.010	0.94 (0.93, 0.96)	<0.001
60-69	1.00 (reference)		1.00 (reference)	
70-79	1.00 (0.98, 1.01)	0.45	0.97 (0.96, 0.98)	<0.001
≥80	1.03 (1.00, 1.06)	0.036	0.92 (0.90, 0.94)	<0.001
Sex				
Male	1.00 (reference)		1.00 (reference)	
Female	0.99 (0.97, 1.00)	0.081	0.98 (0.97, 0.99)	0.001
ASA grade				
1	1.00 (reference)			
2	0.96 (0.95, 0.98)	<0.001		
3	0.92 (0.90, 0.94)	<0.001		
≥4	0.83 (0.76, 0.91)	<0.001		
IMD				
1 - least deprived			1.00 (reference)	
2			0.99 (0.97, 1.00)	0.050
3			0.98 (0.97, 1.00)	0.11
4			0.96 (0.94, 0.97)	<0.001
5 - most deprived			0.93 (0.91, 0.95)	<0.001
Charlson score				
0			1.00 (reference)	
1			0.89 (0.87, 0.90)	<0.001
2			0.85 (0.83, 0.87)	<0.001
≥3			0.78 (0.75, 0.81)	<0.001
Stage				
1	1.08 (1.05, 1.11)	<0.001	1.14 (1.12, 1.16)	<0.001
2	1.00 (reference)		1.00 (reference)	
3	1.01 (0.99, 1.03)	0.20	0.96 (0.95, 0.97)	<0.001
4	0.87 (0.80, 0.95)	<0.001	0.72 (0.70, 0.75)	<0.001
Tumour site				
Right colon	1.00 (reference)		1.00 (reference)	
Left colon	1.24 (1.09, 1.41)	<0.001	1.01 (0.99, 1.03)	0.53
Colon unspecified	1.02 (0.87, 1.20)	0.79	0.91 (0.86, 0.95)	<0.001
Rectal	1.24 (1.10, 1.40)	<0.001	0.87 (0.83, 0.91)	<0.001
Diagnosis year				
per year	1.04 (1.03, 1.06)	<0.001	1.07 (1.06, 1.08)	<0.001

Comparison of models for conversion to open surgery

Given the difference in the models observed in the previous section, the conversion from MIS to open surgery was modelled using multilevel mixed effects Poisson regression for the two populations. Risk ratios for conversion to open surgery were estimated for all patients who had undergone an attempted minimally invasive major resection. Data were available for patients diagnosed between 2010 and 2017. As before, independent fixed effects in the models were age group, sex, tumour site, stage of disease (1 to 4), diagnosis year and CCI (England only), IMD (England only) and ASA grade (Denmark only).

Results of the models for Denmark and England are given in Table 4.4. When compared to those age 60-69 years, older age was not associated with conversion in either population. In both populations, increased conversion was associated with female patients, those with increased comorbidity and those with metastatic disease. When compared to right-sided colon tumours, those with left-sided and rectal tumours had reduced risk of conversion in Denmark, while the opposite was observed in England.

Table 4.4 Adjusted risk ratios and 95% confidence intervals for conversion from minimally invasive surgery to open surgery in patients with colorectal cancer in Denmark and Yorkshire between 2010 and 2017.

	Denmark		**England**	
	RR (95% CI)	**p-value**	**RR (95% CI)**	**p-value**
Age (years)				
18-59	0.94 (0.82, 1.08)	0.40	0.90 (0.85, 0.95)	<0.001
60-69	1.00 (reference)		1.00 (reference)	
70-79	1.02 (0.93, 1.14)	0.60	1.06 (1.02, 1.11)	0.006
≥80	1.06 (0.93, 1.20)	0.39	1.00 (0.95, 1.06)	0.94
Sex				
Male	1.00 (reference)		1.00 (reference)	
Female	0.70 (0.64, 0.77)	<0.001	0.71 (0.68, 0.73)	<0.001
ASA grade				
1	1.00 (reference)			
2	1.48 (1.31, 1.67)	<0.001		
3	2.07 (1.79, 2.38)	<0.001		
≥4	2.12 (1.37, 3.28)	0.001		
IMD				
1 - least deprived			1.00 (reference)	
2			0.99 (0.97, 1.00)	0.050
3			0.98 (0.97, 1.00)	0.11
4			0.96 (0.94, 0.97)	<0.001
5 - most deprived			0.93 (0.91, 0.95)	<0.001
Charlson score				
0			1.00 (reference)	
1			1.19 (1.14, 1.25)	<0.001
2			1.21 (1.11, 1.31)	<0.001
≥3			1.20 (1.08, 1.33)	0.001
Stage				
1	0.64 (0.56, 0.73)	<0.001	0.83 (0.80, 0.87)	<0.001
2	1.00 (reference)		1.00 (reference)	
3	1.10 (0.99, 1.22)	0.067	1.02 (0.98, 1.06)	0.33
4	1.39 (1.20, 1.61)	<0.001	1.33 (1.24, 1.42)	<0.001
Tumour site				
Right colon	1.00 (reference)		1.00 (reference)	
Left colon	0.86 (0.77, 0.95)	0.004	1.21 (1.14, 1.28)	<0.001
Colon unspecified	1.11 (0.24, 5.08)	0.89	1.24 (1.07, 1.43)	0.003
Rectal	0.60 (0.53, 0.67)	<0.001	1.26 (1.19, 1.34)	<0.001
Diagnosis year				
per year	0.93 (0.91, 0.94)	<0.001	0.99 (0.98, 1.00)	0.023

Variation in Danish hospitals

Given the variation observed in the uptake in MIS for hospital in Yorkshire, the variation in uptake in Danish hospitals was investigated. The percentage of resections performed by MIS was calculated by both Danish and Yorkshire hospital and the number of hospitals with a percentage <20%, 20–40%, 40–60%, 60–80% and >80% recorded by study period (Table 4.5). Danish data obtained from the DCCG database was only available for the first two study periods used in the main paper (2007–2011 and 2012–16) and the published data used in the main paper are not made available by hospital.

Table 4.5 Adjusted risk ratios and 95% confidence intervals for conversion from minimally invasive surgery to open surgery in patients with colorectal cancer in Denmark and Yorkshire between 2010 and 2017.

	Danish hospitals n (%)			**Yorkshire hospitals n (%)**		
Resection performed by MIS	2007 to 2011	2012 to 2016	2017 to 2021	2007 to 2011	2012 to 2016	2017 to 2021
<20%	2 (12)	0 (0)		2 (14)	1 (7)	0 (0)
20 – 40%	4 (24)	0 (0)		7 (50)	4 (29)	2 (14)
40 – 60%	5 (29)	3 (18)		3 (21)	2 (14)	0 (0)
60 – 80%	4 (24)	2 (12)		2 (14)	6 (43)	6 (43)
>80%	2 (12)	12 (71)		0 (0)	1 (7)	6 (43)

In the period 2007–2011, 6 out of 17 (36%) Danish hospitals had a MIS percentage >60% and this increased to 14 (82%) hospitals by 2012–2016. All Danish hospitals had a MIS percentage >40% by 2012–16. In comparison, 7 out of 14 (50%) Yorkshire hospitals has a MIS percentage >60% in 2012–16. Five (36%) Yorkshire hospitals still had a MIS percentage <40% in 2012–16.

Use in emergency surgery

Analyses in the main paper were restricted to those patients undergoing an elective resection. However, emergency surgery is defined differently in the two datasets, as previously described in Chapter 3 (Paper 2). This may impact the observed MIS percentage, as those receiving emergency surgery are generally less likely to have a MIS procedure than their elective counterparts. Therefore, the MIS percentage was calculated and compared in the two populations for elective, emergency and all resections (elective and emergency) for patients diagnosed from 2007 to 2016.

The use of MIS in emergency resections in both Denmark and Yorkshire increased steadily from 2007 to 2016, reaching 18% in Denmark by 2016, compared to 12% in Yorkshire. The trend in Yorkshire was broadly reflective of the national trend in England. Including emergency resections together with elective would have had little impact on the results in the main paper when considering the speed of MIS uptake (Figure 4.6).

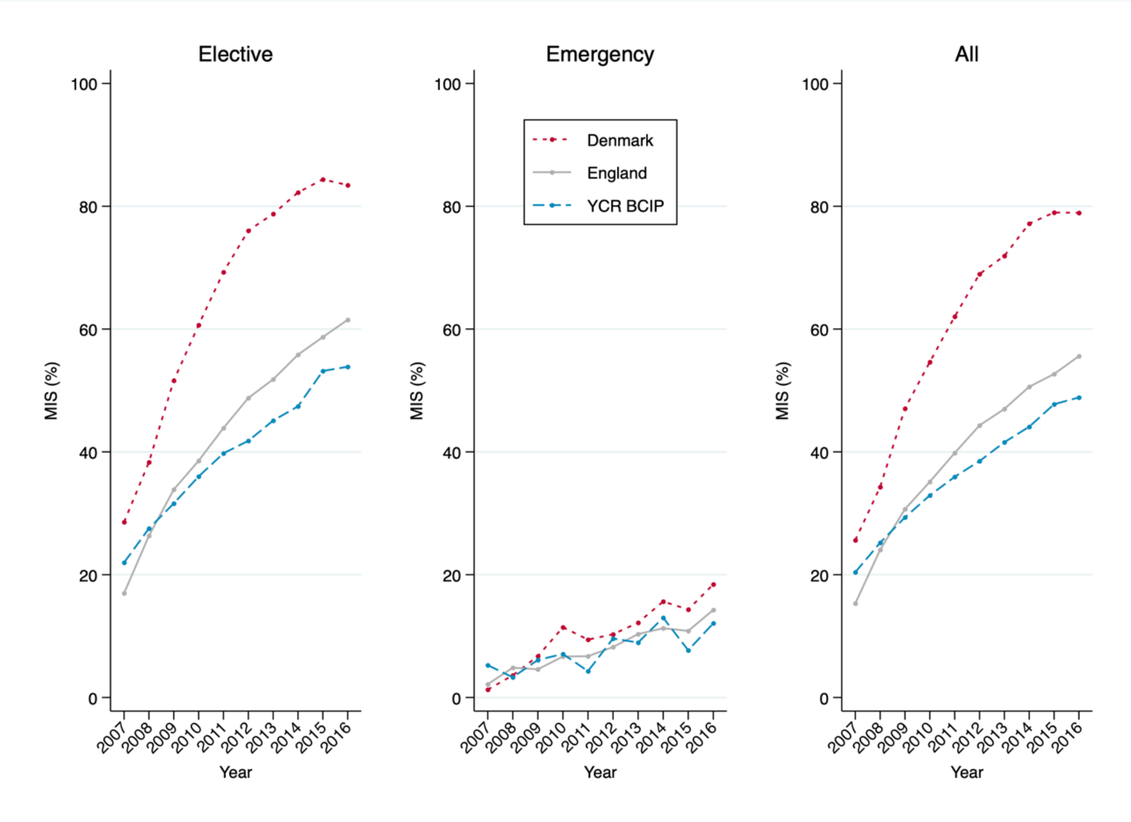


Figure 4.6 Percentage of major resections performed using minimally invasive surgery (MIS) for patients with colorectal cancer undergoing elective and emergency resections in YCR BCIP hospitals compared to the Danish benchmark.

Chapter 5. Discussion

5.1. Overview

Colorectal cancer accounts for more than 1 in 10 new cancer cases in the UK and approximately 120 new cases are diagnosed every day. Incidence rates are higher in older people but recently incidence rates have risen in young adults. Therefore, implementing the optimal treatment for each patient with colorectal cancer and improving outcomes remains a priority for the NHS. Detailed reviews of observational data to quantify patterns of practice has contributed to improvements in patient outcomes in Denmark, and a similar strategy has now been employed in the large English region of Yorkshire.

This study set out to identify differences between these two populations in the management of patients with colorectal cancer. This was done by interrogation of accessible data on the colorectal cancer populations of Yorkshire and Denmark, creating datasets on the surgical aspects of care that were both analogous and robust. The resulting data were compared and analysed to produce three separate, but linked, studies detailing differences in surgical management that produced the following novel findings:

1) Age and surgical treatment of colorectal cancer
This study showed greater use of major resection in the older age groups for the Danish colorectal cancer population compared to Yorkshire. In patients with colon cancer aged ≥80 years, there was an increased short-term risk of death in Danish patients compared to Yorkshire, but relative survival in Denmark was higher and continued to increase over time unlike in Yorkshire.

2) Emergency resection for colon cancer
This study has shown that both Denmark and Yorkshire have substantially reduced postoperative mortality over time in both elective and emergency resections. A larger decrease in overall postoperative mortality in Denmark has coincided with a reduction in the use of emergency resection and an increase in stenting procedures.

3) Minimally invasive surgery for colorectal cancer
Uptake of MIS in patients undergoing elective surgery for colorectal cancer in Yorkshire was slower than in Denmark. The proportion of MIS performed using robotic surgery in Denmark is higher than in Yorkshire, especially for rectal cancer. The study also found wide variation in the use of MIS both across Yorkshire and across the English NHS. Two Yorkshire hospitals were found to have performed MIS in less than 50% of elective colorectal cancer resections.

5.2. Age and surgical treatment of colorectal cancer

Chapter 2 [Paper 1] highlighted a substantial difference between Denmark and Yorkshire in the surgical management of patients with colorectal cancer. In general, major surgical resection was used more in Denmark and this difference increased as age increased. At age ≥80 years, the differences were particularly stark (70% vs 51% in colon cancer and 49% vs 34% in rectal cancer). These results corroborate the findings from a study comparing treatment in Denmark, Sweden, Norway and England using data from 2010-12, which found much higher use of surgical resection in the Scandinavian countries than in England for patients aged ≥85 years in both colon cancer and rectal cancer[68]. A previous study compared resection rates in colon cancer for patients aged ≥80 years across several European countries in 2007-10. The reported rates for Denmark (73%) were similar to those reported here and the rates in the other countries (Belgium 76%, Sweden 79%, Norway 77%, Netherlands 57%) are all higher than we found for patients in Yorkshire[67]. The decrease in resection rates over time observed in Yorkshire in this study suggests that such differences may have widened since then.

The differing rates of major surgical resection in the elderly between Denmark and Yorkshire are likely to be directly related to the surgical risk to the patient. More specifically, one or a combination of the following reasons could account for the difference: elderly patients in Yorkshire carry a higher risk profile than their Danish counterparts, Danish clinicians are more willing to operate on these higher risk patients than Yorkshire clinicians, or Danish patients are more likely to agree to surgery following an informed discussion of the risk with the clinicians. It is difficult to directly compare the risk profiles of the two populations, for instance the life expectancies reported in Chapter 1 are very similar and the UK has a similar prevalence of cardiovascular disease but a considerably higher obesity prevalence than Denmark[90,91].

Evaluating the risk to an elderly patient is far from straightforward for either the clinician or the patient and the decision to treat should not be based on age alone. When an elderly patient presents in good general physical and mental health then a treatment equivalent to that received by younger patients is appropriate[92]. However, elderly patients often present with multiple comorbidities and their chronological age may not reflect their physiological age. Identifying high-risk patients preoperatively may improve outcomes[93].

Among the outcomes that need to be considered in elderly patients are length of hospital stay, discharge destination, short-term and long-term functional outcomes, and short-term and long-term mortality[94]. This study has examined the short-term and long-term mortality and highlighted the possible trade-off between the two when considering surgical resection in the elderly. In colon cancer, a higher short-term mortality was observed in Denmark compared to Yorkshire coinciding with higher Danish rates of resection. Notably, this was only significant in the latest period of the study when the resection rates in Yorkshire had fallen even further behind those seen in Denmark. There was no significant difference between the two populations, though, in 1-year relative survival for resected patients. This reinforces the view that the differences in survival between younger and older patients is generally due to differences in short-term mortality soon after surgery[94,95]. Pilleron et al reported that when conditioning on surviving 6-months after diagnosis, the 3-year relative survival for patients with stage 3 colon cancer were similar for younger and older patients in Denmark, whereas the survival for UK patients decreased with age[96]. Given that the survival rates for resected patients are similar between Denmark and Yorkshire, and since a higher number of patients in Denmark received a resection, this may help to explain why a higher survival rate was observed in Denmark when considering elderly patients.

Since 2013, surgeon-specific outcomes have been reported annually in England, meaning risk-adjusted 90-day mortality rates for elective colorectal cancer resections are publicly available. The reason for introducing the reporting was to drive quality improvement, but it can be controversial as some argue that it increases the chances of risk averse surgeons transferring complex cases to others or the most complicated cases missing out on surgery all together[97]. Under this assumption, Danish surgeons would be less likely to be risk averse and as a result perform more surgery as Denmark do not publish surgeon-specific outcomes. A study analysing English data, found the introduction of reporting surgeon-specific outcomes coincided with a significant reduction in 90-day mortality, but there was no evidence for the introduction also leading to a reduction in the number of high-risk patients undergoing surgical resection[98].

Following the presentation of these study results to colorectal surgeons in Yorkshire, a pilot audit at three MDTs was conducted to investigate potential reasons for patients aged ≥80 years not receiving surgical treatment. Of the 110 patients discussed at the MDT meetings, 42% received a major resection, a similar percentage to that found in the population-based data here. Of the remaining patients, 23% were deemed unfit for surgery (due to frailty or comorbidity), 19% received alternative palliative treatment for advanced disease and 12% reported that not having surgery was the patient's choice. Of particular note was the variation in the reasons given and the demographics of the patients across the three MDTs. In one MDT, 96% of patients had 2 or more cardiovascular comorbidities and 39% of patients were deemed unfit for surgery, whereas in another 49% had 2 or more cardiovascular comorbidities and just 7% were deemed unfit for surgery. To investigate this further, a full region-wide audit has been proposed to compare assessment and treatment strategies at each regional MDT.

Although the sample size in the audit was small, it highlights the complexity in assessing the fitness of a patient for major colorectal surgery and that age alone is not an appropriate prognostic factor. A patient's frailty should also be considered and distinguishing those elderly patients who are frail from those who are not is an essential step on the treatment pathway[99]. In the clinical setting, use of even relatively simple screening tools such as the Clinical Frailty Scale has been shown to be beneficial in predicting adverse outcomes[100]. A measure of frailty was not available for use in this study, so it is not possible to determine whether the differences in resection rates for elderly patients between Denmark and Yorkshire remain once frailty has been accounted for. Measures of frailty for use in population-based data, such as the Hospital Frailty Risk Score, have recently been developed. In follow-up work from this study, these measures have now been compared and assessed for suitability in English colorectal cancer data[101]. This comparison showed that the measures have some value in quantifying frailty in this data, but they also have some overlap with standard measures of comorbidity, demonstrating the difficulties in measuring frailty as this level. Nonetheless, it is feasible that these measures could be applied to colorectal cancer data in Denmark and thus compared with the Yorkshire data to investigate the role of frailty in surgical treatment.

Beyond screening for frailty in the clinical setting, Comprehensive Geriatric Assessment (CGA) may be the most appropriate method of evaluating the health of frail elderly patients. A CGA involves a multidisciplinary approach to examining physical functioning, comorbidities, polypharmacy, nutritional status, cognitive function, emotional function and social support[94]. A small prospective study (n=178 patients) concluded CGA was useful in predicting complications for patients with colorectal cancer undergoing elective surgery[102]. Given that CGA can be time consuming and not always feasible, the results of trials investigating CGA in colorectal cancer care in Denmark (GEPOC) and Sweden will be keenly anticipated[103,104]. While there is currently no evidence that CGA is widely implemented in Danish and Yorkshire hospitals, individual hospital protocols of a similar nature may be in place and thus have a small effect on the number of patients receiving a resection in this study.

The impact of alternative treatment strategies to major surgical resection should be considered in the interpretation of the results in this study. Use of local excisions for early-stage tumours may have impacted the results in this study, particularly in patients with rectal cancer. Historical guidelines from both Denmark and England document that local excisions for patients with T1 rectal tumours should be considered. In the additional results of Chapter 2, there was evidence that local excision was implemented more in Yorkshire than Denmark in rectal cancer (17% v 9%) and that this was consistent across all ages. Given that approximately only 6% of major resections are T1 tumours in England this is unlikely to impact the results to a substantial degree[105]. The TREC trial compared TME surgery with short-course radiotherapy followed by TEM surgery in T1 and T2 tumours, finding the latter achieved high levels of organ preservation and improved quality of life[106]. Alternatively, a “watch and wait” approach may have sometimes been considered in patients with a complete clinical response following preoperative radiotherapy[18]. If such radiotherapy-based approaches have been utilised more frequently in Yorkshire, then it may partly explain the lower resection rates. However, both these treatment strategies are likely to have needed evidence of a stronger effect to have a large impact on the results seen here. Given these treatments are mostly restricted to patients with rectal cancer, they are also very unlikely to have any impact on the results seen with colon cancer.

5.3. Emergency resection for colon cancer

Chapter 3 [Paper 2] identified a considerable difference in the proportion of patients with colon cancer undergoing emergency surgery in Denmark and Yorkshire. Most notably, Denmark significantly reduced their emergency surgery rate for left-sided tumours. The most likely explanation for this is the increased use of stents as a bridge to surgery (SBTS), a procedure first described by Tejero et al (1994)[107], allowing the conversion of an emergency surgical case into an elective one.

Traditionally, surgeons in Denmark have performed most of the endoscopic gastrointestinal procedures[44]. The endoscopic experience gained through this, coupled with studies in the 2000s demonstrating poor outcomes from emergency colorectal surgery[108], may explain the relatively quick uptakes of stent usage in Danish colorectal cancer treatment.

While use of a stent procedure before resections in Yorkshire was significantly more likely in left-sided tumours than right-sided tumours, their overall use was much lower. The low uptake of stents in Yorkshire may be explained by interpretation of the evidence. The reasoning that outcomes following emergency resections were poor compared to elective surgery is difficult to refute, but whether use of SBTS is a superior treatment modality was more controversial. In the early 2010s a number of randomised controlled trials investigating use of SBTS compared to emergency surgery were stopped early for varying reasons at the monitoring and interim analysis stages: an increased anastomotic leak rate in the emergency group, increased 30-day morbidity in the SBTS group, a high failure rate and perforation when placing the stent[109-111] all contributed to this. Additional trials have since been published after the end of the period covered in this study (2016). A trial of 115 patients in Italy and Spain found no difference in postoperative complications after 60 days (52% in the SBTS group and 58% in the emergency surgery group). Secondary outcomes showed no difference in overall survival or recurrence, but did report lower rates of stoma formation in the SBTS group. In the UK, the long-awaited results of the CReST trial were published in 2022. In the 217 participants they found no difference in 30-day mortality or duration of hospital stay (primary outcomes) or perioperative morbidity, critical case use, 3-year recurrence and quality of life (secondary outcomes) but also found lower rates of stoma formation in the SBTS group. The authors concluded the SBTS should be considered as a standard option for patients with obstructing but potentially curable cancer. Given that the results of these two trials have only recently been published, it is feasible that use of stents in Yorkshire have increased since 2016.

The evidence that exists at a particular time will always influence guidelines, so one may expect those guidelines to be broadly similar across countries. However, the timing and detail of those guidelines may differ and consequently result in variation in practice between clinicians in different countries. Both 2010 DCCG guidelines and 2011 NICE guidelines are similar in that they both highlight the technical skill needed for successful stent placement. The Danish guidelines recommend that the treatment should be performed only by those who have the technical skill within each hospital department. The English guidelines recommend the decision on whether to conduct a stent placement should involve a consultant colorectal surgeon together with an endoscopist and/or a radiologist with colonic stent experience. The overall recommendation in the Danish guidelines stated obstructed left-sided tumours without suspected perforation should be treated with a stent if possible (and this is graded "B" using the Oxford Center for Evidence-Based Medicine Levels of Evidence and Grades of Recommendations scheme, which ranks evidence from "A" strongest to "D" weakest[112]). However, the message from the overall recommendation in the NICE guidelines was not as strong and simply recommend that a stent should be considered. By 2014, the Danish guidelines downgraded the recommendation of stent usage somewhat, stating only that the treatment options available are: stent placement, relief stoma placement and resection (graded "C"). By 2019, Danish guidelines strongly recommended that stent, relieving stoma and resection were all equivalent in terms of survival (graded "A"). The change issued in 2014 may explain why, in this study, there was no increase in the use of stents from the period 2011-13 to 2014-16. In 2014 NICE guidelines recommended that it should be explained to patients that the tumour can be managed either by emergency surgery or STBS and that there is no clear evidence that one treatment is better than the other. By 2020 that changed slightly to offering either STBS or emergency surgery; the guidelines acknowledged that this advice could lead to an increase in the provision of stenting.

Chapter 3 looked at stent procedures preceding major resections irrespective of whether the resection was categorised as an elective or an emergency procedure. Ideally, the use of stent procedures for only those with an emergency cancer presentation would have been examined, with a view to identifying definite STBS treatment in each population. However the nature of retrospective population-based data makes it particularly difficult to identify STBS procedures. For instance patients in the DCCG who are acutely relieved with a stent prior to an elective resection, will only have a registration of the elective procedure. Further linkage to the NPR would be required but this was not available. A Danish study which did use DCCG-NPR linked data, found that 44% of patients undergoing an emergency procedure between 2005 and 2015 were treated with stents[52].

In Chapter 3, the estimated RRs for 30-day mortality in patients undergoing an emergency resection compared with elective resections were stratified over study intervals (2005-07, 2008-10, 2011-2013 and 2014-16). As expected, overall, those undergoing an emergency resection were more likely to have died than those undergoing an elective resection (RRs >2.5 in all study intervals and both populations).

However, in Denmark the RR increased over time (2.6, 3.6, 4.3 and 4.7 over study intervals). This provides some evidence of Danish practice that converts potential emergency resections into elective resections, as those patients who could not be converted and with a relatively high morbidity were mostly undergoing an emergency resection towards the end of the study period. As more patients were receiving elective resections at the end of the study period instead of emergency resections, this could also help explain the larger decrease in 30-day mortality overall (from 7.7% to 3.0%) than that observed in Yorkshire (7.1% to 3.3%).

There are few clinical contraindications for conversion of an emergency case to an elective case, other than bowel perforation. Only limited factors were available to investigate in Chapter 3, which included age, sex, tumour site and stage of disease. Unsurprisingly, left-sided tumours were associated with increased use of stenting in both Denmark and Yorkshire and similar increasing RRs were observed with an increase in stage. However, a significant association was also observed between stenting and age in Denmark alone, as patients aged ≥80 years were more likely to have received a stent procedure prior to their resection compared to those of a younger age. As proposed in Chapter 2, this could indicate a difference in the management of elderly patients, but given the low numbers of stent procedures in Yorkshire the present study may not have sufficient power to detect this.

As well as the patient's clinical contradictions and issued guidelines, another reason for not converting emergency cases to elective could be a lack of available stenting facilities. This could include factors such as the number of clinicians available to perform the stenting procedures or when such clinicians are available. An organisational survey of NHS sites in England to provide details on the services provided by Hospital Trusts was conducted by NBOCA in 2017[113]. As part of the survey, Trusts were asked whether on-site bowel stenting facilities were available 24 hours a day, 7 days a week. In the Yorkshire region, 3 of the 14 Trusts (21%) confirmed that they had 24/7 facilities available, slightly less than the 28% of Trusts nationally. A survey performed by Lam et al, found only 25% of English hospitals performed stents out of hours and 23% at weekend (of the hospitals that responded)[114]. Additionally, of those receiving referrals from other hospitals, only 3 hospitals had protocols in place. A regional referral network with standardised stenting protocols may therefore improve care for those patients who would benefit from this type of treatment.

Significantly better outcomes for patients undergoing emergency colorectal surgery have been reported when they are treated by a surgeon with a specialist interest in colorectal surgery[115,116]. Acknowledgement of this in both Denmark and England may have contributed to the improved 30-day mortality that was seen in Chapter 3. In England, the National Emergency Laparotomy Audit (NELA) was established in 2012 after it was concluded that the standards of care for patients undergoing emergency laparotomy required improvement. The NELA audit reported that approximately 60% of emergency procedures were performed by a consultant with a specialist interest in colorectal surgery, and that 30-day mortality was lower (9.5%) than for non-specialists (14.2%)[117]. Since 2012, emergency surgery performed by a colorectal specialist has been included as a Quality Performance Indicator (QPI) in Denmark (with a desired standard rate set at 90%)[45]. In 2005-2007 the actual rate was approximately 50%, but this steadily increased to approximately 80% in 2014-2016. Although current data are not available to compare the equivalent figure within Yorkshire, it is likely to be similar in 2014-2016 to the 60% national figure reported by the NELA study. Additionally, the NBOCA organisational audit reported that only 2 of the 14 regional MDTs had a specialist colorectal surgeon on-call at all times. Despite this, in Chapter 3 a larger decrease in 30-day mortality after emergency surgery was seen in Yorkshire (8.5%) than in Denmark (6.5%). Further investigation would be needed to determine whether this is due to a higher quality of emergency surgery in Yorkshire, or due to a higher remaining patient morbidity in Denmark after the conversion of some patients into elective procedures.

5.4. Minimally invasive surgery for colorectal cancer

Surgeons in Denmark were seen to adopt the use of laparoscopic surgery for elective resections substantially quicker than those in Yorkshire. This may be for a number of reasons including access to suitable training, adherence to guidelines and adequate provision of the necessary equipment needed to perform such operations.

The availability of suitable training is not likely to explain the differences seen in this study, as a national training plan was implemented in England and Denmark employed a more *ad-hoc* regional approach. The NHS-funded English national training plan (LAPCO) was conducted at 11 training centres throughout the country from 2006 to 2013[118], and open only to colorectal specialist surgeons who were required to have basic laparoscopic skills. LAPCO was considered a success in terms of increasing the rate of laparoscopic surgery and was cost-neutral due to a reduction in postoperative complications and the resulting length of hospital stay[119]. The total number of attendances by region has not been published so it is not possible to determine how many of Yorkshire's colorectal surgeons attended the training. In contrast, Denmark did not employ a formal national training plan. Training in Denmark was instigated by several surgeons who themselves had been trained by international experts in the UK. As delegates in LAPCO were required to go through a more formal application process to attend the training programme, this may have resulted in quicker training of surgeons in Denmark but a less thorough assessment of both the quality of training and the proficiency of the trainee.

Similarly to Chapter 3, historical guidelines are likely to influence how laparoscopic surgery was used during the study period. Since the publication of its technological appraisal in 2006, NICE guidelines have changed little, recommending laparoscopic surgery as an alternative to open resection for suitable patients and requiring that it should only be performed by trained surgeons and those who perform enough procedures to maintain competence. Danish guidelines have gone beyond simply stating that laparoscopic surgery is an alternative to open surgery and in some cases recommended it as the standard treatment. In 2010, laparoscopic colonic surgery was recommended, citing better short-term outcomes (Graded "A") with the similar caveat to the NICE guidelines that laparoscopic surgery should only be performed by experienced surgeons who conduct a sufficient number of operations (Graded "B"). Subsequent guidelines recommended laparoscopic surgery as the standard for non-advanced colon cancer (Graded "A") and that laparoscopic procedures are equivalent to open surgery in <T4 tumours and reduce hospital length of stay in rectal tumours (Graded “A”).

In the Chapter 4 study, the majority of Yorkshire hospitals achieved a rate of MIS above the national average in the latter part of the study period, as can be seen from the funnel and tunnel plots (Chapter 4, Figures 4.4 and 4.5). It is not surprising that the hospital that achieved the highest rate of MIS was the only regional hospital that was selected as a LAPCO training centre. The regional variation observed is not unique to Yorkshire, as wide variation was also seen at a national level. What is of greater concern is that while several hospitals increased rates of MIS and were no longer regarded as outliers, two hospitals still had a rate <40% in the last study period. Visits to the hospitals by the YCR BCIP surgical lead in 2021 to investigate barriers to performing MIS, found that one cited low numbers of adequately trained surgeons while the other explained that there were major issues with laparoscopic equipment that required addressing at the Trust level. While open surgery is associated with lower surgical costs and operating time, laparoscopic surgery is more cost-effective for colorectal surgery when postoperative complications and length of hospital stay are taken into consideration[120]. Therefore, addressing problems with laparoscopic equipment would be justifiable and, as more recent data become available to YCR BCIP, further monitoring is required to determine whether this had been successfully achieved. This may be harder to achieve than in Denmark due to relative levels of government spending on healthcare, as Denmark spends more on health *per capita* ($5,429 vs $4,539 in 2021)[121].

The uptake of robotic surgery in rectal cancer appears to be following a similar trend to that of laparoscopic surgery, with quicker uptake in Denmark than in Yorkshire. As a relatively new surgical approach, the evidence base for any improved outcomes with robotic surgery is inevitably limited. The ROLARR trial (published in 2017) compared robotic surgery to conventional laparoscopic surgery in low anterior and abdominoperineal resections. There was no significant difference between the two groups in conversion to open surgery (the primary outcome) or in CRM positivity, complications, functional outcomes or 30-day mortality and there was no evidence of cost-effectiveness for robotic surgery. More recently, in 2023 the results of the COLRAR trial in Korea were published, comparing TME quality between robotic and laparoscopic approaches[122]. There was no difference in the rates of complete TME between the two groups, however the trial was stopped early due to the high cost burden to the patient since robotic surgery consumables were non-reimbursable through health insurance.

Current guidelines in both England and Denmark now consider robotic surgery as an option for patients with rectal cancer but highlight the limited evidence base. NICE 2020 guidelines state it should only be considered within established programmes that have audited outcomes, because it has not yet been found to be cost-effective. However, if an investment in a robot has been made then the outcome data should be collected to further inform effectiveness, safety and cost. Danish guidelines state that robotic surgery for rectal cancer is equivalent to similar laparoscopic procedures for short-term outcomes (Graded “B”). Similar to NICE guidelines, they also recommend internal auditing of the procedures and await the results of further studies to inform future guidance. Despite this, uptake in both Denmark and Yorkshire appears to be increasing. The 2022 NBOCA organizational survey reported that 5 of Yorkshire’s hospitals provide on-site routine use of robotic surgery. These 5 are the larger of the region’s hospitals and correspond to those highlighted in Chapter 4, Supplementary Figure 4.1. One of the region’s hospitals performed approximately 40% of all MIS using robotic surgery, considerably more than any of the other 4 that were using robotic surgery and closer to the rates achieved in Denmark. Further investigation will be needed to assess the level of robotic training attained and robotic operating capacity at each of the regional hospitals.

The results from Chapter 4 provide additional evidence that points to a difference in the management of elderly patients. When modelling the use of MIS, lower use in Yorkshire was associated with older age, particularly in those aged ≥80 years compared to those aged 60-69 years (RR<1). This was not the case in Denmark, in fact slightly higher use was associated with those aged ≥80 years (RR>1). This did not translate to any evidence of association with rates of conversion to open surgery for those age ≥80 years compared to 60-69 years in either population.

Previous studies suggested that elderly patients should not be denied laparoscopic surgery based on age alone. An audit of elderly patients undergoing laparoscopic surgery at 3 LAPCO training centres concluded that octogenarians had an acceptable mortality and morbidity but lacked any formal statistical analysis in support of these conclusions[123]. A larger analysis of audit data in Australia and New Zealand used propensity-score matching to investigate the safety and efficacy of MIS in elderly patients with rectal cancer[124]. Those aged ≥75 years had lower rates of MIS compared to younger patients, but within that older group patients undergoing MIS had fewer wound complications and a shorter length of hospital stay than those undergoing open surgery. Similarly, a Canadian study found lower uptake of MIS in elderly patients with early stage colorectal cancer, while older patients benefitted the most from MIS in terms of the survival difference when compared to open surgery[125]. Given that nearly 40% of all patients with colorectal cancer in Yorkshire are aged at least 75 years, increasing the rate of MIS in these older patients may help to improve outcomes in the region.

5.5. Additional considerations in surgical management

There are several other interventions that should be considered in the wider context when comparing the surgical management and improvement in outcomes of the Danish and Yorkshire populations. While many of these are beyond the scope of this study, some of those that may impact the results presented here, are considered below.

The first and second Danish National Cancer Plans were implemented in 2000 and 2005 in an attempt to bring treatment of cancer on a par with the highest international standards[126]. This resulted in the establishment of MDTs and the development of the Danish Cancer Patient Pathways, which has reduced waiting times and contributed to an improvement in survival. Centralisation of surgical management in the 2000s may partly explain the improvement in outcomes in Denmark[38]. In 2001 the number of Danish hospitals treating colon and rectal cancer was 50, falling to 34 and 32 respectively by 2005. Following further centralization in 2007, this number reduced to 20 and 17[44] respectively. In this study, by the 2010s, it appeared to have reduced even further to 17 and 14 respectively. This is similar to the current number treating colorectal cancer in Yorkshire (14 for both colon and rectal cancer). However, Danish incidence rates and resection rates are currently higher than in Yorkshire, resulting in a higher surgical caseload in Danish hospitals. For example, the smallest hospitals in Yorkshire perform approximately 20 rectal major resections a year, most do 25-50 per year and the largest 50-75 per year. In Denmark, the smallest perform approximately 40 per year, most 70-100 per year and the largest 100-190 per year. Therefore, most hospitals in Denmark are performing at least twice the number of major rectal resections than their equivalent Yorkshire hospitals. This could impact the outcomes investigated in this study, as higher hospital and surgeon caseload has been associated with better short-term and long-term outcomes[127-129]. While it is clear from this study that Denmark does indeed have a higher hospital caseload, no information could be obtained on the number of surgeons that were operating at each hospital and consequently whether individual surgeon caseloads were different between the two populations.

Enhanced recovery after surgery (ERAS) was developed from the multimodal approach to recovery that was first proposed in Denmark for surgery in patients with colonic cancer. It is a multidisciplinary approach which takes into consideration several aspects of care for patients undergoing major surgery[130,131]. A meta-analysis of randomized controlled trials reported a significant reduction in postoperative complication rates and hospital length of stay with use of ERAS in patients undergoing colorectal surgery[132]. The use of ERAS protocols is seen as the gold-standard of perioperative care in Denmark and has been widely adopted[25,133]. Since there was limited knowledge of perioperative care practice in Yorkshire, a sprint audit was conducted through YCR BCIP to understand the present status. The audit saw full participation by the regional Trusts, with items covering the pre-, intra-, and post-operative phases of the surgical pathway for 216 patients undergoing a first elective procedure for colorectal cancer. As part of the audit, Trusts recorded whether an ERAS nurse was involved in each patient’s care. In approximately two thirds of cases (63%), an ERAS nurse was not involved in care, the majority of those because there was no ERAS nurse employed in the department. While this is not comprehensive evidence of low use of ERAS protocols, there was wide variation between Trusts. Results showed that 100% of patients had an ERAS nurse involved with care at two Trusts, compared to no patients at 8 of the Trusts. Other items of the audit displayed similar variation, and this suggests the region may benefit from harmonisation of protocols around aspects of perioperative care such as ERAS, opioid-sparing techniques and bowel preparation.

Screening influences the number of patients presenting as an emergency admission and those presenting as an emergency generally have more advanced disease, are less likely to be treated with curative intent, and have poorer survival[134]. Therefore, differences in the national screening programmes of Denmark and England may contribute to the disparities in the colorectal cancer populations and outcomes compared in this study. The main difference between the screening programmes was the timing of their introduction. The English programme was rolled-out between 2006 and 2010, while the Danish programme was introduced in 2014. These times correlate approximately with the start and end points of the data used in this study. This may explain some of the increases in survival experienced in Denmark for the 2013-2016 period observed in Chapter 2. The age of participants invited to screening also differed at the time of the study: 50-74 years in the Danish programme and 60-74 years in the English programme. However, the increases in survival in Denmark in Chapter 2 were observed across all age groups including those aged <60 and ≥80 years. Participation rates in Yorkshire (and the North East of England) were reported to be 53% in 2010-15 compared to 64% in Denmark in 2014-2017 and in both populations the participation was higher in areas with a higher socioeconomic status[135,136]. A higher participation rate in Denmark may have helped reduced the number of emergency admissions (and therefore emergency resections), however the reduction was observed irrespective of whether screened patients were included or not, as described in Chapter 3.

5.6. Implications of the study

The continued improvement in Danish survival rates from colorectal cancer over that in England has been well established, but the root causes have proved difficult to identify. This study has focused on one major aspect of care for patients with unique access to comparative data from a quality improvement programme. Several differences between surgical management of patients have been identified that may have contributed to the differences in outcomes.

Colorectal cancer patients have a median age of approximately 70 years, meaning treating increasingly elderly patients is a common occurrence in surgical departments. This study has highlighted the need to consider improved assessment of elderly patients being considered for surgery. The DCCG has long employed QPIs for hospitals and regions and recently they have split their postoperative mortality indicators by age, resulting in separate indicators for patients aged <75 and ≥75 years. In Yorkshire, while not yet introducing formal QPIs, the YCR BCIP performed similar analyses to identify regional outliers on a range of management metrics. Following the results of this study, the resection rates in patients aged ≥80 years has been introduced as a new metric and the results have informed a newly developed multidisciplinary working group of surgeons, oncologists and anaesthetists investigating the role of frailty in the treatment of colorectal cancer. Early initiatives will involve a full audit of surgery in patients aged ≥80 years and investigation of the frailty measures used in pre-assessment clinics across the region.

The study has highlighted the need not only to identify variation in treatment management, but also to identify the reasons behind this. While it is clear that the uptake of MIS in Denmark was much quicker than in Yorkshire, there was large variation within the country. Now that the trusts with low rates of MIS surgery have been identified, these results should highlight the need to address the reasons behind it, such as adequately trained surgeons and access to the correct laparoscopic equipment. The anticipated introduction of formal QPIs, not only in the YCR BCIP metrics reports, but also in the NBOCA dataset has the potential to further reduce variation both regionally and nationally.

5.7. Strengths and limitations

This study has provided a comprehensive comparison of aspects of surgical management of colorectal cancer between two groups with a similar population size (5.7 million). A key strength of this study is the large sample size and the access to data covering an extended period to assess trends over time. The DCCG database and NCRAS data both have high ascertainment rates for colorectal cancer and are well-established high-quality data sources. In addition to the strengths, there are a number of limitations to this study that need to be considered.

The DCCG database has largely evolved as a clinical database that uses a surgical proforma to capture patient, tumour and treatment characteristics, supplemented with data from the National Pathology Registry and Danish Civil Registration System. This is different from the cancer registry data (NCRAS) used to analyse the Yorkshire data. The main difference is that the surgical procedures in Yorkshire were derived retrospectively by linking HES data to the NCRAS data. This should not impact broad treatment categories such as whether the patients received a major resection or not and the approach to that resection, as these aspects are well captured in HES. It is however difficult to assess treatment intent, such as whether a stent was intended as a bridge to surgery. Additionally, urgency of surgery is not clearly defined in the DCCG proforma and the derivation for Yorkshire was based on the nature of the admission and when the resection took place. To mitigate for this, a sensitivity analysis was performed in Chapter 3 by varying the time between admission and surgery for the Yorkshire data. The results were broadly the same in terms of the trends and RRs.

Comparability of data is also an issue when defining tumour characteristics such as stage of disease and site of tumour. While the DCCG and CORECT-R methodologies were generally similar in defining overall stage of disease to categories into stage 1, 2, 3, 4 or unknown, complete staging improved for Yorkshire over time while more patients were staged as unknown for Denmark towards the end of the study period. This was due to revised TNM guidelines where patients were not given a stage due to the possibility of downstaging through neoadjuvant therapy. Similarly, the exact proportions of colon and rectal tumours may not be directly comparable since the DCCG do not use the ICD C19 coding to register rectosigmoid tumours, simply defining rectal cancer as tumours within 15cm of the anal verge. This study classed C19 tumours as colon cancer, but it is not clear whether to treat rectosigmoid tumours as colonic or rectal cancer[137].

Analyses were limited to include only a few covariates due to limited directly comparable data on other potential risk factors known to be associated with outcomes, such as comorbidities, socioeconomic status and physical status. The Charlson Comorbidity Index score is commonly used in population-based data and a version was available in both datasets, however the score was calculated using admissions data over a longer time period in Denmark (10 years) than that in Yorkshire (1 year). The availability of a common index describing socioeconomic status, such as the European Deprivation Index[138] would have allowed a comparison between Danish and Yorkshire patients to be made, albeit it at a geographical area level rather than patient level basis. These additional covariates may be important, as models predicting outcomes do not always translate between different populations, for example, a model predicting postoperative mortality after colorectal cancer surgery in the UK was found not be highly accurate for prediction in Denmark[139].

A further limitation to this study was that it could not be extended to include comparisons on additional outcomes. A key outcome cited in the use of surgical resection is postoperative complications. A study in Denmark, predating the data used in this study, found that postoperative complications such as heart failure and sepsis were the major causes of death after colonic cancer surgery. Since 2014, the DCCG record postoperative complications using Clavien-Dindo scale; previously it was noted whether a reoperation was needed. This includes 7 specific surgical complications and 11 specific medical complications. A similar measure for Yorkshire would be extremely valuable for comparing postoperative outcomes with Denmark. The closest measure available for use is a derived variable indicating an unplanned return to theatre after the initial operation[140]. Given that it would be unsuitable to compare this with the recorded Danish complications, an attempt was made to categorize returns to theatre data as part of the surgical complication categories to compare reoperation rates.

Unfortunately, this did not prove possible due to the lack of detail and information on surgical intent within the HES data.

5.8. Future research recommendations

This thesis has focused on three areas of surgical treatment for comparison between the two populations: overall use of resection, emergency resection and approach to resections. However, the surgical treatment of colorectal cancer can be complex and covers many aspects. For example, local excision for early rectal cancers is an established but challenging treatment. Local excision is becoming increasingly common as it avoids the invasiveness of radical surgery and the associated morbidity as well as preserving normal bowel function without use of a stoma[141]. Although CORECT-R methodology currently identifies patients in NCRAS undergoing a 'minor resection', the coding used to do this has yet to be verified. Consequently, through collaboration with surgical colleagues in the region, YCR BCIP has now developed an early rectal cancer database to record the characteristics, procedures and resultant outcomes of patients undergoing treatment by local excision. Collection is ongoing and it is planned to use the database to verify local excision coding with the NCRAS data and assess national variation. Furthermore, as T-stage is one of the items being collected, direct comparison of the regional database will enable a local excision comparison with Denmark for those with early rectal cancer.

While this study has investigated the overall use of major resection, the type of resection performed in rectal cancer treatment is of interest. The use of APE as a surgical treatment for rectal cancer necessitates a permanent stoma. Though APE may sometimes be the only option for some low rectal cancer tumours, rates of its usage has been reported to vary widely in England[142]. Recent surgical metric reports produced through YCR BCIP has found continuing wide variation of APE rates in the region that is unlikely to be explained entirely by tumour height, with some MDTs observing an APE rate of close to 50%. The rate of APE in Denmark has not been reported to date. A direct comparison using equivalent data on the measurement of tumour height would be of interest as it would show whether the higher rates of resections in Denmark translate into lower or higher rates of APEs.

An extension of comparisons beyond that of surgical treatments is also recommended. A process to identify adjuvant chemotherapy treatment and regimen type in Yorkshire and England was developed using linkage of the SACT dataset to NCRAS data[71]. After discussion about the observed variation in this treatment, regional oncologists developed an adjuvant treatment algorithm to try to reduce this variation. The DCCG has previously developed a similar algorithm using the Danish NPR, however, regular processing of these data ceased in 2014. This coincides with the first introduction of the SACT dataset, resulting in a lack of overlap between the two data sources. Reapplication of the Danish algorithm to recent data would allow a comparative analysis of the use of adjuvant chemotherapy treatment, the types of regimens used and the interval between resection and regimen administration.

Comparison of additional outcomes is also recommended in future studies. The papers from this study used postoperative mortality and survival as patient outcomes. Other important outcomes that should be explored include postoperative complications, length of hospital stay, recurrence and quality of life.

A recent study using the DCCG database showed a considerable decrease in the rates of recurrence for both colonic and rectal cancer across three time periods (2004-08, 2009-13 and 2014-19)[143]. The crucial factor in the ability to explore recurrence rates in the DCCG data was the development of a recurrence algorithm. The published algorithm identifies recurrence from 4 sources: a metastatic code registered in the NPR or DCR, cytostatic codes within a given time period, a combination of topography and morphology codes registered 6-months after surgery, and a specific recurrence code which has only been used since 2012[144]. The algorithm has been validated in several cohorts, giving a high sensitivity and specificity. Validating a modified version or similar algorithm should be seen as a high priority for future population-based studies in colorectal cancer, as this would give the ability to compare English (and subsequently Yorkshire) recurrence rates with Denmark and others.

Given the differences in surgical management highlighted in this study, an important factor to consider next is the quality of life of surgically treated patients. For example, studies have shown that living with a stoma may impact negatively on quality of life scores. Prospective studies such as the one established by YCR BCIP and currently in its recruitment phase, might allow comparison with Denmark on a limited number of quality of life scores. Initial investigations with a similar prospective study underway in Denmark have identified possible comparison using the EQ-5D-5L (comprising of 5 health states: mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and the Low Anterior Resection Syndrome (LARS) score for bowel dysfunction in rectal cancer.

5.9. Conclusions

Outcomes from colorectal cancer such as survival and postoperative mortality can be impacted by multiple factors. Despite this, those responsible for the care of patients can influence and implement initiatives to improve outcomes. This study has used a data-driven approach to identify several differences in the surgical management of patients with colorectal cancer between the region of Yorkshire in England and the country of Denmark, including surgical treatment rates in the elderly population, the amount of emergency surgery being performed and the use of MIS.

Particular attention should be focused on the management of elderly patients, as higher rates of resection in Denmark coincided with a high postoperative mortality, but better overall survival. Therefore, teams managing elderly patients should balance the short-term risk versus long-term benefit, and effectively communicate those to the patient. A regional consensus should be agreed on the treatment pathway of elderly patients that considers effective assessments of frailty, improved selection of surgically appropriate patients and optimal postoperative care.

Clearer guidelines and a sufficient provision of training has contributed to a reduction in emergency surgery and a quicker uptake of MIS in Denmark than Yorkshire. Consensus guidelines for converting potential emergency resections into elective resections may help lower rates of emergency surgery and ensuring adequate training and access to laparoscopic equipment should increase use of MIS in Yorkshire.

Continued monitoring of treatment within Yorkshire and Denmark should be continued through the use of QPIs. However, these should be dynamic as treatment options develop and the evidence base expands in modalities such as STBS and robot-assisted surgery.

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