Using National Routine Data to Explore the Utilisation and Outcomes of Multimodal Treatment in the Management of Colorectal Cancer

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DECLARATION

I, Jemma Megan Boyle, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated appropriately within the thesis.

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ABSTRACT

Background

The multimodal treatment of colorectal cancer (CRC) is becoming progressively more complex with multidisciplinary input required to make appropriate decisions about patient suitability for neo-adjuvant and adjuvant therapies, local excision, watch-and-wait strategies, and choice of surgical procedure, whilst simultaneously taking into account an increasingly old and comorbid population. In addition, there are rapidly evolving advancements, for example, the approval and use of novel systemic anti-cancer therapy (SACT) treatments and surgical innovations such as the increasing uptake of robotic surgery.

Large national routinely collected datasets such as the National Bowel Cancer Audit (NBOCA) and SACT dataset are becoming increasingly important for facilitating a better understanding of these complex multimodal care pathways. They allow the identification of unwarranted variation and can help to better understand disparities in care and outcomes. The continuous collection of this data facilitates ongoing public reporting and benchmarking processes via performance indicators and can be used to stimulate national quality improvement processes.

The work within this thesis aims to utilise national routinely collected data with the broad intention of translating findings into clinical practice in two important areas within the multimodal management of CRC: (i) the use and outcomes of SACT, and (ii) the volume-outcome relationship for rectal cancer surgery. It is presented in the format of six observational studies, including two methodological development studies and four clinical research studies.

Methods

In this research, detailed CRC patient care pathways are constructed using NBOCA data linked to Hospital Episode Statistics Admitted Patient Care (HES-APC) (hospital administrative data), Office for National Statistics mortality data, the SACT dataset (chemotherapy data), the National Radiotherapy Dataset (radiotherapy data), and General Medical Council (GMC) surgeon-level data. The unique linkage of these datasets provides a wealth of information, but also requires careful interpretation and validation.

This thesis involves two essential components of underpinning methodological work. First, the validation of critical information is undertaken to ensure that the routinely collected data is robust. This includes the validation of routinely collected chemotherapy information using SACT and HES-APC data, and the validation of surgeon-level information for the rectal cancer volume-outcome work using NBOCA, HES-APC, and GMC data.

Second, performance indicators are identified and developed to help evaluate the quality of the national delivery of CRC care. For the SACT work, these performance indicators are derived through the development and validation of a series of coding frameworks and clinical algorithms using SACT and HES-APC data. The first enables the identification of adjuvant chemotherapy use (process measure), and the second identifies severe acute toxicity from SACT (outcome measure). For the rectal cancer volume-outcome work, hospital-level rectal cancer surgery volume is established as a performance indicator (process measure). In addition, a panel of relevant performance indicators (outcome measures) are selected and adapted to evaluate the volume-outcome relationship.

This methodological work is then used to address pertinent clinical research gaps in the use and outcomes of multimodal treatment for CRC patients. For the SACT work, this involves three areas: (i) the exploration of determinants of variation in the use of adjuvant chemotherapy for stage III colon cancer, (ii) the impact of completion of oxaliplatin-based adjuvant chemotherapy and treatment modifications on survival for stage III colon cancer, and (iii) the evaluation of the severe acute toxicity coding framework as a performance indicator for examining between-hospital variation in toxicity rates. The volume-outcome relationship for rectal cancer surgery is explored at hospital- and surgeon-level with volume modelled as a continuous variable in relation to the selected panel of performance indicators.

Results

The methodological work demonstrates that chemotherapy information is accurately captured in national routinely collected data, including receipt, regimen, and cycle number. The findings indicate that both SACT and HES-APC should be used in conjunction, where possible, to give the most robust information.

A broad and comprehensive coding framework using diagnostic codes in HES-APC is used to identify severe acute toxicity (requiring overnight hospitalisation), mapped across organ systems. The coding framework demonstrates validity by identifying differential rates of toxicity according to clinical group (no chemotherapy, adjuvant cohort, and metastatic cohort), and regimen (toxicity profiles in keeping with those expected from clinical trials). In addition, severe acute toxicity is associated with expected patient and clinical factors.

For the SACT work, the first clinical research study demonstrates unwarranted variation in the use of adjuvant chemotherapy in stage III colon cancer, particularly in elderly patients (>70 years). The second clinical research study shows that, for patients having oxaliplatin-based adjuvant chemotherapy, those who complete all of their treatment have significantly better survival outcomes compared to those who complete less than 50% of their treatment. However, only half of patients actually complete their treatment. Amongst patients that complete all of their chemotherapy, there are no survival differences if they have treatment modifications. The third clinical research study shows unwarranted variation in the rates of severe acute toxicity between individual hospitals for both adjuvant and metastatic CRC patients.

For the rectal cancer volume-outcome work, the clinical research study demonstrates that 45% of surgeons are not meeting minimum annual rectal cancer surgery volumes as per national recommendations. Adjusting for patient and tumour characteristics, length of stay is significantly lower for high volume surgeons. No other volume-outcome relationships are demonstrated at hospital- or surgeon-level.

Conclusions

This research demonstrates that multiple national routinely collected datasets can be effectively combined and subjected to novel analysis with clinically important findings. It shows that the SACT dataset provides a unique, rich, and accurate source of data, with a huge scope for addressing clinical research gaps. In addition, it demonstrates that chemotherapy information can be derived from hospital administrative data to supplement this data, or else provide chemotherapy information when bespoke SACT datasets do not exist. This work provides a rationale and basis to adapt the novel methodology across different tumour types.

This work also demonstrates the translation of findings from routinely collected data into clinical practice through the development of performance indicators which facilitate the ongoing reporting and monitoring of important aspects of the multimodal treatment of CRC patients. These will be used to identify and better understand unwarranted variation as already demonstrated in this work with rates of adjuvant chemotherapy use, severe acute toxicity, and rectal cancer surgery volumes. In addition, they will trigger ongoing targeted quality improvement initiatives in order to improve the quality of CRC care on a national scale.

With progressively more complex multidisciplinary decisions and management in CRC care, and an increasingly old and comorbid population, routinely collected data is paramount for the exploration of use and outcomes in "real-world" clinical practice, and to complement trial findings. Finally, it is essential for the continued development of performance indicators for timely and ongoing monitoring across the whole CRC pathway and to inform policy-makers and commissioners with regards to areas such as the specialisation of CRC services.

LIST OF ABBREVIATIONS

5-FU	5-fluoropyrimidine
APR	Abdominoperineal resection
ASA	American Society of Anesthesiologists
CAP	Clinical Audit Platform
CAPOX	Capecitabine and oxaliplatin
CARMS	Clinical Audit & Registries Management Service
cCR	Complete clinical response
CGA	Comprehensive geriatric assessment
CRC	Colorectal cancer
CRG	Clinical reference group
CRM	Circumferential resection margin
CTCAE	Common Terminology Criteria for Adverse Events
DARS	Data Access and Request Service
DPD	Dihydropyrimidine dehydrogenase
ESMO	European Society of Medical Oncology
FOLFOX	5-fluorouracil and oxaliplatin
FOLFIRI	5-fluorouracil and irinotecan
GMC	General Medical Council
HES-APC	Hospital Episode Statistics Admitted Patient Care
HQIP	Healthcare Quality Improvement Partnership
ICC	Intra-class correlation coefficient
ICD-10	International Classification of Diseases, 10th revision
IMDQ	Index of Multiple Deprivation Quintile
LCCRT	Long-course chemoradiotherapy
MDT	Multidisciplinary team
MMR	Mismatch repair

MSI	Microsatellite instability
MSS	Microsatellite stability
NBOCA	National Bowel Cancer Audit
NCEPOD	National Confidential Enquiry into Patient Outcome and Death
NCRAS	National Cancer Registration and Analysis Service
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
ONS	Office for National Statistics
OPCS-4	Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures
OR	Odds ratio
PROMs	Patient-reported Outcome Measures
RCS	Royal College of Surgeons
RCT	Randomised controlled trial
RTDS	National Radiotherapy Dataset
SACT	Systemic anti-cancer therapy
SCRT	Short-course radiotherapy
SEER	Surveillance, Epidemiology, and End Results
sHR	Subdistribution hazard ratio
SIOG	International Society of Geriatric Oncology
TAMIS	Transanal minimally invasive surgery
TEMS	Transanal endoscopic microsurgery
TME	Total mesorectal excision
TNM	Tumour, Nodes, Metastasis
UK	United Kingdom
UKCB	United Kingdom Chemotherapy Board

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1. INTRODUCTION

1.1 Overview

The work presented within this thesis aims to utilise national routinely collected data with the broad intention of translating findings into clinical practice in two important areas within the multimodal management of colorectal cancer (CRC): (i) the use and outcomes of Systemic Anti-Cancer Therapy (SACT), and ii) the volume-outcome relationship for rectal cancer surgery. Both strands of the thesis involve two essential elements of underpinning methodological work: i) ensuring the information captured in routinely collected data is robust through validation of critical information, and (ii) identifying and developing appropriate performance indicators to help evaluate the quality of care being delivered.

This work can facilitate the identification of "unwarranted variation" and help to better understand disparities in care and outcomes. Unwarranted variation is variation in the use of healthcare services which cannot be explained by variation in patient illness or patient preference, and can involve under- or over-treatment. Possible reasons for unwarranted variation include clinician preferences and attitudes, differential access to healthcare resources, and discrepancies in the treatment of particular groups (e.g., elderly or socioeconomically deprived patients).[1]

This thesis presents research using routinely collected data in the format of six observational studies, including two methodological development studies and four clinical research studies. The remainder of this introduction provides an overview of what routinely collected data are, descriptions of the routinely collected datasets used within this thesis, and why the application of routinely collected data in studies such as those presented here, are important. It then provides a brief overview of the epidemiology, staging, and multimodal management of CRC, with an increased focus on the topics of interest for the six studies. The methodological and clinical research gaps that have been identified will be highlighted explicitly within each section.

1.2 Routinely collected data

1.2.1 Overview

Routinely collected healthcare data are defined as "data collected without specific a priori research questions developed prior to utilisation for research".[2] Large national routinely collected datasets are becoming increasingly important for facilitating a better understanding of complex multimodal care pathways, such as those within CRC care.

Relating to the provision of CRC care within the English NHS, there are many examples of large national routinely collected healthcare datasets which are used throughout this thesis. These will be described briefly now, with additional detail in Chapter 3.

1.2.2 The National Bowel Cancer Audit (NBOCA)

The purpose of the National Bowel Cancer Audit (NBOCA) is to measure and compare the quality of care and outcomes for CRC patients in the NHS in England and Wales.[3] The NBOCA has been collecting data in a primitive form since 2005, and publishing national annual reports since 2010. More recently, each annual report has included mandatory prospective data collection for approximately 30,000 patients newly diagnosed with CRC, including all English NHS hospitals and Welsh MDTs providing CRC care.

Data collection usually occurs at the time of diagnosis and following primary treatment within local MDT meetings. Data submission occurs via the Clinical Audit Platform (CAP) system. Data collected includes patient and tumour characteristics, as well as pathological, surgical, and other treatment details including pre- and post-operative treatments such as SACT (Appendix 1). However, no further details on SACT are captured.

1.2.3 Systemic Anti-Cancer Therapy (SACT) dataset

The primary purpose of the SACT dataset is to collect information on the use of SACT (including oral and biologic agents) across England and, with linkage to other national datasets (e.g., NBOCA), facilitate better understanding of the whole patient cancer pathway. The aim of the SACT data is threefold: to provide a national picture of the pattern of SACT use, support the improvement of care processes and outcomes, and inform commissioning and service provision.[4]

The SACT dataset provides more detailed chemotherapy information than is available from other data sources, for example, insurance claims or cancer registries.[5 6] It includes information such as treating hospital, treatment dates, individual chemotherapy drugs, dosing information, drug administration route, and intent of treatment (Appendix 2).

Most of the studies included within this thesis involve the use of the SACT dataset. Before the work presented in this thesis, there had been limited published data from the SACT dataset, and no published data for CRC patients.[7-9] This provides an opportunity for novel methodological work including the exploration, cleaning, validation, analysis, and interpretation of SACT data. In addition, the only study to attempt to validate the SACT dataset was undertaken in lung cancer patients. It used SACT data from 2012 to 2016 when the dataset was in its infancy, and only examined cycle number.[8]

1.2.4 Hospital Episode Statistics Admitted Patient Care (HES-APC)

The HES-APC dataset is an administrative hospital database which provides detailed information about all inpatient hospital attendances for each patient in the English NHS, including day case and overnight admissions. Records include 'episodes' of care which relate to treatment in hospital under one consultant, with some patients having multiple episodes within one admission which constitute a 'spell'. HES-APC data therefore consists of multiple rows per patient with one row per episode.[10] Unique patient identifiers within HES-APC enable patient records to be linked to other datasets.

Diagnoses are coded according to International Classification of Diseases, 10th revision (ICD-10) codes with up to 20 diagnostic fields available for each episode of care.[11] Procedures and operations are coded according to Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS-4) codes with up to 24 procedural fields available.[12] Although bespoke chemotherapy information is not contained with HES-APC, there is the potential for identifying chemotherapy use through these ICD-10 and OPCS-4 codes.[13]

1.2.5 National Radiotherapy Dataset (RTDS)

The National Radiotherapy Dataset (RTDS) has been collecting data from all English NHS providers of radiotherapy treatment since April 2009.[14] Data collected includes the anatomical treatment site, treatment intent, first appointment date, number of attendances, prescribed and actual doses, and detailed information about which type of radiotherapy was used (e.g. photon versus electron beam). Dose information is captured from the radiotherapy machines.

1.2.6 Office for National Statistics (ONS)

The Office for National Statistics (ONS) is the recognised national statistical institute and the largest independent producer of national statistics in the United Kingdom (UK). ONS mortality data includes date, place, and cause of death.[15]

1.2.7 General Medical Council (GMC)

The General Medical Council (GMC) is a public body which maintains the official register of all doctors within the UK. GMC records are publically available on the GMC website for all doctors who have practiced within the

UK. For each doctor, the GMC holds information for gender, speciality, date of entry on the specialist register, revalidation status, registration status, and designated body.

1.2.8 Advantages of routinely collected data

Although randomised controlled trials (RCTs) are the gold standard for measuring the efficacy and relevant outcomes of a specific intervention, there are particular advantages to using routinely collected data which can complement RCT findings (Table 1.1).

1.2.9 Limitations of routinely collected data

A major limitation of routinely collected data is the potential for variability in both data completeness and data quality which needs to be taken into consideration to avoid misclassification and minimise bias. For example, as mentioned previously, the HES-APC database uses standardised coding in the form of the ICD-10 and OPCS-4 codes.[16] The introduction of "Payment by Results", a financial incentive for hospitals to input codes correctly, coincided with a marked improvement in coding accuracy and the database is deemed a reputable source for clinical research. [17]

However, despite clear guidelines for inputting diagnostic and procedural codes, variability in coding practices may be problematic in certain studies. This variability, as well as the fact that routinely collected data is not directly captured for research purposes, highlights the requirement for careful evaluation and validation of the accuracy of such data. This is especially important if it has not been validated previously, as is the case with the SACT dataset.

Routinely collected data needs to be methodically cleaned and organised in a way that enables consistent interpretation of the information contained (e.g., through the use of structured coding frameworks and clinical algorithms), and facilitates translation of this information into clinical practice. For example, this might include identifying any coding discrepancies between different hospitals, identifying changes in coding over time, or checking the validity of data items within the same dataset (e.g., agreement between tumour location and operation performed). The availability of multiple linked datasets expands the possibilities for this process, enabling validation by checking the agreement of key data items between different data sources.[18] [19]

Previous studies have developed and validated coding frameworks using diagnostic and procedural codes within HES-APC to allow the identification of genitourinary and gastrointestinal toxicity following radiotherapy, and skeletal-related events in patients with prostate cancer.[20 21] Similar coding frameworks could be used to determine chemotherapy details within HES-APC. However, systematic validation standards for assessing the accuracy of coding frameworks used for the identification of patients, conditions, treatments, or outcomes, do not currently exist.[22]

Table 1.1 – Advantages of using routinely collected data

Advantages
Ongoing collection of data
• More cost-efficient and less labour-intensive compared to alternative methods of collecting data (e.g., medical note abstraction). • Data available over a long timeframe meaning that survival can be assessed over a decent period and historical assessments can be carried out (e.g., previous comorbidities). • Ability to link multiple different routinely collected datasets (usually at the patient level) and therefore providing a wealth of information as well as the opportunity to validate information between datasets.
Inclusive
• Elderly, comorbid, and frail patients can be included, as well as all socioeconomic and ethnic minority groups.[23] [24] • Results may be more generalisable to the national population compared to other sources (e.g., Medicare insurance claims data includes only patients aged 65 and above).[25]
Large sample size
• Allows rarer outcomes to be compared with sufficient statistical power. • Enables the reliable comparison of the quality of care between individual hospitals.
Scope to examine specific gaps in clinical research
• Allows an assessment of treatment effectiveness, toxicity, and longer term outcomes under routine clinical conditions rather than the rigorously controlled RCT setting.[26 27] • Certain comparisons cannot be made in an RCT setting due to practical or ethical reasons (e.g., hospital and surgeon rectal cancer surgery volumes). • Allows the examination of "natural" variation in treatment strategies which cannot be done in an RCT setting due to the allocation of treatment by study design (e.g., non-completion and modification of chemotherapy treatments). • Enables the identification and examination of "non-standard" treatment strategies that would not be found in an RCT setting (e.g., use of non-standard SACT drugs). • National coverage allows national evaluations of the quality of care.

1.2.4 Research gaps identified

Identification and validation of SACT usage and completion in routinely collected data

HES-APC does not contain bespoke chemotherapy information like the SACT dataset. However, the use of HES-APC diagnostic and procedural codes, alongside national chemotherapy coding guidelines, should allow the development of a novel structured coding framework to identify chemotherapy use within HES-APC, including regimen and number of cycles.

Chemotherapy information contained within both datasets needs to be captured in a way that facilitates the most accurate clinical interpretation of the data. In order to do this, clinical algorithms will be developed with the input of oncology experts to ensure that the findings from the routinely collected data are being translated appropriately.

For example, a clinical algorithm will be developed to ensure that the chemotherapy information captured relates as closely as possible to just adjuvant (post-operative) chemotherapy, rather than treatments for CRC that has progressed. This can be done by restricting the inclusion of chemotherapy by particular timeframes and regimens. This is important because, for example, if the patient were to switch to a different line of chemotherapy because their CRC had progressed and this wasn't identified, the number of cycles received in the adjuvant setting would be overestimated. The same clinical algorithm should be applied to both the SACT and HES-APC datasets to ensure consistency. Different clinical algorithms can be developed dependent on the chemotherapy treatment being analysed.

Once chemotherapy information has been established in HES-APC using the coding framework, and the same clinical algorithm applied to both HES-APC and SACT data, linkage of the HES-APC and SACT datasets will allow validation. Validation is imperative because, outside of the empirical studies presented within this thesis, SACT data has not been used in CRC patients before.

Validation can be carried out by assessing the agreement of critical chemotherapy information between the two data sources and ensuring the robustness of the classification of patients (i.e., patients correctly identified as receiving SACT treatment or not). To begin with, validation can be conducted in an exemplar population of CRC patients. Subsequently, the validation framework should be adaptable to any CRC patients receiving chemotherapy, as well as across different tumour types.

1.3 Overview of colorectal cancer

1.3.1 Epidemiology

There are over 42,000 new CRC cases diagnosed each year in the UK. It is the fourth most common cancer in the UK, accounting for 11% of all new cancer cases. In addition, it is the second most common cause of cancer-specific mortality with almost 17,000 deaths per year.[28]

CRC is more common in men.[29] CRC patients have a median age of 72 years with 59% of patients aged 70 years or older.[30] It is also more common in developed countries. Reasons for this are thought to be increased obesity, red meat consumption, alcohol intake, tobacco use, and sedentary lifestyle choices. An increasing incidence of CRC has been noted in developing countries that have adopted a more "westernised" lifestyle.[29]

Given its prevalence and the ageing population, CRC is exerting an increasing burden on healthcare resources. Despite an overall decreasing trend in CRC survival prior to COVID-19, the UK still lags behind much of Europe, particularly in the elderly. This makes the exploration of unwarranted variation in practice and outcomes extremely important for identifying areas for improvement.[31]

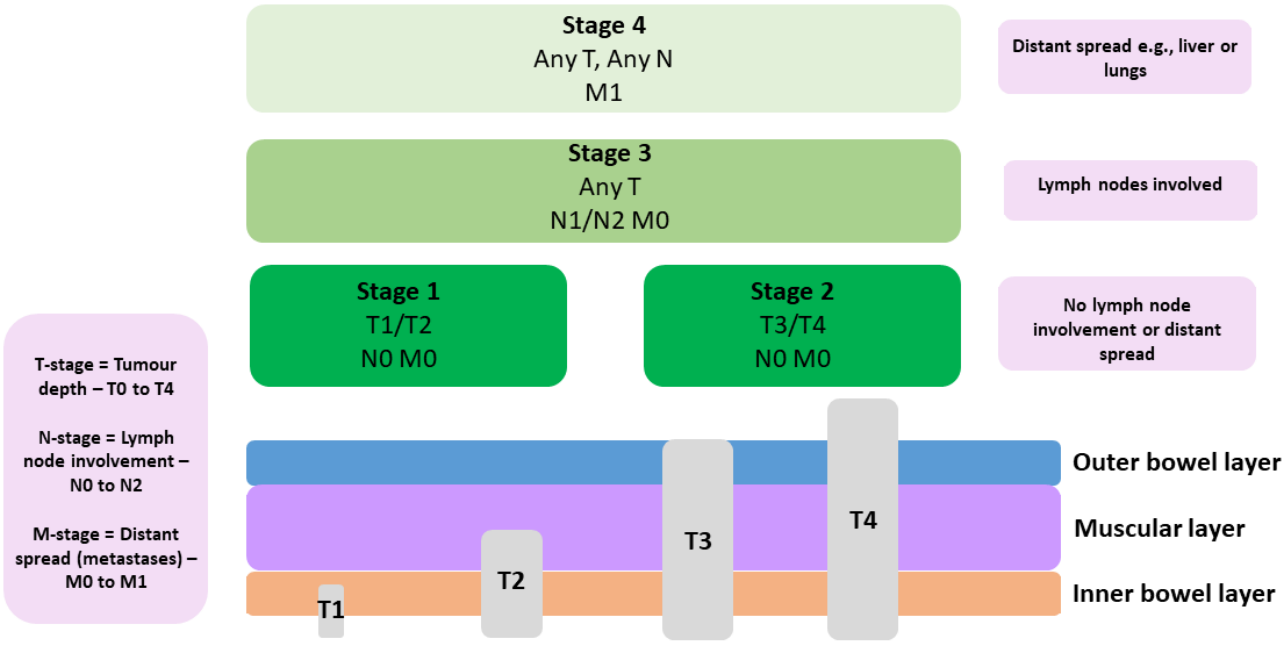
1.3.2 Staging

Following a diagnosis of CRC, the local and distant extent of the disease is established in order to plan treatment and establish prognosis. The most commonly accepted method of staging CRC is the tumour, node, metastasis (TNM) staging system.[32] This involves assessment of the depth of invasion of the primary tumour (T-stage), involvement of lymph nodes (N-stage), and any distant spread of the cancer (M-stage) (Figure 1.1).

The American Joint Committee on Cancer adapted the TNM staging system in order to generate four prognostic groups (Figure 1.1).[33] Stage I disease is CRC that has not spread beyond the bowel wall, compared to stage II disease where the tumour has invaded into or beyond the outer layer of the bowel wall. Stage III CRC involves spread to the lymph nodes. Stage IV CRC involves spread to other parts of the body, most frequently the liver and lungs.

Within England, proportion of patients presenting at diagnosis with stage I, II, III, and IV disease is approximately 17%, 23%, 27%, and 23% respectively, with the remainder unknown.[28] Survival is largely dependent on the stage of disease at diagnosis. The five-year relative survival for patients presenting with stage I, II, III, and IV disease is 83%, 64%, 38%, and 3% respectively.[34]

Figure 1.1 - Diagram showing relation of TNM staging to the American Joint Committee on Cancer staging



1.4 Multimodal treatment of non-metastatic disease

Colon and rectal cancers, and indeed right and left-sided disease, are increasingly recognised as distinct disease processes (Figure 1.2).[35] Approximately two-thirds of tumours are found within the colon and the remainder in the rectum. The definition of rectal cancer is a tumour with a distal margin at or below 15cm from the anal verge, measured by rigid sigmoidoscopy. Low rectal tumours are defined as those within 5-6cm of the anal verge.[36] [37]

For patients with curative disease (stage I to III), surgical excision is the mainstay of treatment. Approximately, two-thirds of these patients in England will undergo major resection.[38] Unlike colon cancer, rectal cancer confers a significant risk of local recurrence in addition to distant spread. For this reason, the multimodal treatment pathways for colon and rectal cancer differ and will be described separately in this section.

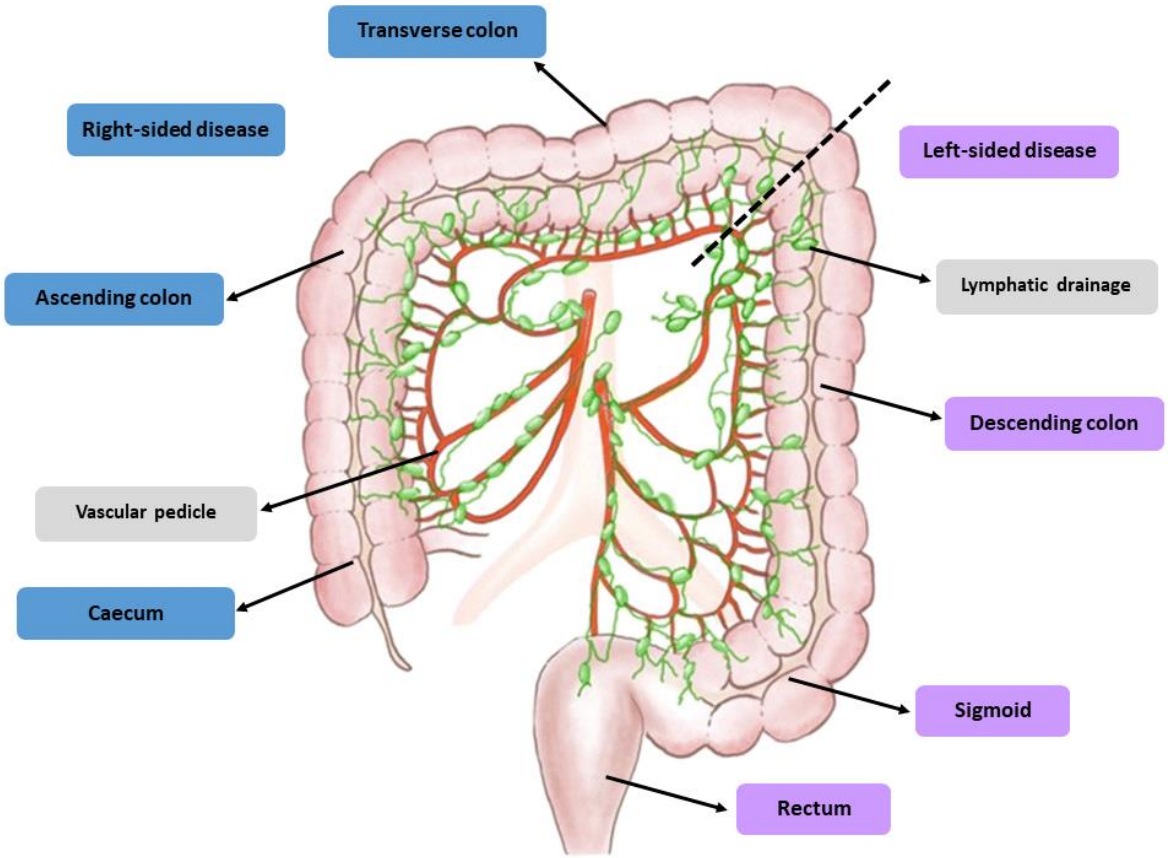
1.4.1 Overview of the management of non-metastatic colon cancer

The primary treatment modality for non-metastatic colon cancer is surgical excision (removal of the section of colon containing the tumour). Despite surgical resection, up to 55% of patients may go on to develop recurrent disease, mostly involving distant spread secondary to clinically occult micrometastatic disease at the time of surgery.[39 40] Adjuvant chemotherapy is therefore standard practice in stage III colon cancer for all patients fit enough to tolerate it.[41] It reduces the risk of recurrence and subsequently death by an absolute 10-15% with fluoropyrimidines alone, and an extra 4-5% with oxaliplatin-containing combination therapy (Chapter 1.4.2).[40]

The use of adjuvant chemotherapy for stage II colon cancer infers smaller survival advantages (absolute 3-5% reduced risk of death).[42] Patients should be selected carefully according to high-risk factors: T4 disease, emergency presentation, extramural lymphovascular or perineural invasion, inadequate lymph node sampling, high grade, mucinous, or poorly differentiated histology, or high pre-operative carcinoembryonic antigen levels.[36 40] The benefits and disadvantages of treatments should be discussed to inform shared decision-making.

Mismatch repair (MMR) deficient or microsatellite instability (MSI) (Chapter 1.5.3) high tumours have been identified as having an improved prognosis in stage II and III colon cancer with associated uncertainties for the benefits of adjuvant chemotherapy.[43] [40] Patients with locally advanced (T4 N0-2 M0) colon cancer can now be considered for neo-adjuvant (pre-operative) chemotherapy based on the FOxTROT trial results.[44]

Figure 1.2 - Diagram showing the anatomy of the colon and rectum. *Adapted from Kim JY et al.* [45]



1.4.2 Adjuvant chemotherapy for stage III colon cancer

Standard adjuvant chemotherapy regimens

Since 1990, the regimens for adjuvant chemotherapy have evolved based upon the results of RCTs (Appendix 3). The mainstay of treatment are the fluoropyrimidines which can be administered intravenously as 5-FU, or in oral tablet form (e.g., capecitabine). Fluoropyrimidines can be given alone as monotherapy, or with oxaliplatin as combination therapy.

The combination of 5-FU with oxaliplatin is FOLFOX, and the combination of capecitabine and oxaliplatin is CAPOX. In England, NICE guidelines recommend any of these regimens, although CAPOX is off-label.[41] Since the X-ACT trial, patients selected for monotherapy are generally given capecitabine due to its convenience and favourable toxicity profile.[46] Further details regarding these SACT drugs are provided in Appendix 4.

Variation in adjuvant chemotherapy use

Variation in the use of adjuvant chemotherapy for stage III colon cancer has been widely described within the literature. The largest study to date reported on 124,008 patients in the US using National Cancer Database data, and showed an adjuvant chemotherapy rate of 66%.[47] A systematic review of 22 US studies evaluating the rates and predictors of chemotherapy in stage III colon cancer showed variable rates of 39% to 71%.[48] However, most of these studies were outdated (pre-2003), with almost half using the Surveillance, Epidemiology, and End Results (SEER)-Medicare dataset and thus only including patients aged 65 and over. Several studies have also highlighted varying rates of adjuvant chemotherapy administration across Europe.[49] [50]

Advanced age has been consistently identified as a determinant of reduced use of adjuvant chemotherapy.[47-50] Race, socioeconomic status, insurance status, and geographical location, have also been identified as determining factors.[47 51-57] Between-hospital variation in adjuvant chemotherapy use has been demonstrated in other countries.[58 59]

Within the UK, prior to work conducted in this thesis, there were no studies evaluating variation in the determinants of use of adjuvant chemotherapy for stage III colon cancer patients. One large study investigated variation in the use of chemotherapy in the South East of England but included all stages of disease across four cancer types between 1993 and 2002. It demonstrated significant variation in the use of chemotherapy, particularly according to age and cancer network.[60]

Duration of oxaliplatin-based adjuvant chemotherapy

Historically, the standard duration of treatment for FOLFOX and CAPOX adjuvant chemotherapy was six months (Appendix 3). However, cumulative neurotoxicity sustained from oxaliplatin treatment can cause significant and sometimes irreversible morbidity.[61]

The IDEA collaborative study was a pooled analysis of six phase 3 RCTs undertaken to evaluate the non-inferiority of three months of CAPOX or FOLFOX compared to six months with the primary end-point of three-year disease-free survival, a surrogate marker for overall survival.[62] [63] Non-inferiority was not confirmed in the overall population. However, a subgroup analysis suggested that three months CAPOX, particularly in patients with low-risk disease (T1-T3/N1 staging), may be superior to six months with less neurotoxicity. Patients with high-risk disease (T4/N2 staging), particularly those receiving FOLFOX, could still benefit from completing six months treatment but the small differences in survival need to be weighed against the risks of long-term toxicity. Current NICE guidelines advocate the use of three months CAPOX, three to six months FOLFOX, or six months fluoropyrimidine monotherapy.[41]

Completion of adjuvant chemotherapy

Patients may not always manage to complete all cycles of their adjuvant chemotherapy. Reasons for this include severe acute toxicities, general deterioration in a patient's condition, intercurrent illness or other comorbidities, and patient choice. Unless patients experience life-threatening toxicities or refuse further chemotherapy, most should have treatment modifications (e.g., dose reductions or early discontinuation of oxaliplatin) in order to complete their treatment.

A recent RCT showed a median completion rate of 83% for fluoropyrimidine and 70% for oxaliplatin adjuvant chemotherapy.[64] Observational studies have suggested that completion rates for adjuvant chemotherapy may vary between 54%-79%.[65-68] These lower completion rates might be expected outside of a strict RCT setting where there is less intensive follow-up and monitoring, and inclusion of elderly and unfit patients (Chapter 1.2).

To date, observational studies evaluating the completion of adjuvant chemotherapy in patients with stage III colon cancer have had significant methodological limitations. A systematic review and meta-analysis including two RCTs and 20 observational studies, found that included studies had small sample sizes (generally fewer than 500 patients) and, of the 20 observational studies included, 12 had a serious risk of bias and eight had a moderate risk of bias.[69] This was predominantly due to inadequate risk-adjustment for important confounders such as age, sex, and staging.

Previous observational studies have also been limited by chemotherapy information lacking granularity such as specific regimen details, administration dates, and dosing.[66-68] For this reason, no previous observational studies have evaluated the impact of treatment modifications on survival.

1.4.3 Research gaps identified

Determinants of variation in adjuvant chemotherapy use

No previous studies have examined the use of adjuvant chemotherapy in stage III colon cancer patients within the English NHS, including evaluation of determinants of its use, the extent of between-hospital variation, and

the possible underlying reasons for this variation. Methodological considerations for examining between-hospital variation in adjuvant chemotherapy use include ensuring that the capture of chemotherapy information is as robust as possible, and appropriately risk adjusting for case-mix differences.

The prior methodological work to develop a coding framework to interpret chemotherapy information in HES-APC, and the clinical algorithm to capture adjuvant chemotherapy information from both SACT and HES-APC, can be translated into a performance indicator which identifies adjuvant chemotherapy use (process outcome). This will enable continuous reporting and monitoring of this aspect of care within NBOCA, as well as facilitating targeted quality improvement initiatives to improve outcomes.

Although other areas of interest were highlighted, histopathological and genetic information have poor data completion within NBOCA, precluding the identification of patients with stage II disease who might be expected to receive adjuvant chemotherapy, and those patients with stage II or III colon cancer who may not benefit from adjuvant chemotherapy due to their genomics. The data used in this thesis largely predated the FOxTROT results and therefore neo-adjuvant chemotherapy for colon cancer could not be examined.

Impact of adjuvant chemotherapy completion and treatment modification on survival
There is a clear lack of high-quality information from observational studies regarding the impact of completion of adjuvant chemotherapy in "real-world" practice on survival outcomes. In addition, the granularity of the SACT dataset will allow the examination of treatment modifications on survival outcomes.

An improved understanding of 'real-world' regimen-specific completion rates will complement trial findings and is important for several reasons. Firstly, it may identify subgroups of patients who require additional support to promote completion, which might subsequently improve survival outcomes. Secondly, it will aid shared patient-clinician decision-making processes regarding whether patients should commence chemotherapy at all, particularly for any groups identified as stopping chemotherapy very quickly. Finally, it might help with choice of regimen and improved counselling of patients.

1.4.4 Overview of the management of non-metastatic rectal cancer

The anatomical constraints of the bony pelvis coupled with the proximity of the rectum to other pelvic organs (e.g., bladder and gynaecological organs) means that adequate oncological resection of rectal tumours is challenging. Achieving this alongside good functional outcomes (e.g., avoiding compromise to bowel, sexual, and urinary function) is critical. In addition, the rectum lacks a serosal layer (outer layer of bowel) (Figure 1.1) which enables disease to spread to surrounding fatty tissues (mesorectum) more readily.

Due to these factors, unlike colon cancer, there are equal concerns about both local and distant recurrence of disease and the complexity of multimodal treatment is reflective of this (Figure 1.3). Locoregional recurrence

rates for rectal cancer are between 2-15%, and overall recurrence rates 20-30%.[70] Local recurrence is associated with significant morbidity and poor prognosis with five-year overall survival rates below 10%.[71]

A key determinant for local recurrence is the presence of a positive circumferential resection margin (CRM). This means that there is a distance of 1mm or less between the tumour border and the surgical resection margin. High-resolution magnetic resonance imaging is used to stratify the risks of local recurrence by pre-operatively evaluating CRM involvement.[72] This involves ascertaining whether the CRM is threatened by tumour involvement, extramural vascular invasion, or suspicious lymph nodes.

Rectal cancer surgical procedures

A significant advancement in surgical technique, total mesorectal excision (TME), was described in 1982 and is now deemed the gold standard surgical technique for patients with curative disease.[73] TME involves the removal of the rectum and surrounding mesorectum, improves negative CRM rates, and has contributed to improved local recurrence and survival rates.

TME is employed during the three main procedures performed for rectal cancer: anterior resection, low Hartmann's procedure, and abdominoperineal resection (APR). Anterior resection involves removing the part of the rectum containing the tumour and joining the two ends back together immediately. There is a risk of anastomotic leak (a potentially life-threatening complication where bowel content leaks out of the join into the abdomen), and approximately 75% of patients will have a temporary stoma (bowel brought out through the abdominal wall with a bag to collect stool) to reduce the potential consequences of such a leak.[30]

Once the patient has recovered from their initial surgery, the stoma should be reversed (bowel put back inside the abdomen). However, in over 25% of patients the stoma is not reversed. This might be due to anastomotic leak, disease progression, patient choice, or administrative issues such as waiting list pressures.[30] Retaining a stoma can have negative consequences including reduced tolerance to adjuvant chemotherapy, as well as impaired long-term renal function and survival.[74]

A Hartmann's procedure involves removing the part of the rectum containing the tumour, but bringing the proximal end of bowel out through the abdominal wall as a stoma. This stoma has the potential to be reversed. However, a previous study suggested that 95% of patients undergoing a Hartmann's procedure had a stoma at 18 months.[75]

An APR involves removing the part of the rectum containing the tumour as well as the entire anal canal, leaving patients with a permanent stoma. This procedure is generally used for low rectal tumours, but the decision to perform an APR also depends on other factors including tumour staging and likely residual bowel function if the bowel were to be joined back together immediately. Wide variation in APR rates have been demonstrated previously.[30 76]

Each of these rectal cancer procedures is associated with potential complications including a 2-5% risk of mortality, 3-11% risk of anastomotic leak, permanent stoma formation, and long-term bowel, bladder and sexual sequelae.[77 78]

Patients with stage I rectal cancer may also require a TME procedure. However, there are other less-invasive options available which involve local excision of the tumour (i.e., the bowel is not resected), for example, transanal minimally invasive surgery (TAMIS). Each procedure has advantages and disadvantages which should be discussed as part of the shared decision-making process.[41]

Surgical access for rectal cancer procedures

The use of open versus laparoscopic technique within rectal cancer surgery has been contentious. The evidence suggests that open and laparoscopic techniques for rectal cancer surgery have similar outcomes, with more short-term benefits (e.g., reduced length of stay, reduced pain, and faster return of bowel function) for laparoscopic surgery. Currently, guidelines recommend the use of laparoscopic surgery for rectal cancer in appropriate clinical cases (i.e., open surgery might be favoured for locally advanced tumours or patients who have had prior abdominal or pelvic surgery) and if undertaken by an appropriately trained surgeon.[41]

The first colorectal series of robotic cases was published in 2002. Since then, there has been an increasing uptake of the technique with at least 30 English NHS hospitals reporting that they regularly perform robotic CRC resections.[30] To date, the evidence suggests that robotic surgery is a safe and feasible alternative to laparoscopic surgery in appropriately trained surgeons with a potentially lower conversion-to-open rate, but with increased operative duration and costs compared to laparoscopy.[79] Current guidelines advise that robotic surgery can be used in hospitals with established programmes.[41]

Radiotherapy

In addition to surgery, neo-adjuvant radiotherapy is used to reduce local recurrence rates and facilitate successful resection through pre-operative tumour shrinkage. It can be given in two ways. Short-course radiotherapy (SCRT) involves hypofractionated (higher radiation doses per treatment over shorter treatment durations) doses (5 Gy) given daily over five consecutive days to provide a total dose of 25Gy. It is usually followed by surgery within seven days of completion. Long-course chemoradiotherapy (LCCRT) involves standard fractionated doses (1.8 to 2.0 Gy) given for five days each week for five weeks to provide a total dose of 45-50 Gy. This is given with concomitant fluoropyrimidine-based SACT which acts as a radiosensitiser. Surgery is generally undertaken after a minimum delay of six weeks to maximise tumour shrinkage, although there is uncertainty regarding the optimal timing.[80]

In operable rectal cancer, two large randomised controlled trials have directly compared SCRT and LCCRT and did not find any difference in permanent stoma rates, local recurrence, disease-free and overall survival, or late effects (e.g., bowel and sexual function).[81 82] The choice of radiotherapy delivery is influenced by many

factors including staging, tumour height, CRM involvement, patient fitness, and patient choice. LCCRT is often favoured for low rectal tumours to facilitate resection and potentially avoid the need for a permanent stoma (Figure 1.3). In UK clinical practice, there is significant heterogeneity in rates of neo-adjuvant radiotherapy treatment, as well as wide variation in the type of radiotherapy utilised between different regions and hospitals.[38]

Finally, approximately 10-15% of patients treated with LCCRT will have a complete clinical response (cCR).[83] This means that there is no clinically detectable tumour following LCCRT according to physical examination, or endoscopic and radiological findings. Although surgical resection remains the gold-standard, following the publication of the OnCoRe trial results in 2016, patients with cCR have the option to be treated via a "watch-and-wait" strategy, potentially avoiding surgical resection and a permanent stoma (Figure 1.3).[83] These patients will undergo intensive surveillance and if there is any evidence of "local regrowth" (rates of 3-33%) they will require salvage surgery.[84]

Systemic anti-cancer therapy

For adjuvant chemotherapy use in rectal cancer patients, results have generally been extrapolated from RCTs conducted in colon cancer patients. The evidence considered for the NICE guidelines did not include any RCTs where LCCRT was used. Consequently, the NICE guidelines only make recommendations for considering adjuvant chemotherapy in stage III rectal cancer patients who have had surgery alone or SCRT, not for those undergoing LCCRT (Figure 1.3).[41]

The evidence for patients who have LCCRT is more uncertain. LCCRT infers both pre-operative delays (e.g., waiting for re-staging) and post-operative delays (e.g., patient has an APR), and there are uncertainties regarding the benefits of adjuvant chemotherapy after such delays. Trials evaluating adjuvant chemotherapy following LCCRT have faced difficulties recruiting patients because they are unable to tolerate treatment in the post-operative period and the findings regarding the benefits have been inconsistent but largely in favour of no definite benefit.[85-88]

Neo-adjuvant chemotherapy is sometimes used for bulkier rectal tumours, particularly those in the upper rectum which are less amenable to radiotherapy treatment. Total neo-adjuvant therapy refers to the use of neo-adjuvant chemotherapy, and either LCCRT or SCRT, prior to surgery (Figure 1.3). The benefits of total neo-adjuvant therapy are that it precludes the delays associated with adjuvant treatment, and means that patients are treated when they are better able to tolerate chemotherapy. Trials have shown it to have improved disease-free survival but at the expense of increased toxicity and, for this reason, it is generally used in younger, fitter patients with high-risk disease.[89 90] The preferential choice of radiotherapy in this scenario is uncertain. Data regarding total neo-adjuvant treatment has only been published and started to affect standard practice over the last two years and so it was not possible to examine within this thesis.

Multimodal combinations of treatment

Decisions regarding multimodal treatment with varying combinations of surgery, radiotherapy, and chemotherapy are dependent on clinical factors including CRM involvement, staging, and the location of the tumour, in combination with patient factors such as age, fitness, and pre-operative bowel function (Figure 1.3). The decision-making is extremely complex and requires comprehensive discussion in a multidisciplinary team (MDT) setting as well as taking into account patient preference.

1.5 Multimodal treatment of advanced disease

1.5.1 Locally advanced disease

For patients with locally advanced CRC, referral for pelvic exenteration surgery is recommended.[41] In addition to this, sacral and pelvic wall resections may be necessary to achieve complete resection. This is highly complex surgery with significant post-operative morbidity and should be managed within a specialised MDT.[91]

1.5.2 Metastatic disease

Approximately a quarter of patients with CRC will present with metastatic disease. In addition to this, around half of patients with CRC will go on to develop metastases at some point in their disease trajectory.[92]

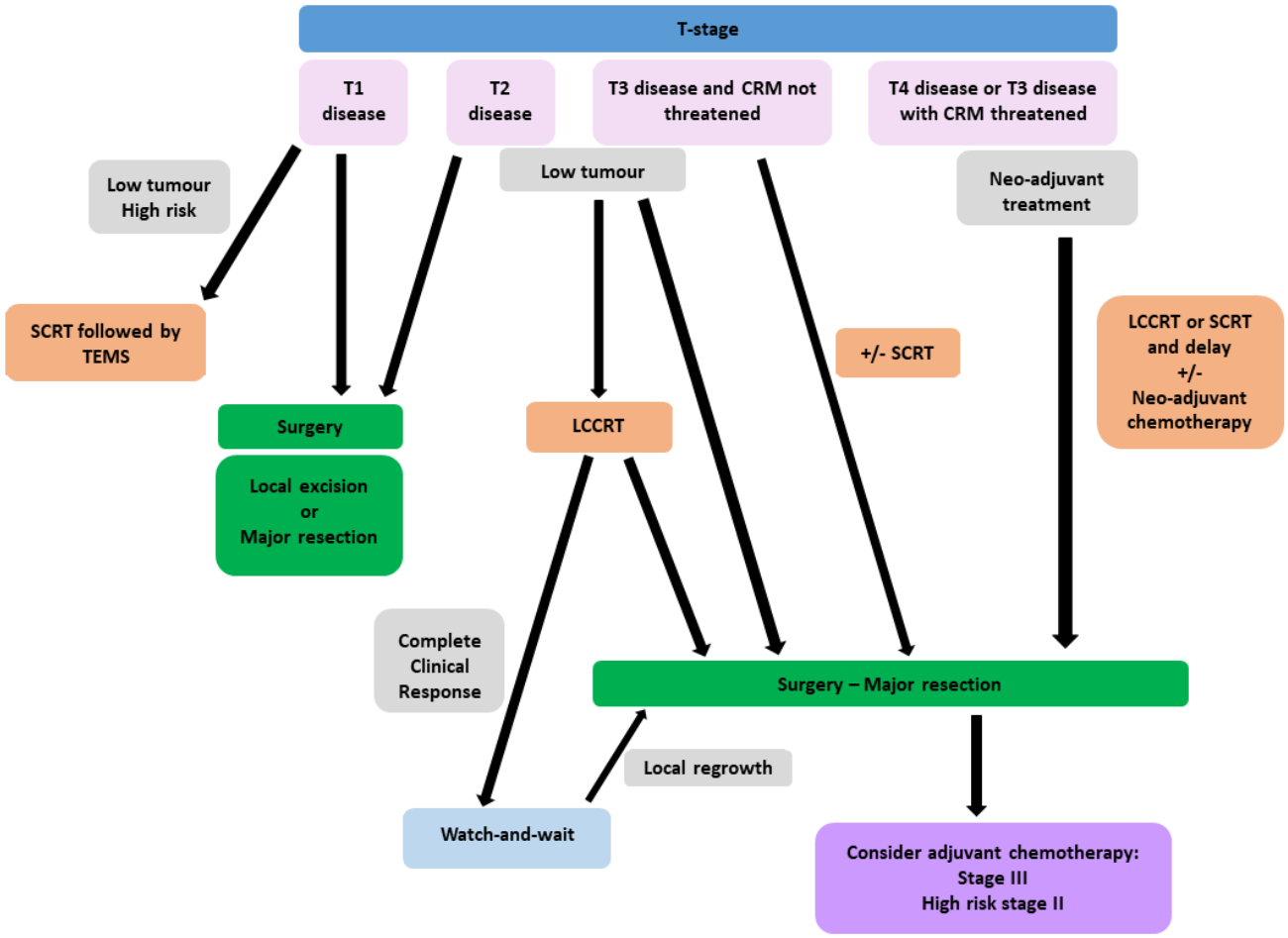
For stage IV CRC, international guidelines suggest that patients are divided into groups broadly based on whether the metastases are amenable to surgical resection, as well as taking into account patient fitness and choice. Patients with clearly resectable disease will have treatment of liver and/or lung metastases, along with resection of their primary tumour, and differing combinations of SACT. Those with potentially resectable disease may have SACT first with the aim of downsizing the tumour burden prior to undertaking definitive treatment.[92]

Patients with unresectable disease generally have disseminated CRC and may receive palliative treatments that include combinations of SACT, radiotherapy, ablative techniques, and other interventions for their primary and metastatic disease dependent on symptoms. Some patients with unresectable disease will still undergo stenting (insertion of a flexible hollow tube into the bowel to keep it open when it has become blocked by tumour) or palliative resection of the primary tumour. The aims of treating patients with unresectable disease include prolonging survival by reducing disease progression, symptom control, and maintenance of quality of life.[92] A small proportion of patients may respond so well to palliative SACT that surgical interventions with the aim of cure can be considered.

1.5.3 Molecular biomarker testing

Tissue obtained from either the primary CRC tumour or metastasis, often from the liver, is generally used to undertake biomarker testing. The key biomarker tests are for RAS (KRAS and NRAS) and BRAF (V600E) mutations, and MMR deficiency or MSI status. Current NICE guidelines recommend that all patients with metastatic CRC should be tested for each of these biomarkers to guide treatment selection and evaluate prognosis (Figure 1.4).[41]

Figure 1.3 – Schematic overview of multimodal treatment pathways for non-metastatic rectal cancer



RAS and BRAF are described as “wild-type” if mutations are not present. Both of these mutations have been associated with poor prognosis and lack of benefit from epidermal growth factor receptor therapies (Appendix 4).[92 93]

MMR function can be determined via immunohistochemical testing for MMR proteins (assigned as proficient or deficient), or MSI testing (assigned as MSI-high, MSI-low, or MSS (microsatellite stable)). Results from these techniques are highly correlated but 1-2% of patients can have normal (proficient) MMR proteins but be MSI-high. Testing is recommended in advanced disease to identify patients who may benefit from immunotherapy (Figure 1.4).[94]

Prior to the use of immunotherapy, it was thought that the prognosis in metastatic CRC for patients who are MMR deficient was worse, largely due to uncertainties over how effective standard chemotherapy is in this subgroup. More recently, neurotrophic tyrosine receptor kinase (NTRK) fusions can be assessed for patients who do not have RAS/BRAF mutations to guide third-line treatment (Figure 1.4).[95] NBOCA has recently started capturing biomarker data, but data completion is currently poor.

1.5.4 Systemic anti-cancer therapy for advanced disease

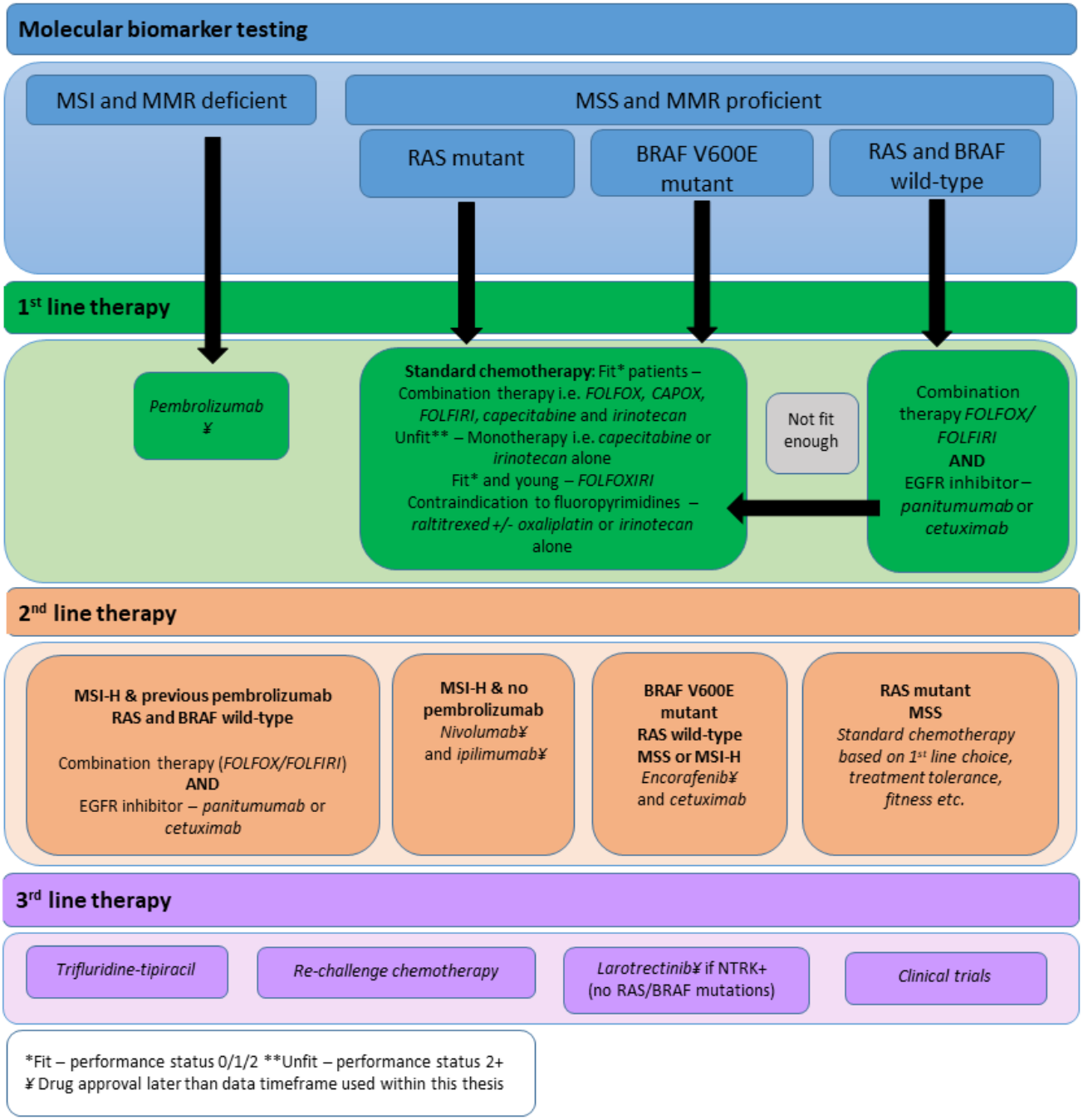
The median overall survival for patients with metastatic CRC has improved significantly and is currently estimated to be up to 30 months, double what it was two decades ago. This improvement is likely partially due to advancements in SACT treatments.[92]

As SACT therapy is constantly evolving, a clear understanding of which drugs were available during the studied timeframe, and which line of therapy and combination of treatment they were approved for, has been crucial for the interpretation of SACT data. Figure 1.4 outlines the different SACT drugs currently used within the metastatic setting in the English NHS, as well as highlighting the drugs which were not captured in the data reported within this thesis because they had not been approved at that point. Further details are provided about each drug in Appendix 4.

Patients with metastatic CRC who are fit enough are generally treated with SACT. The choice for first-line therapy is broadly dependent on molecular biomarker testing (Chapter 1.5.3), and then more specifically on patient comorbidities, performance status, and preference (e.g., irinotecan or raltitrexed might be favoured for patients with cardiac disease in whom fluoropyrimidines are contraindicated) (Figure 1.4).[41]

Second-line therapy involves giving a different drug to that which was given first-line. For example, if the patient received first-line FOLFOX, they could be given FOLFIRI (5-FU and irinotecan), or vice versa. If a patient was given capecitabine monotherapy initially, oxaliplatin could be added (CAPOX), or they could switch to FOLFOX or FOLFIRI.[41]

Figure 1.4 – Current SACT treatment algorithm for metastatic CRC in the English NHS



Similarly, third-line therapy involves giving a drug which has not yet been used to ensure the patient has been exposed to a fluoropyrimidine, oxaliplatin, and irinotecan. If all of these drugs have been given, trifluridine-tipiracil can be used (Figure 1.4).[41] The other options following third-line therapy are referral for early phase clinical trials or best supportive care.

Bevacizumab and aflibercept were previously approved for metastatic CRC and were captured in the data used within this thesis. These drugs were stopped due to withdrawal of funding.[41]

1.6 Toxicity from systemic anti-cancer therapy

1.6.1 Overview

Cytotoxic SACT drugs are designed to damage human cells. They are not able to differentiate between cancerous and non-cancerous cells which means that normal cells are also damaged during treatment, leading to toxic side effects. Cytotoxic drugs often target rapidly dividing cells meaning that areas of the body with a high cell turnover such as haemopoietic cells of the bone marrow and mucosal cells of the gastrointestinal tract are particularly susceptible. Biologic SACT drugs work by targeting tumour cells directly or stimulating the body's immune system to target them indirectly (Appendix 4). For this reason, they often have more unique toxicity profiles.

Due to their narrow therapeutic index, and therefore the associated high levels of toxicity, SACT drugs require stringent reporting of adverse events within clinical trials. An adverse event is defined as "any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure".[96] The Common Terminology Criteria for Adverse Events (CTCAE) is a classification system designed for use in RCTs to help clinicians detect and more accurately document the nature and severity of adverse events (Table 1.2). It is now the international standard for reporting adverse events in cancer RCTs.[96]

1.6.2 Toxicity profiles

Appendix 4 summarises the specific toxicities for each SACT drug included within the scope of this thesis. Details are provided here for the different toxicity profiles which are important for later chapters.

Fluoropyrimidines

The common toxic side effects of fluoropyrimidine treatments include gastrointestinal disturbances, cardiotoxicity, myelosuppression, and skin disorders (hand-foot syndrome) (Appendix 4).[97] Continuous infusion 5-FU and capecitabine share more favourable toxicity profiles than bolus 5-FU, excluding an increased incidence of hand-foot syndrome.[98-100]

Of note, it has been estimated that approximately 10-40% of patients treated with fluoropyrimidines will develop severe toxicity and this is fatal in approximately 1%.[97] Around 3-5% of the population are partially or completely deficient in the enzyme dihydropyrimidine dehydrogenase (DPD) which metabolises 80-90% of fluoropyrimidines. This is due to a mutation in the DPYD gene which makes them susceptible to severe fluoropyrimidine toxicity.[101] In March 2020, routine testing for DPD deficiency prior to fluoropyrimidine treatment was recommended by the European Medicines Agency. Testing is thought to

Table 1.2 – Common Terminology Criteria for Adverse Events (CTCAE) [96]

Grades	Clinical description
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
3	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care activities of daily living.
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to adverse event.

predict around 30% of life-threatening toxicities. In the English NHS, testing has been made routinely available via NHS Genomic Laboratory Hubs, but is not yet captured in routinely collected data.[97]

Oxaliplatin

The predominant dose-limiting toxic effect from oxaliplatin use is cumulative neurotoxicity which can be irreversible. Within the MOSAIC trial, 92% of patients had neurotoxicity during treatment and 12.5% of these were CTCAE Grade 3 or above.[102] However, at 4 years follow-up this had reduced to 15.4% and 0.7% respectively.[103] Other common toxic effects include ototoxicity, cardiotoxicity, nephrotoxicity, and gastrointestinal disturbances (Appendix 4).

FOLFOX versus CAPOX

The SCOT trial and IDEA collaborative study have shown that there are some differences in toxicity profiles between the two oxaliplatin-based combination regimens. Patients receiving FOLFOX tend to have more neutropenia. Patients receiving CAPOX tend to have more diarrhoea and hand-foot syndrome.[62 64]

Irinotecan

It has been reported that up to 36% of patients treated with irinotecan experience severe, life-threatening toxicities.[104] The most common toxicities are myelosuppression (specifically neutropenia), gastrointestinal disturbances (largely diarrhoea), alopecia, and cholinergic syndrome during administration (Appendix 4).[105 106]

Bevacizumab

The most frequent toxicities associated with bevacizumab use include hypertension, fatigue or asthenia, diarrhoea, abdominal pain, and renal dysfunction (Appendix 4). As bevacizumab inhibits the growth of new blood vessels it interferes with the body's normal healing mechanisms and can also therefore cause wound healing complications. The most common severe toxicities include gastrointestinal perforation and fistulation, haemorrhage, and venous or arterial thromboembolism. Patients with CRC are particularly prone to gastrointestinal perforation, particularly if they have a history of pelvic irradiation.[107]

Panitumumab

Two of the more specific toxicities associated with panitumumab use include skin reactions and electrolyte disturbances (Appendix 4). In one RCT, 35% of patients receiving panitumumab had a CTCAE grade 3 or 4 adverse event recorded.[108]

Cetuximab

Toxicities associated with cetuximab use include skin reactions, infusion-related reactions, and electrolyte disorders (Appendix 4).[109]

1.6.3 Capturing toxicity in routinely collected data

The use and complexity of SACT is constantly increasing and evolving, with several new combinations of biologic agents approved for use in the treatment of metastatic CRC during the course of this thesis alone (Chapter 1.5). Most evidence for SACT toxicities comes from RCTs. However, there are advantages to using routinely collected data to complement this information (Chapter 1.2).

A previous study in breast cancer patients demonstrated that 43% of those receiving SACT required hospitalisation and 75% of those hospital admissions were confirmed as being directly related to SACT treatment.[110] Another study showed that the most frequent reasons for 90-day unplanned hospital readmissions following CRC resection within the English NHS are SACT-related complications.[111] This suggests that SACT toxicity has the potential to put a huge burden on both healthcare systems and patients.

There is a lack of data in the literature regarding toxicities in "real-world" clinical practice for SACT drugs used in CRC. The available observational studies are often limited by small size, exclusions within the cohort (i.e., elderly only), or by focus on a particular regimen or specific type of toxicity.[112-114]

To date, observational studies evaluating toxicities in CRC patients have tended to use either medical note abstraction or insurance claims data to identify toxicities.[112-114] Medical note abstraction is time-consuming and impractical on a large scale. Insurance claims data such as SEER are not designed to collect detailed chemotherapy information and have been shown to be inaccurate in their capture of SACT regimens and toxicities.[5 115] These studies can lack basic information such as administration dates which are essential to establish the precise timeframe during which toxicity would be expected to occur.

Previous studies have attempted to validate coding frameworks which were designed to capture toxicity from insurance claims or hospital administrative data, largely in breast cancer patients.[110 115-118] These studies used various ways of validating the capture of toxicities including comparing rates of codes in patients receiving chemotherapy versus those not receiving chemotherapy, cross-checking information with medical notes, or comparing rates to trial data. The overarching limitations of these studies include using old data (predating the approval of many biologic therapies)[116], using a restricted set of toxicity codes (e.g., several studies used just eight codes)[116 118], exclusions based on age and insurance status[115 118], small sample sizes (two of these studies validated in less than 200 patients)[115 117], and the use of arbitrary timeframes within which to identify toxicities (e.g., in the 12 month period following diagnosis rather than the actual timeframe during which the patient was receiving chemotherapy).[118]

In one particular study, validation involved assessing the sensitivity and specificity of the coding framework by cross-checking results with medical note abstraction.[110] The coding framework was deemed to perform best for SACT-related visits necessitating hospitalisation from A&E (sensitivity 90% and specificity 100%) or directly

from home (sensitivity 91% and specificity 93%). Another study concluded that insurance claims data were of restricted value in measuring clinically significant toxicities.[115]

1.6.4 Research gap identified

Measuring severe acute toxicity following SACT in routinely collected data

The capture of toxicities in "real-world" data for the purposes of ongoing national reporting and monitoring is not feasible using medical note abstraction and does not appear robust enough using insurance claims data. In addition, insurance claims data are not always available in all settings, and not at all within the UK. Therefore, the main methodological issue is the ability to capture toxicities in "real-world" practice from routinely collected data in a way that is standardised, validated, and reproducible, as well as being broad enough to capture toxicities across an ever-evolving spectrum of SACT drugs which may have unique toxicity profiles.

The ability to measure and better understand the patterns of severe acute toxicity within "real-world" clinical practice is crucial for several reasons. First, it will allow comparisons of toxicity profiles for different regimens and thus help to inform patient-clinician decision-making processes. This is particularly important with so many new SACT drugs being recently approved. Second, an understanding of the "real-world" incidence of particular toxicities will help to target interventions for prevention as well as assessing the economic implications. Third, being able to capture this information from routinely collected data will mean that the ongoing reporting and monitoring of toxicities could occur at hospital level which should facilitate national clinical benchmarking and quality improvement processes.

1.7 Quality of systemic anti-cancer therapy delivery

1.7.1 Overview of performance monitoring processes

Within cancer care, it is widely acknowledged that significant variations in the quality of care exist. Broadly, this variation might be explained by differences including the skill of the individuals within the MDT delivering care, care pathways available and chosen for patients, and the infrastructure and resources available within each hospital.[119] Due to the recognised variation in care quality, the measurement and reporting of performance indicators has become an integral part of driving quality improvement.

Once appropriately validated, routinely collected data can be used to develop performance indicators. Performance indicators are defined as "measurable elements of practice performance for which there is evidence or consensus that they can be used to assess the quality, and hence change the quality, of care provided".[120] In this way, performance indicators can help translate the findings from routinely collected data into meaningful changes in healthcare practice through the ongoing monitoring and reporting of the quality of structure, processes, and outcomes.[119] Performance indicators can also be used to better understand variation in care and outcomes.

Care quality can be measured via four broad categories: (i) outcomes (e.g., toxicity from SACT), (ii) processes (e.g., use of adjuvant chemotherapy), (iii) structures (e.g., availability of on-site chemotherapy), and (iv) patient-reported measures (e.g., quality of life).[121] Use of performance indicators can stimulate quality improvement by facilitating the identification and prioritisation of actionable areas. In order to exert the most impact, performance indicators should be meaningful, achievable, actionable, and impact a significant number of patients. It has been suggested that indicators showing the most variation are the ones that should be targeted in order to improve overall performance.[122]

Healthcare systems may also publish these performance indicators in the public domain (e.g., NHS England Clinical Outcomes Publication programme).[123] This provides transparency of results to patients, clinicians, and policy makers. Public reporting may further enhance quality improvement processes through accountability and competition mechanisms.[124] It can also stimulate clinical engagement and serve to improve data quality and completeness.

Performance indicators can be used within quality assurance processes to monitor trends over time in the same provider, evaluate differences between providers, and benchmark against best practice according to a predefined or arbitrary standard. They can also be used to identify outlying hospitals at both ends of the spectrum (i.e., high and low performers). As part of this process, low performing hospitals (usually at least two standard deviations above the national average) are expected to verify their data, and then formulate a formal response and action plan to address any issues identified.[125] High performing hospitals provide an opportunity for the identification and dissemination of best practice.

The NBOCA has been reporting on the structure, processes, and outcomes of CRC care since 2010 and this has enabled comparative provider performance monitoring at individual hospital- and surgeon-level. It has also facilitated clinical benchmarking including involvement in the NHS England Clinical Outcomes Publication programme which publishes quality measures for 27 other national clinical audits in the public domain to stimulate quality improvement.[123]

Continuous engagement with quality improvement processes is associated with high-quality care, with specific examples of individual service redesigns contributing to improved care as a result of outlier reporting in national audits.[125] The public reporting of a 90-day post-operative mortality performance indicator at surgeon- and hospital-level for CRC patients was shown to coincide with a significant reduction in mortality rates, with no evidence of risk-aversive behaviours or manipulation of data.[126]

1.7.2 Measuring the quality of SACT delivery

Given the complexities of the processes involved in delivering SACT such as the MDT approach to patient selection and optimisation, dosage, prescription and preparation, treatment administration, and the monitoring and management of toxicities, it is clear that there is huge scope for variation in practice, and therefore outcomes. As previously mentioned, the use and complexity of SACT is constantly increasing with novel drugs continuously being approved. This means that there is a huge potential to improve care for a large number of patients with robust reporting and monitoring. In addition, the wider literature has suggested that there are high rates of unplanned hospital admissions due to toxicity from SACT (Chapter 1.6).

NHS England Specialised Commissioning is responsible for all SACT services across England and is supported by a dedicated Clinical Reference Group which provides clinical advice and patient input. The UK Chemotherapy Board (UKCB) is also involved in providing advice and guidance for the development and delivery of high-quality chemotherapy services, as well as supporting commissioning and local service provision.

In 2009, a report was published on the quality and safety of chemotherapy services within England based on safety concerns raised in several other reports including the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) and the National Patient Safety Agency (NPSA) reports.[127] The NCEPOD report had suggested that there were significant deviations from the standards set in the “Manual for Cancer Services: Chemotherapy Measures”; part of the National Cancer Peer Review quality assurance programme which aims to facilitate quality improvement. It concluded that half of patients receiving SACT could have had improvements in the quality of care received.[128]

In response to this, three key areas were highlighted in a subsequent report including the need for: safer provision of elective chemotherapy services, acute oncology services for any hospital with an A&E department, and improvements to broader aspects of chemotherapy delivery (e.g., leadership, information systems, and

governance). Following on from this, the standards of care expected across the entire care pathway from initial oncology referral to completion of treatment have been defined for English NHS providers of SACT.[129]

To date, there do not appear to be any established national reporting programmes for SACT delivery globally. Within the English NHS, the only measure of chemotherapy quality which is publicly reported, with risk-adjustment and outlier reporting, is 30-day mortality after the last SACT treatment received.[7] Only very recently, in January 2022, have risk-adjusted 30-day mortality rates after SACT for CRC been published by individual hospital. As a result of work conducted within this thesis, NBOCA has been publicly reporting the rates of adjuvant chemotherapy use for stage III colon cancer.[30]

Within the remit of specialised services, there are also "Specialised Services Quality Dashboards" which are designed to monitor the quality of services by collecting information from SACT for a list of agreed measures from hospitals. Chemotherapy measures were only implemented in 2020/2021 and include: 30-day mortality after SACT treatment, extravasation (leakage of the SACT drug into the surrounding tissues) after intravenous SACT administration, the proportion of patients entered into a clinical trial, 30-day emergency admissions after SACT treatment, and the proportion of patients with suspected neutropenic sepsis given antibiotics within an hour of identification.[130] The results of these measures are only available to service providers and commissioners. It is unclear whether the reporting of these will be stratified by tumour type or regimen, and whether specific details on the admission reason will be provided as this information is not captured within the SACT dataset and would require linkage to other data sources (e.g., HES-APC).

A systematic review of population-based studies evaluating the quality of SACT delivery in routine practice suggests that quality of care can be split across five domains: access, treatment delivery, safety, toxicity, and outcome, with equity featured in each.[131] This review found that the vast majority of studies (77%) evaluated access, with particular gaps for treatment delivery and safety, as well as for advanced cancer and biologic therapies. In addition to the limited research on the quality of SACT in routine practice, there is a lack of research on the identification, development, and implementation of performance indicators for SACT, particularly those relating to outcomes.[132]

A recent study identified existing SACT performance indicators within the literature and used the Delphi method to reach a consensus on which were the most appropriate. Outcomes identified included: 30-day mortality after SACT, neutropenia and neutropenic sepsis rates, neurotoxicity rates, 30-day unplanned readmissions after SACT, unplanned visits to the emergency department after SACT, and involvement of palliative care services.[133] Another study in breast cancer patients found that electronic prescribing, hospitalisations during chemotherapy, and timely receipt of chemotherapy, were the measures with the most potential to improve the quality of care based on the degree of between-hospital variation and the volumes of patients affected.[122]

1.7.3 Research gap identified

Development of severe acute toxicity as a hospital-level performance indicator

There is a clear need for more stringent monitoring of SACT delivery, and yet there is lack of reporting of SACT performance indicators, particularly within the public domain. Once validated, the coding framework for severe acute toxicity can be used as the basis for an outcome performance indicator for the national public reporting and monitoring of SACT in CRC patients, and be used to trigger national and local quality improvement initiatives.

Due to the unique linkage of datasets available, more granularity regarding the hospitalisation for severe acute toxicity is available. For example, specific toxicity profiles for individual SACT regimens can be ascertained for CRC patients rather than simply a proportion of all patients with any tumour type, receiving any regimen, who have experienced hospitalisation within a particular timeframe. This will be important for better understanding any variation and enabling meaningful improvements in “real-world” clinical practice.

Given the comprehensive and broad nature of the coding framework and the use of internationally applicable codes, this work should also be transferable to other cancer types and different SACT drugs following appropriate validation.

1.8 Volume-outcome relationship for rectal cancer surgery

1.8.1 Overview of the volume-outcome relationship

A relationship between hospital volume and outcomes was first described in 1979.[134] This work examined mortality rates for 12 surgical procedures to determine whether a hospital's average annual number of surgical procedures was associated with surgical mortality. There was variation in the volume-outcome relationship dependent on the type of procedure performed.

Over time, an increasing body of evidence has shown improved post-operative and long-term oncological outcomes for hospitals performing high volumes of what are considered to be "more complex" surgical procedures such as oesophagectomy, gastrectomy, pancreatectomy, and hepatectomy.[135-137] As a result, specialisation of these procedures to high volume hospitals (also called "centralisation") has occurred within the English NHS via hub-and-spoke models.[138] The specialisation of oesophago-gastric cancer care in England coincided with a reduction in post-operative mortality from 7.4% to 2.5%, although this could not be explained by volume increases alone.[139]

A similar focus has been applied to the surgeon volume-outcome relationship. A US study using insurance claims data sought to evaluate the impact of surgeon volume on surgical mortality by evaluating cardiovascular procedures and cancer resections (not including CRC).[140] This study demonstrated that high surgeon volumes were associated with reduced mortality for all procedures examined. Again, evidence has accrued to suggest that high volume surgeons have improved outcomes for certain procedures.[141]

1.8.2 Volume-outcome relationship for rectal cancer surgery

The management of rectal cancer is challenging and continuing to evolve rapidly in complexity with MDT input required to make appropriate decisions about suitability for neo-adjuvant and adjuvant therapies, local excision, "watch-and-wait" strategies, surgical procedure, surgical approach, and avoidance or need for a temporary stoma (Chapter 1.4.4). Despite this, evidence for the specialisation of rectal cancer surgery remains conflicting, and the vast majority of English NHS trusts perform rectal cancer surgery.[142]

A recent review of available evidence was undertaken by NICE.[143] This review aimed to evaluate the volume-outcome relationship for hospitals and surgeons in the treatment of primary and recurrent rectal cancer. It included one systematic review containing nine publications and 19 other population-based studies. At hospital-level, studies were identified which showed a relationship between high volumes and improved outcomes including overall survival (three studies), peri-operative complications (one study), local recurrence (three studies), permanent stoma rate (three studies), and perioperative mortality (four studies) (Appendix 5).

At surgeon-level, studies were identified which showed a relationship between high volumes and improved outcomes including positive CRM rate (one low-quality study), overall survival (one study), peri-operative complications (two studies), local recurrence (one study), permanent stoma rate (one low-quality study), and peri-operative mortality (one study) (Appendix 6).

However, significant methodological limitations were present within the included studies. The main issues were the low quality of the individual studies and the fact that the results could not be pooled due to heterogeneity in the definitions of what constituted a high volume hospital or surgeon. Additionally, many of the studies used old data and predated the uptake of laparoscopic surgery, with significant heterogeneity in study populations (e.g., operations included), risk-adjustment methods, and outcomes examined.[143]

Overall, the NICE review suggested that there was some evidence for improved outcomes when the threshold for annual hospital volumes was set at 10-20. Similarly, there was some evidence for improved outcomes when the threshold for surgeon volumes was set at 5-10 rectal resections per year. However, the evidence was not deemed strong enough and therefore the current annual recommendations are 10 cases per hospital and five cases per surgeon.[41]

Two additional UK studies were not included in the NICE review because they included colon cancer.[77 144] Both studies presented analyses of hospital and surgeon volume as categorical variables. One study was limited by the inclusion of 17 hospitals in a single region. It demonstrated improved five-year overall survival with high hospital volume, and improved CRM rates, 18-month permanent stoma rate after anterior resection, and length of stay with high surgeon volume.[77] The other study used HES data for 109,621 elective CRC resections, finding an association for only length of stay with high volume hospitals and surgeons.[144] Limitations of this study included the use of old data (just 6.1% of patients had a laparoscopic procedure), lack of important risk-adjustment factors (i.e., staging), and analysis of CRC cases together.

1.8.3 Performance indicators for assessing the volume-outcome relationship

The NICE review of evidence suggested a series of critical performance indicators for evaluating the volume-outcome relationship. These were positive CRM rate, five-year overall survival, perioperative complication rate, and unplanned return to theatre rate. In addition, there was a series of important performance indicators suggested including local recurrence rate, quality of life, permanent stoma rate, and perioperative mortality rate.[143]

1.8.4 Research gap identified

Volume-outcome relationship for rectal cancer surgery

There is a need to evaluate the volume-outcome relationship for rectal cancer surgery at hospital- and surgeon-level within the English NHS for those performance indicators identified by NICE which can be measured using routinely collected data.

In addition, it is important to attempt to overcome prior methodological limitations by modelling volume as a continuous variable rather than using arbitrary categories, using contemporary national data to ensure it is reflective of current practice, and undertaking comprehensive risk-adjustment. This evidence will be important to help further inform the debate on the specialisation of rectal cancer surgery within the English NHS.

2. AIMS AND OBJECTIVES

2.1 Summary of research gaps identified

The research gaps identified are summarised to make it explicit which areas the remainder of this thesis will address (Table 2.1).

2.2 Aims

The broad aims of the studies presented within this thesis are two-fold. Firstly, to undertake methodological development in order to validate information contained within multiple linked datasets, and develop appropriate performance indicators to support the high-quality national reporting of care processes and outcomes for the multimodal treatment of CRC in the English NHS. Secondly, to utilise this work to explore variation in the multimodal treatment and outcomes of CRC patients, and possible reasons for this, in two important clinical areas: (i) the use of SACT, and (ii) the volume-outcome relationship for rectal cancer surgery.

For the SACT work, there are two methodological papers which will facilitate the robust capture of chemotherapy information and the identification of severe acute toxicity following SACT, using routinely collected data. This work will be applied in three observational studies exploring the use and outcomes of SACT. For the rectal volume-outcome work, underlying methodological work will aim to improve the accuracy of the reporting of hospital and surgeon volumes, validate surgeon-level information across multiple data sources, and identify and develop appropriate performance indicators. The final observational study will then use this work to explore the rectal cancer surgery volume-outcome relationship.

2.3 Objectives

This thesis aims to address the following research questions where gaps have been identified in the current literature:

2.3.1 Methodological

1. How can we best capture receipt, regimens, and numbers of cycles of adjuvant chemotherapy for stage III colon cancer using linked routinely collected data?
2. Can a valid coding framework be developed for the capture of severe acute toxicity from SACT using routinely collected data?

Table 2.1 – Summary of research gaps to be addressed

Chapter	Research gap
1.2	• Lack of studies using SACT dataset and no prior studies in CRC patients. • No previous validation of chemotherapy information from SACT dataset in CRC patients. • Lack of bespoke chemotherapy information within HES-APC. • No studies describing how to interpret chemotherapy information from SACT and HES-APC datasets in a clinically accurate and meaningful way.
1.4	• No observational studies evaluating use of adjuvant chemotherapy for stage III colon cancer in the English NHS. • Limited understanding of determinants of unwarranted variation in adjuvant chemotherapy use.
1.4	• Lack of good quality observational studies evaluating the impact of completion of adjuvant chemotherapy on survival in stage III colon cancer patients in "real-world" practice. • No observational studies evaluating the impact of treatment modifications on survival in "real-world" practice.
1.6	• Lack of broad and comprehensive coding framework for identifying severe acute toxicities from SACT in routinely collected data.
1.7	• Limited national reporting and monitoring of SACT performance indicators, particularly for outcome measures.
1.8	• Lack of high-quality, contemporary observational studies evaluating the volume-outcome relationship for rectal cancer surgery at hospital- and surgeon-level in the English NHS.

2.3.2 Variation in the multimodal treatment and outcomes of CRC patients

Use and outcomes of SACT

3. What are the determinants of variation in the use of adjuvant chemotherapy for stage III colon cancer in the English NHS?
4. What is the impact of adjuvant chemotherapy completion on "real-world" survival outcomes of patients with stage III colon cancer?
5. Does the coding framework for identifying severe acute toxicity have the potential to be used as a performance indicator to stimulate quality improvement within a national audit setting?

Volume-outcome relationship for rectal cancer surgery

6. What are the impacts of hospital- and surgeon-level volumes on outcomes in rectal cancer surgery?

3. RESEARCH DESIGN

3.1 Data sources

The following provides further details regarding the national healthcare datasets, linked at patient-level, which are used throughout the thesis.

3.1.1 The National Bowel Cancer Audit (NBOCA)

The NBOCA is a well-established audit commissioned by the Healthcare Quality Improvement Partnership (HQIP) on behalf of NHS England and the Welsh government. The contract for the audit is held by the Clinical Effectiveness Unit (affiliated with the London School of Hygiene and Tropical Medicine) which is based at the Royal College of Surgeons of England. Project management and infrastructure is provided by NHS Digital.

Regular clinical input is provided to the audit by a consultant colorectal surgeon and consultant medical oncologist who form part of the NBOCA Project Team. There is biannual input from an extensive multidisciplinary clinical advisory group including expert individuals from radiology, pathology, palliative care medicine, CRC charities, and commissioning services. In addition, regular feedback on audit outputs is sought from the Patient and Carer Panel.

The data consists of one row of information per patient (Appendix 1). This includes 5-digit provider codes which allow the identification of individual English NHS hospital sites within hospital trusts.

The NBOCA case ascertainment is above 95% when compared to HES-APC and the National Cancer Registration and Analysis Service (NCRAS).[38] Previous work which aimed to better understand the differences in the capture of cases between NBOCA and NCRAS showed that patients that tended to not be captured by NBOCA were those with limited secondary care contact. This includes patients with advanced disease, those having an emergency presentation, and those dying very quickly after diagnosis.[145]

Data completeness for most longstanding data items is very good. For example, there is approximately 90% data completeness for age, sex, American Society of Anesthesiologists (ASA) grade, pathological TNM staging, and site of cancer for patients undergoing major resection. Newer data items are less well completed. For example, in patients undergoing major surgery for rectal cancer, CRM status is missing in approximately 25% of patients, although improving over time.

In 2019, I led an organisational survey of all English NHS hospitals providing CRC care through the NBOCA.[146] The survey provided the location and availability of specific facets of CRC care, for example, diagnostic facilities, oncological services, and advanced disease services. It is usually repeated on an annual basis to

reflect changing service organisation. However, due to the impact of the COVID-19 pandemic on hospital staff resources, the survey was paused in 2020. The survey results provide additional hospital-level information for analyses within this thesis.

3.1.2 Systemic Anti-Cancer Therapy (SACT) dataset

The SACT dataset is collected and curated by NCRAS and is the first comprehensive, dedicated chemotherapy dataset in the world. The SACT dataset was introduced in April 2012 and data submission became mandatory for all English NHS providers of chemotherapy in any inpatient, day case, outpatient, or community setting from April 2014.[147] However, this was not achieved by all providers until July 2014.[148]

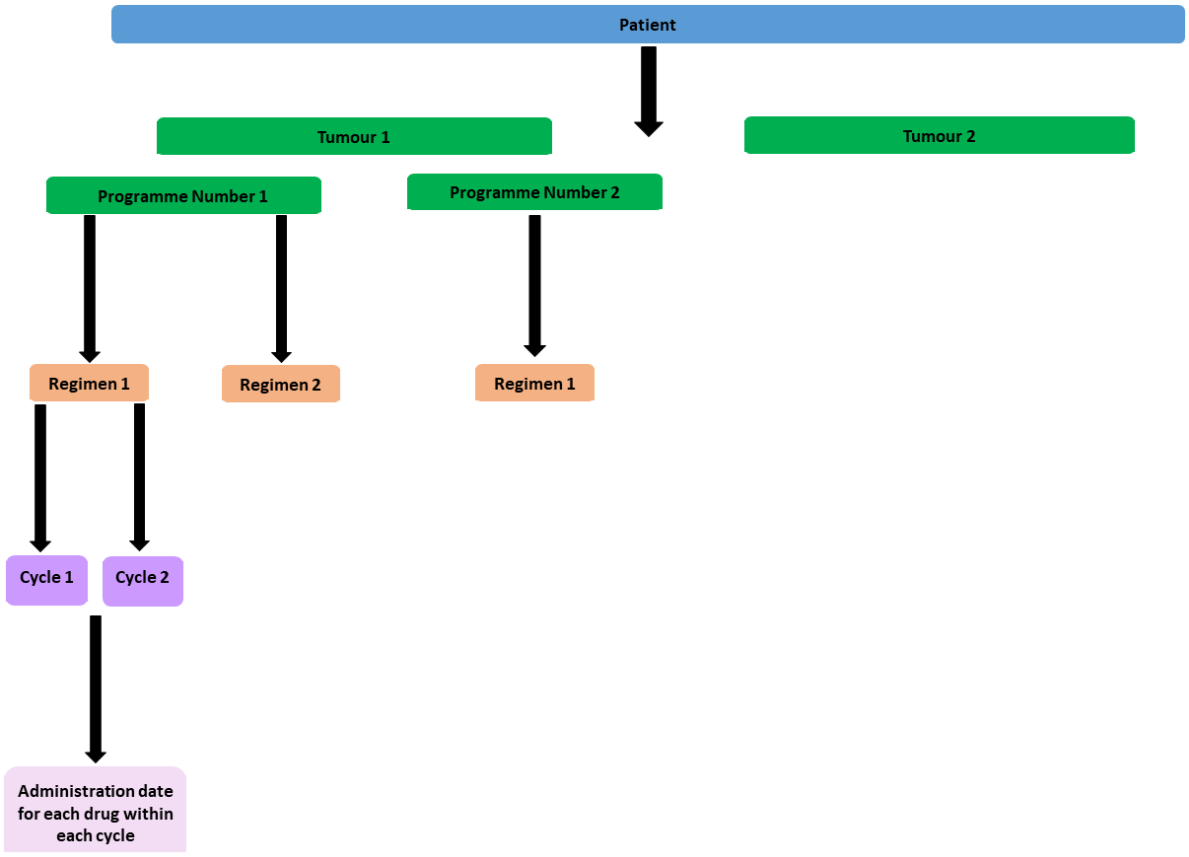
The SACT dataset is only available within England, restricting all studies to patients diagnosed and treated within the English NHS. Generally, only 3-digit provider codes are available meaning that hospital trusts rather than individual hospital sites can be identified.

Most data is collected via electronic prescribing systems which generate a SACT data extract in a standard format which can then be uploaded on a monthly basis to a secure portal by a responsible individual. Hospitals without electronic prescribing systems use either Patient Administration Systems (PAS) or manual systems to produce their data extracts. Data extracts are subject to validation checks prior to their successful upload and a summary report is generated to allow users to check the data before submission.[148]

The SACT data itself consists of a complex hierarchical structure (Figure 3.1).[147] Chemotherapy data is inherently complex as patients may stop and start treatment over many years. The programme number refers to each progressive 'line of treatment' for the overall treatment of a particular tumour. If the intent of treatment changes, for example, moving from curative to palliative chemotherapy, a new programme number should be assigned. A programme may consist of one or more chemotherapy regimens. A regimen can include single or multiple drugs. Each regimen can consist of an indefinite number of cycles. For each cycle, the individual drugs administered within that cycle are listed along with administration details. As a consequence of this structure, SACT contains multiple rows per patient with one row of data per drug administered.

As mentioned earlier, there has been limited use of SACT data within the literature. A data resource profile released by NCRAS reported that "data quality is thought to be sufficient for most purposes from 2013".[148] This work also evaluated each data item and highlighted those for which caution should be excised in their use due to issues with data quality. This included data items for ethnicity, primary diagnosis, morphology, TNM staging, programme number, regimen number, clinical trial indicator, chemo-radiation indicator, and final treatment date.

Figure 3.1 – SACT data structure



In terms of data completeness, data items with <90% completeness for lower GI cancers were highlighted as being morphology, TNM staging, performance status, comorbidity indicator, date of final treatment, and regimen outcome summary.[148] TNM staging, performance status, and comorbidity information are available from the other linked datasets.

3.1.3 Hospital Episode Statistics Admitted Patient Care (HES-APC)

Within this thesis, the purpose of HES-APC is threefold. First, it provides information on multiple hospital admissions over time for patients with a diagnosis of CRC. This includes more detailed information about diagnoses and management, and provides a more complete picture of each patient's CRC care experience. Due to this additional information over time, further measures can be derived including the Royal College of Surgeon's (RCS) Charlson comorbidity score[149], length of stay, unplanned readmission, unplanned return to theatre, and stoma reversal. The coding of diagnoses also allows the identification of severe acute toxicities from SACT.

Second, HES-APC provides an additional data source for the validation of information within other datasets. Specifically, this is important for the validation of chemotherapy information within the SACT dataset, as well as the validation of surgeon-level information for the rectal cancer volume work.

Finally, HES-APC is used to improve procedural case ascertainment for the rectal cancer volume-outcome work, and data completeness when information is missing from other data sources, for example, sex, the Index of Multiple Deprivation Quintile (IMDQ), and surgical access.[3] Also, 5-digit provider codes are available which allow the identification of individual hospital sites within hospital trusts.

3.1.4 National Radiotherapy Dataset (RTDS)

Within this thesis, RTDS data is only used in the rectal volume-outcome work (Chapter 9) to determine whether patients undergoing major resection for rectal cancer received neo-adjuvant radiotherapy, and whether this was SCRT or LCCRT. The type of radiotherapy administered is determined based on the fractions administered and the number of attendances to the radiotherapy unit. This uses pre-existing NBOCA methodology based on previously published work on the RTDS dataset in CRC patients.[150]

3.1.5 Office for National Statistics (ONS)

Mortality data is obtained from official death certificates, with the underlying cause of death identified as the primary cause listed on this legal document. This is defined as "the disease or injury which initiated the train of morbid events leading directly to death…". ONS data enables the calculation of 90-day mortality, cancer-specific mortality, and all-cause mortality rates.[15]

CRC-specific mortality is defined as death with bowel cancer or cancer of an unspecified site as the underlying cause of death within the specified timeframe. The ONS data includes ICD-10 codes for the underlying cause of death. Any ICD-10 codes relating to bowel cancer, metastatic disease, or cancer of an unspecified site were deemed to be CRC-related deaths. All other deaths, including cancer of a different site, were deemed to be non-cancer deaths.

3.1.6 General Medical Council (GMC)

GMC records are linked via the GMC numbers recorded in both the NBOCA and HES-APC datasets. Linkage to the GMC dataset is used to provide additional surgeon-level information and enable the validation of GMC numbers recorded in NBOCA and HES-APC (Chapter 3.4.3).

3.2 Data linkage and flow

The NBOCA dataset is linked at patient-level to the other national datasets described in Chapter 3.1. The NBOCA data submitted by English NHS hospitals via the CAP system is handled by the Clinical Audit & Registries Management Service (CARMS) at NHS Digital. This data contains identifiable information including NHS number, date of birth, sex, and postcode. CARMS extract this data and assign a tumour ID which serves as a unique identifier. The NBOCA identifiers act as the spine for data linkage.

The Data Access Request Service (DARS) team at NHS Digital processes the data linkage for HES-APC and ONS using a deterministic approach based on the following patient identifiers: NHS number, gender, date of birth, and postcode. For SACT and RTDS, NHS Digital send the following identifiers to NCRAS who then process the data linkage: NHS number, date of birth, postcode, and NBOCA tumour ID. All patient identifiable information (apart from date of death) is removed from the linked datasets so that only a tumour ID remains. NHS Digital are responsible for sending the NBOCA data and all of the linked datasets using the Secure File Transfer Accounts system to the CEU at the RCS. At the CEU, the pseudonymised datasets are stored on a restricted access folder on a secure server.

The linkage rate for NBOCA to HES-APC is above 95% for patients undergoing major resection.[38] For HES-APC, data is also received for CRC patients who don't link to NBOCA ("unlinked HES-APC"). The unlinked HES-APC is used to improve case ascertainment for the rectal cancer volume-outcome work (Chapter 9).

For SACT, patients identified within NBOCA and sent to NCRAS by NHS Digital are linked if there is a corresponding SACT record paired with a CRC diagnosis within the specified diagnostic timeframe. There is an NBOCA data item for "post-operative treatment modality" for which chemotherapy is an option. For patients identified as undergoing a major resection for stage III colon cancer and having chemotherapy according to this NBOCA data item, 80% have a linked SACT record and this increases to 90% with the use of HES-APC.
In addition, a report comparing SACT to Cancer Waiting Times data suggested that 91% of patients reported to have received chemotherapy for lower GI cancer in Cancer Waiting Times were identified within SACT.[151] Case ascertainment has also been found to be higher in SACT compared to HES inpatient and outpatient data.[148]

3.3 Data preparation and management

All data preparation and analyses were conducted in Stata version 15. General steps involved for the use of each dataset included the cleaning and labelling of all variables, sense-checking the data, and evaluating the data quality and completeness for each variable required within every analysis.

The NBOCA, HES-APC, RTDS, and ONS datasets used throughout this thesis already existed as data files within Stata but still required preparation and cleaning, with relevant information captured across multiple records per patient in most of the datasets. Data on the same patient had to be merged across datasets to capture the complete care pathway, including diagnostic and multimodal treatments taking place across multiple hospital visits, complications of treatment (including severe acute toxicities), and later patient outcomes (e.g., death).

The SACT and GMC data were both received as raw data in comma-separated values (CSV) files which I inputted myself into Stata. I was responsible for the general preparation of the data in order to get it into a suitable format for analyses as described above. These data were merged with the NBOCA data (and subsequently any additional data) and data quality checks undertaken (e.g., checking the distribution of data over time).

As mentioned previously, the SACT dataset contains one row of information for each drug administered. Prior to undertaking any analyses this meant that I needed to extract all the relevant information from each record of drug administration. This also required clinical knowledge and interpretation of the data. For example, when patients are administered a SACT drug called 5-fluoropyrimidine, they are given two separate doses: a loading and maintenance dose. It was important to be aware of this when calculating how many cycles of adjuvant chemotherapy each patient was given to avoid over-estimating cycle numbers. In addition, a combined understanding of the data and clinical interpretation were required to inform the development of the various clinical algorithms (Chapter 3.5).

Finally, I was responsible for restricting each of the datasets to suitable patient cohorts for each analysis, and undertaking individual analyses myself. This required the derivation of additional variables and further manipulation of the data with complex statistical coding and modelling (Chapters 3.5, 3.6 and 3.7).

3.4 Study design

This section provides a brief overview of the design of each study. The thesis consists of six observational studies which are presented in the form of peer-reviewed research papers (Figure 3.2).

3.4.1 Methodological

Identification and validation of SACT usage and completion in routinely collected data

The research study relating to Objective 1 is methodological and involves the validation of chemotherapy information derived from SACT and HES-APC. This includes a series of coding and validation steps which are described in further detail in Chapter 3.5.

Briefly, this work involves using forwards and backwards coding strategies (Chapter 3.5.1) to develop a coding framework to identify chemotherapy information (including regimens) from HES-APC, and then develop a clinical algorithm (Chapter 3.5.2) to identify adjuvant chemotherapy specifically. Validation of chemotherapy information between HES-APC and SACT is then undertaken (Chapter 3.5.3) and the results of this analysis are published in a peer-reviewed paper which forms Chapter 4.

Measuring severe acute toxicity following SACT in routinely collected data

The research study relating to Objective 2 is also methodological and similarly involves using forwards and backwards coding strategies (Chapter 3.5.1). This time a comprehensive coding framework is developed in order to capture severe acute toxicity from SACT using diagnostic information in HES-APC. Validation of this coding framework is undertaken (Chapter 3.4.3) and the results of this are published in a peer-reviewed paper which forms Chapter 5.

3.4.2 Variation in the multimodal treatment and outcomes of CRC patients

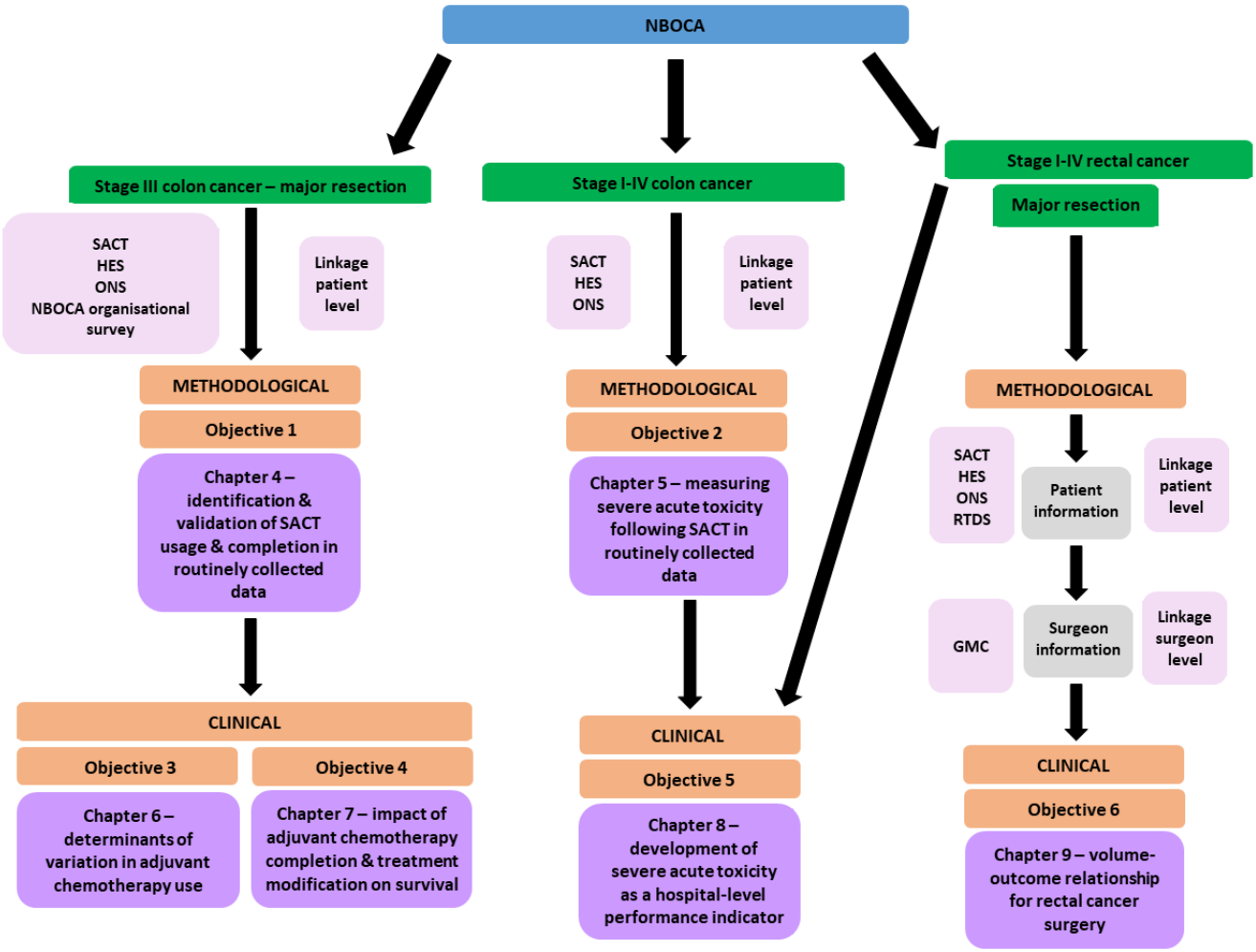
Use and outcomes of SACT

The research studies relating to Objectives 3 and 4 use the methodological work undertaken for Objective 1 to address gaps identified in clinical research. All of the analyses conducted using SACT data allocate patients to hospital trusts (Chapter 3.1).

Determinants of variation in adjuvant chemotherapy use

This research study relates to Objective 3 and includes establishing current national practice in the English NHS for the use of adjuvant chemotherapy for stage III colon cancer. In addition, the exploration of determinants for adjuvant chemotherapy use according to patient, clinical, and hospital characteristics is undertaken using multilevel multivariable logistic regression modelling. Finally, this work establishes the extent of between-hospital variation in adjuvant chemotherapy use and investigates possible reasons for this. In order to do this,

Figure 3.2 – Flowchart of objectives, studies and data sources



funnel plot methodology and intra-class correlation coefficients (ICC) are used (Chapter 3.7.1). The results of this analysis are published in a peer-reviewed paper which forms Chapter 6.

Impact of adjuvant chemotherapy completion and treatment modification on survival
This research study relates to Objective 4 and includes assessing the impact of the completion of oxaliplatin-based adjuvant chemotherapy (FOLFOX or CAPOX) on cancer-specific mortality for stage III colon cancer patients.

This is the largest observational study to date and involves using competing risk regression models to estimate subdistribution hazard ratios (SHRs) for the risk of death between levels of completion (<50%, 50-92%, and 100%) for each regimen, adjusting for patient, clinical, and hospital characteristics. In addition, the effects of treatment modifications (dose reduction and early discontinuation of oxaliplatin) on those patients completing 100% of their treatment are analysed. The results of this analysis are published in a peer-reviewed paper which forms Chapter 7.

Development of severe acute toxicity as a hospital-level performance indicator
This research study relates to Objective 5 and uses the methodological work undertaken in Objective 2 to develop the coding framework for severe acute toxicity into a national hospital-level performance indicator.

Development includes evaluating the statistical power of the performance indicator and ensuring "fairness" by making sure that adequate risk-adjustment is feasible. For the risk-adjustment, case-mix factors are identified from the literature and using clinical expertise. The data quality and completeness of case-mix factors within the available routinely collected data are also checked. The goodness of fit of the risk-adjustment model are assessed using the C-statistic for discrimination and the Hosmer-Lemeshow test for calibration. Finally, the extent of between-hospital variation in severe acute toxicity rates are evaluated using funnel plot methodology in adjuvant and metastatic CRC patients.

The implications of publicly reporting this performance indicator are explored by evaluating the number of potentially outlying hospitals. In addition, a conceptual framework is generated using the literature and clinical expertise to begin to identify points along the SACT care pathway which might be targeted to drive quality improvement initiatives. The results of this analysis are presented in the form of a research paper which has been submitted for peer-reviewed publication and forms Chapter 8.

Volume-outcome relationship for rectal cancer surgery

The final research study relates to Objective 6 and involves the exploration of the volume-outcome relationship for rectal cancer surgery. This chapter utilises the methodological themes common to the thesis with the validation of surgeon-level information using multiple linked national datasets (Chapter 3.5.3), and

the identification and development of rectal cancer performance indicators from the available routinely collected data to evaluate the volume-outcome relationship (Chapter 3.6).

Mean annual hospital site (using 5-digit codes available in NBOCA and HES-APC) and surgeon volumes are calculated for rectal cancer surgery using HES-APC to increase case ascertainment. Volume is modelled as a continuous variable with a linear plus quadratic relationship for each outcome. Extensive risk-adjustment for patient and clinical factors is undertaken. A random intercept at hospital- or surgeon-level is used to account for clustering.

Outcomes include 90-day mortality, 30-day unplanned readmission, unplanned return to theatre, stoma at 18 months following anterior resection, positive CRM, length of stay, and 2-year all-cause mortality rate (Appendix 7). The results of this analysis are presented in the form of a research paper which will be submitted for peer-reviewed publication and forms Chapter 9.

3.5 Coding and validation strategies

A number of coding and validation strategies are used throughout this thesis to aid the robust interpretation of the routinely collected data available and will now be described in more detail. Figure 3.3 is a schematic diagram of how each of these strategies link together for the SACT work.

3.5.1 Development of coding frameworks

Coding frameworks

Drug-level chemotherapy information is readily available within the SACT dataset. In contrast, HES-APC does not contain bespoke chemotherapy information. Instead, chemotherapy use is identified from HES-APC using a coding framework containing OPCS-4 and ICD-10 codes ascertained through the "forwards" and "backwards" code-searching strategies described below. Novel methodology is then used to assign adjuvant chemotherapy regimens within HES-APC using these codes in relation to the National Tariff Chemotherapy Regimens List, a coding guide for chemotherapy for financial reimbursement (Figure 3.3).[13]

Similarly, information regarding toxicities for patients receiving SACT is not directly available in any data source. Within SACT, there is a data item called "regimen outcome summary" and responses can be selected from disease progression, toxicity, death, patient choice, or other. However, this data item is poorly completed and does not give any indication of the type or severity of toxicity experienced, making it somewhat subjective for the clinician entering the information. In Chapter 5, severe acute toxicities are identified from HES-APC using a coding framework of ICD-10 codes also ascertained through the "forwards" and "backwards" code-searching strategies described below (Figure 3.3).

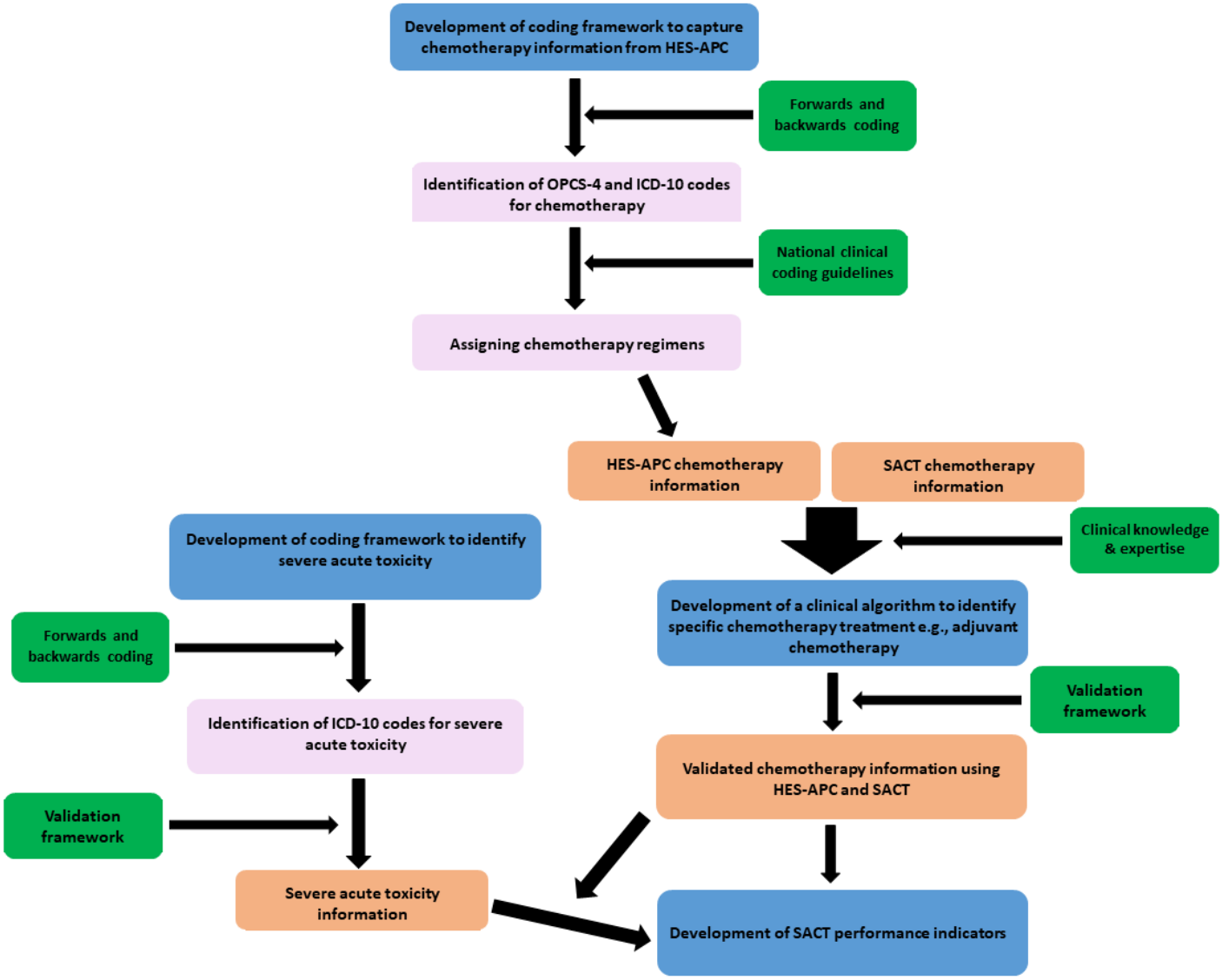
Code-searching strategies

"Forwards" and "backwards" code-searching strategies are used to ensure that all relevant diagnostic and/or procedural codes within HES-APC are included to identify a particular treatment (e.g., chemotherapy use in Chapter 4), or define a particular outcome measure (e.g., severe acute toxicity in Chapter 5) (Figure 3.3).

"Forwards" code-searching involves identifying a priori a list of the ICD-10 or OPCS-4 codes for a particular treatment or outcome measure, which may be found in the literature and/or from expert clinical consensus. "Backwards" code-searching involves identifying a cohort of patients in whom you would expect the treatment or outcome measure to be common, and exploring their diagnostic and procedural fields within HES-APC for any additional relevant codes. This helps to capture any codes that may have been missed due to idiosyncrasies in coding practice that are otherwise easy to miss. Expert consensus is also obtained for any codes identified via this method.

"Forwards" and "backwards" code-searching strategies have been successfully validated and employed previously by colleagues to identify severe urinary complications in patients who have undergone

Figure 3.3 – Schematic diagram showing different coding and validation strategies for SACT work



prostatectomy, and to identify skeletal-related events in men with prostate cancer.[20 21]

3.5.2 Development of clinical algorithms

Once chemotherapy information has been established within HES-APC, it is necessary to develop clinical algorithms to enable the appropriate interpretation of this information for individual patients. In Chapter 4, oncology expertise is used to develop a clinical algorithm which ensures that only chemotherapy likely to represent an individual's adjuvant chemotherapy is captured. For example, chemotherapy has to be started within 4 months of the date of surgery for a colon cancer resection, and patients starting non-standard adjuvant chemotherapy regimens are assumed to have had disease progression and be receiving treatment for metastatic disease. The final clinical algorithm is applied to both the SACT and HES-APC datasets.

Rectal cancer patients receive the same adjuvant chemotherapy regimens. Following the validation in colon cancer patients, the clinical algorithm is therefore transferable to stage III rectal cancer patients in Chapter 8. A clinical algorithm is also developed to identify the appropriate chemotherapy treatments for stage IV CRC patients in Chapters 5 and 8 (Appendix 8).

3.5.3 Validation frameworks

Adjuvant chemotherapy

In Chapter 4, the validation of chemotherapy information established in SACT and HES-APC is undertaken using a four-step framework. First, agreement for adjuvant chemotherapy use is compared between the data sources. Second, agreement for regimen and cycle number are compared between the data sources. Third, clinical characteristics are compared for patients captured in SACT alone, HES alone, and both data sources to identify potential bias from using each dataset in isolation. Lastly, the sensitivity of the findings are evaluated by comparing CRC-specific mortality for patients receiving and not receiving adjuvant chemotherapy between the data sources.

Severe acute toxicity

Validation of the coding framework for severe acute toxicity involves a three-step framework. The rationale is to ascertain that the capture of severe acute toxicity using the coding framework is valid by firstly comparing rates across different clinical groups (no chemotherapy, chemotherapy in the adjuvant setting, and chemotherapy in the metastatic setting), and secondly comparing toxicity profiles (as would be expected from RCTs) across different regimens. In particular, the ability to capture unique toxicities (e.g., electrolyte disturbance for bevacizumab) is examined. Third, clinical factors expected to predict severe acute toxicity (e.g., cardiac and renal disease), and factors expected to be influenced by severe acute toxicity (e.g., completion of chemotherapy) are evaluated. Patterns of toxicity are shown to be similar for rectal cancer patients (Appendix 9).

Surgeon-level information

Since the publication of the Francis report [152], both NBOCA and HES-APC contain information regarding the consultant surgeon responsible for a patient's care. However, the accuracy of this information is not known and is therefore validated by comparing information between the two data sources.

For records where there is a discrepancy between NBOCA and HES-APC, the information recorded in NBOCA is deemed to be the more accurate source of information. This is because data reported to NBOCA is used to publicly report individual surgeon outcomes as part of the Clinical Outcomes Publication. Surgeons are therefore encouraged to carefully check data recorded under their name.[123]

A further validation step is to use the linked GMC information to ensure that recorded GMC numbers correspond to a doctor with General Surgery registered as their speciality. In cases where the GMC number is not a general surgeon in one of the data sources, the data source where it does correspond to a general surgeon is assumed to be correct. If neither record contains a GMC number relating to a general surgeon, the patient is excluded from surgeon-level analyses.[153]

3.6 Performance indicators

The strategies described so far provide the methodological groundwork for helping to develop a number of national hospital-level performance indicators.

Use and outcomes of SACT

The methodological work conducted in Chapter 4 is used to develop a performance indicator for capturing adjuvant chemotherapy use (process measure) in stage III colon cancer patients in a robust way using both SACT and HES-APC data.

The methodological work conducted in Chapter 5 is used to develop a performance indicator for severe acute toxicity following SACT (outcome measure). Chapter 8 demonstrates further development work to ensure adequate statistical power and fair risk-adjustment, as well as assessing the extent of between-hospital variation in toxicity rates.

Volume-outcome relationship for rectal cancer surgery

Unlinked HES-APC is used to increase the case ascertainment for reporting rectal surgery volumes.[153] This methodological work is used to develop a performance indicator for annual hospital rectal cancer surgery volumes (process measure).

In Chapter 9, the vast majority of performance indicators used have been validated previously and are already regularly reported by the NBOCA (Appendix 7). For the first time in the 2020 NBOCA annual report, two separate stoma performance indicators were developed. The first captured the permanent stoma rate at the time of initial procedure (e.g., patient undergoes APR, Hartmann's or pelvic exenteration), and the second captured the 18-month unclosed diverting ileostomy rate for anterior resections.[30]

Within this thesis, further development work is undertaken to refine the latter performance indicator. This includes adjusting the timeframe in which the stoma was identified, relative to the primary surgery, in order to ascertain whether the stoma was likely to be planned (as part of the original operation) or unplanned (the result of a complication). An adapted performance indicator is then defined for all patients undergoing anterior resection who had any type of stoma remaining at 18 months, in order to capture both planned and unplanned stoma formation.

3.7 Statistical methods

The statistical methods for each study are outlined in more detail within each research paper. This section highlights the overarching methods which are used frequently throughout the thesis.

3.7.1 Multivariable modelling of clustered data

The work within this thesis largely uses multi-level multivariable logistic regression modelling because the vast majority of outcomes are binary. Associations estimated in logistic regression models can be interpreted in the form of odds ratios (ORs). The OR represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure. Multi-level multivariable logistic regression modelling is used to describe the associations between patient, clinical, and hospital characteristics, and binary outcomes such as receipt of adjuvant chemotherapy and severe acute toxicity. Multivariable modelling allows independent risk factors to be identified and adjustment for multiple confounders at the same time.

In terms of covariates, hospital and surgeon volumes are modelled as continuous variables in Chapter 9. This is performed by using a linear plus quadratic term for volume. One advantage of this is the increase in statistical power compared to categorisation which leads to a loss of information with the pooling of volumes that might have different risks. Categorisation can lead to bias and significantly different results dependent on where the cut-offs are applied. It also inhibits the pooling or comparison of results between different studies if category definitions vary. The adequacy of a linear plus quadratic relationship between volume and each binary outcome is assessed by superimposing the fitted line onto a graph of the predicted outcome with 95% confidence intervals, in six equally sized categories of volume. The only risk factor which is a continuous variable is age and this is modelled as a categorical variable throughout the thesis for risk-adjustment purposes.

With multivariable modelling, the outcomes within the same hospital or surgeon are likely to be correlated and this is termed “clustering”. With clustered data, estimated standard errors in a conventional regression model are smaller than actual standard errors due to a failure to account for the correlation of responses among observations within the same cluster. This underestimation of standard errors subsequently increases the likelihood of a Type 1 error.[154]

There are two main ways to deal with the underestimation of standard errors within a multilevel multivariable model. First, robust standard errors can be used. This approach only affects the standard error estimates. Second, multi-level models with a random intercept for hospital or surgeon can be used. This will affect the effect estimates (ORs) as well as the standard error estimates.

A benefit of using multi-level multivariable models is that they also enable ICCs to be determined. The ICC quantifies the between-hospital or between-surgeon variation and represents the proportion of the total variance that is between hospitals or surgeons, despite adjustment for all other determinants, with larger values showing greater between-hospital or between-surgeon variation. ICCs are used in Chapter 6 to evaluate possible reasons for between-hospital variation in adjuvant chemotherapy use including age, comorbidity, performance status, and socioeconomic status. Each of the risk factors are stratified (e.g., young versus elderly) and ICCs compared between the strata.

It is particularly important to deal with the clustering of hospitals when hospital-level factors are included in the model. For example, when evaluating the determinants of adjuvant chemotherapy receipt in Chapter 6 and survival according to adjuvant chemotherapy completion in Chapter 7. Similarly, it is important to deal with clustering at surgeon-level when modelling surgeon-level factors such as in the rectal cancer surgery volume-outcome work in Chapter 9.

In Chapter 9, Poisson regression models are used to evaluate the association between hospital and surgeon volumes, and 2-year all-cause mortality rate. Poisson regression models are used to model time-to-event outcomes and associations are interpreted as rate ratios. Rate refers to the numbers of events per unit time. The model therefore takes into account how quickly each patient dies.

Unlike Cox regression models, an assumption of Poisson regression models is that the baseline rate is constant over time. For the analysis in Chapter 9, an advantage of using the Poisson regression model over the Cox regression model is that it is fully parametric and therefore simpler to predict rates by levels of covariates (e.g., hospital and surgeon volumes).

3.7.2 Competing risks analysis

Competing risk analysis is used in Chapter 4 and Chapter 7 to calculate CRC-specific mortality with other causes of death as the competing risk. For example, where the primary outcome is death from CRC but the patient dies from pneumonia, they are then no longer at risk of death from CRC.

The purpose of competing risk analysis is to try to minimise the overestimation of the risk of the outcome of interest if patients were censored after dying of the competing risk. ONS mortality data identifies the underlying cause of death and is used to conduct each competing risk analysis (Chapter 3.6.2). Fine and Gray competing risk regression models are used to estimate adjusted SHRs, adjusting for the relevant patient, clinical, and hospital characteristics.[155]

3.7.3 Funnel plot methodology

Funnel plot methodology is used to compare individual hospital rates of adjuvant chemotherapy use in Chapter 6 and rates of severe acute toxicity in Chapter 8.[156] Funnel plots allow the evaluation of whether the

rate of a particular outcome within an individual hospital varies significantly from the average rate in all patients in the analysis, assuming that the rate is influenced only by random errors.

The rate for each hospital is plotted against the total number of patients used to estimate the rate. The 'target' is the national average. The funnel limits depend on both the target and number of patients included in the estimate. Hospitals fall outside the inner limits if they are statistically significantly different from the target at a 0.05 level and outer limits if they are different from the target at a 0.002 level. If all hospitals were performing according to the target, 95% would be expected to lie within the inner limits and 98% within the outer limits, assuming differences arise from random errors alone.

Adjusted funnel plots are used to account for case-mix differences. The adjusted outcomes are estimated using indirect standardisation.[157] The observed number of events for a hospital are divided by the expected number on the basis of the multivariable regression model. The adjusted rates are then estimated by multiplying this ratio by the average rate in all patients included.

3.7.4 Handling missing data

The inadequate handling of missing data in a statistical analysis can lead to biased or inefficient estimates. Data can be: (i) missing completely at random, (ii) missing at random, or (iii) missing not at random. Throughout this thesis, missing data for determinants has been assumed to be missing at random, meaning that missing values occur at random conditional on other determinants and outcomes.

Based on these assumptions, the method for handling missing data which is used is multiple imputation using chained equations.[158] Essentially, this method uses the distribution of the observed data to estimate a set of plausible values for those that are missing. This is done by using a patient's other risk factors to help predict information that is missing, whilst taking into account the uncertainty due to their missing data. For example, patients who have emergency surgery are more likely to have advanced disease and undergo an open surgical procedure.

The imputation method includes logistic regression for binary variables and multinomial regression for categorical variables with more than two categories. The imputation procedure includes all variables used in risk-adjustment, as well as the outcomes of interest, to predict missing values. Based on the recommendation that at least as many imputed datasets as the percentage of incomplete cases should be used, ten imputed datasets are used for the majority of analyses.[158] Estimates from each imputed dataset are combined using Rubin's rules.[159]

For each chapter within the thesis, multiple imputation is used to determine missing values for factors used in risk-adjustment. The overall mean proportion of missing data for each variable used for risk-adjustment is summarised in Appendix 10. The variables with the least complete data in all patients are pre-treatment T-

stage (18%) and performance status (17% missing). Chapters 4, 6, 7 and 9 include only patients undergoing major surgical resection. Data completeness is improved within surgical patients with the least complete data being performance status (14%) and pathological M-stage (10%). Appendix 11 summarises data completeness at patient-level.

The advantages of using imputation techniques is that they have the potential to increase statistical power compared to complete case analysis in which all patients with missing data on any variable are excluded. In addition, it helps to reduce the bias that may occur if the cases excluded due to missing data are systematically different from those without missing data. For all analyses, only patients with complete information for outcome measures are included.

3.8 Ethics

This research has been carried out under the NBOCA data permissions through my role as the NBOCA Clinical Fellow. NBOCA has existing approvals in place for collecting healthcare information under Section 251 (reference number: CAG ECC 1-3(d)/2012) for all patients diagnosed with CRC in England and Wales. Work conducted within this thesis falls under the remit of the audit work and is therefore covered by these pre-existing approvals. I only had access to fully anonymised patient-level data meaning that individual patients were not identifiable. NBOCA has approval for the processing of data under articles 6(1)(e) and 9(2)(i) of the General Data Protection Regulation (GDPR).

This research was therefore exempt from UK National Research Ethics Committee approval. However, as part of the upgrade process, my research plans were reviewed by the London School of Hygiene and Tropical Medicine's Research Ethics Committee. Ethics approval was granted on 4th September 2019, approval number 15712 (Appendix 12).

3.9 Patient and public involvement

The NBOCA clinical advisory group has representation from CRC charities (Bowel Cancer UK) and patients. In addition, I co-led the more recent establishment of a dedicated Patient and Carer Panel which has been set up with the specific intention of increasing the involvement of patients and the public in the audit's work and outputs.

This research has been subject to input from patients to ensure that the work is relevant to their needs. For example, patients have highlighted the importance of understanding the patient experience beyond surgical outcomes and survival, supporting the focus on severe acute toxicity from SACT as an outcome measure. In addition, patient input has been particularly important with regards to the interpretation and dissemination of results for patients and the public.

3.10 Additional outputs

Through my role as the NBOCA Clinical Fellow I have been involved in additional work which has not always contributed directly to this thesis, but has given me the opportunity to enhance and broaden my research skills and improve my understanding of important areas for health services research for CRC patients. The following sections list additional research papers, national reports, and presentations that I have significantly contributed to during the course of my research.

3.10.1 Additional peer-reviewed publications

- Boyle JM, Kuryba A, Blake H et al. The impact of the first peak of the COVID-19 pandemic on colorectal cancer services in England and Wales: A national survey. *Colorectal Dis.* 2021; 23(7): 1733-1744
- Boyle JM, Hegarty G, Frampton C et al. Real-world outcomes associated with new cancer medicines approved by the Food and Drug Administration and European Medicines Agency: a retrospective cohort study. *Eur J Cancer*. 2021; 155: 136-144
- Kuryba A, Boyle JM, Blake H et al. Surgical treatment and outcomes of colorectal cancer patients during the COVID-19 pandemic: A national population-based study in England. *Ann Surg Open*. 2021; 2(2): e071
- Parry M, Boyle JM, Nossiter J et al. Determinants of variation in radical local treatment for men with high-risk localised or locally advanced prostate cancer in England. *Prostate Cancer Prostatic Dis.* 2021; doi: 10.1038/s41391-021-00439-9
- Cowling TE, Bellot A, Boyle JM et al. One-year mortality of colorectal cancer patients: development and validation of a prediction model using linked national electronic data. *Br J Cancer*. 2020; 123(10): 1474-1480

3.10.2 National Bowel Cancer Audit annual reports

- National Bowel Cancer Audit. Annual Report 2017. London, RCS England, 2017.
- National Bowel Cancer Audit. Annual Report 2018. London, RCS England, 2018.
- National Bowel Cancer Audit. Patient Report 2018. London, RCS England, 2018.
- National Bowel Cancer Audit. Organisational Survey Results 2018. London, RCS England, 2018.
- National Bowel Cancer Audit. Annual Report 2019. London, RCS England, 2020.
- National Bowel Cancer Audit. Organisational Survey Results 2019. London, RCS England, 2020.
- National Bowel Cancer Audit. Patient Report 2019. London, RCS England, 2020.
- National Bowel Cancer Audit. Annual Report 2020. London, RCS England, 2020.
- National Bowel Cancer Audit. Patient Report 2020. London RCS England, 2020.
- National Bowel Cancer Audit. Annual Report 2021. London, RCS England, 2021.
- National Bowel Cancer Audit. Patient Report 2021. London, RCS England, 2021.

3.10.3 National Bowel Cancer Audit short reports

- National Bowel Cancer Audit. PROMS Feasibility Study. London, RCS England, 2018.
- National Bowel Cancer Audit. Adjuvant Chemotherapy Short Report. London, RCS England, 2019.
- National Bowel Cancer Audit. End of Life Short Report. London, RCS England, 2019.
- National Bowel Cancer Audit. PREMS Feasibility Study. London, RCS England, 2020.
- National Bowel Cancer Audit. How to best capture adjuvant chemotherapy in stage III colon cancer with linked HES-APC and SACT data. London, RCS England, 2020.

- National Bowel Cancer Audit. Trends, characteristics and outcomes for patients diagnosed under 50 years old with metastatic colon cancer in England. London, RCS England, 2021.
- National Bowel Cancer Audit. Hospital- and surgeon-level volumes for rectal cancer surgery in England and implications for Wales. London, RCS England, 2021.

3.10.4 International/national oral presentations & poster prize

- Variation in receipt of adjuvant chemotherapy for Stage III colon cancer in England. Boyle JM, Kuryba A, Walker K *et al. Association of Coloproctologists of Great Britain and Ireland. Dublin, Ireland.* 1st-3rd July 2019 – prize best poster.
- A Feasibility Study of Reporting Patient Reported Outcome Measures as part of a National Colorectal Cancer Audit. Vallance A, Boyle JM, Hill J *et al. Public Health England Cancer Services, Data and Outcomes Conference, Manchester, UK.* 21st June 2018
- A Feasibility Study of Reporting Patient Reported Outcome Measures as part of a National Colorectal Cancer Audit. Vallance A, Boyle JM, Hill J *et al. European Society of Coloproctology. Nice, France.* 26th-28th September 2018
- Variation in use of adjuvant chemotherapy for stage III colon cancer in the English National Health Service. Boyle JM, Kuryba A, Walker K *et al. The Moynihan Chirurgical Club. Manchester, UK. 4th October* 2019
- Variation in use of adjuvant chemotherapy for stage III colon cancer in the English National Health Service. Boyle JM, Kuryba A, Walker K *et al. European Society of Coloproctology. Vienna, Austria. 25th-27th* September 2019
- Trends, characteristics, and outcomes for patients diagnosed with colorectal cancer under 50 years.
- Boyle JM, Kuryba A, Cowling TE *et al. Association of Coloproctologists of Great Britain and Ireland. Dublin, Ireland.* 6th-8th July 2020

4. IDENTIFICATION & VALIDATION OF SACT USAGE & COMPLETION IN ROUTINELY COLLECTED DATA

4.1 Methodological paper 1

Title: Validity of chemotherapy information derived from routinely collected healthcare data: A national cohort study of colon cancer patients.

The online PDF version can be accessed here.

Supplementary material is contained within the paper.

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1802390	**Title**	Dr
First Name(s)	Jemma Megan		
Surname/Family Name	Boyle		
Thesis Title	Using National Routine Data to Explore the Utilisation and Outcomes of Multimodal Treatment in the Management of Colorectal Cancer		
Primary Supervisor	Dr Kate Walker		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Cancer Epidemiology		
When was the work published?	2nd July 2021		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	N/a		
Have you retained the copyright for the work?*	Choose an item. No	Was the work subject to academic peer review?	Choose an item. Yes

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Designed the work, analysed and interpreted the data, drafted the article, and approved final version for submission.

SECTION E

Student Signature	
Date	15th February 2022

Supervisor Signature	K. Walker
Date	15th February 2022

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Validity of chemotherapy information derived from routinely collected healthcare data: A national cohort study of colon cancer patients

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ABSTRACT

Background: We used a structured approach to validate chemotherapy information derived from a national routinely collected chemotherapy dataset and from national administrative hospital data.
Methods: 10,280 patients who had surgical resection with stage III colon cancer were included. First, we compared information derived from the national chemotherapy dataset (SACT) and from the administrative hospital dataset (HES) in the English NHS with respect to receipt of adjuvant chemotherapy (ACT). Second, we compared regimen and number of cycles in linked patient-level records. Third, we carried out a sensitivity analysis to establish to what extent the impact of ACT receipt differed according to data source.
Results: 6,012 patients (58 %) received ACT according to either dataset. Of these patients, 3,460 (58 %) had ACT records in both datasets, 1,649 (27 %) in SACT alone, and 903 (15 %) in HES alone. Of the 3,460 patients with records in both datasets, 3,320 (96 %) had matching regimens. There was good agreement on cycle number with similar proportions of patients recorded with a single cycle (6 % in SACT vs. 7 % in HES) and slightly fewer patients recorded with more than 8 cycles in SACT (32 % in SACT vs. 35 % in HES). 3-year cancer-specific mortality was similar for patients receiving ACT, regardless of whether a patient received ACT according to SACT alone (16.6 %), according to HES alone (16.8 %), or according to either SACT or HES (17.1 %).
Conclusion: Routinely collected national chemotherapy data and administrative hospital data are highly accurate in recording regimen and number of chemotherapy cycles. However, chemotherapy information should ideally be captured from both datasets to avoid under-capture, particularly of oral chemotherapy from administrative hospital data, and to minimise bias.

1. Introduction

Chemotherapy is a critical component of oncological treatment. Evidence regarding the efficacy of chemotherapy treatment has come from high quality, large randomised controlled trials (RCTs) [1–3]. RCTs, however, include highly selected patient populations under rigorously controlled conditions, generally under-representing older patients, and those who are frail or comorbid. Population-based studies, using data such as electronic healthcare records, are needed to assess outcomes in diverse non-selected populations under realistic clinical conditions, and can be used to complement RCT findings [4–8].

All English National Health Service (NHS) chemotherapy providers are mandated to collect data for all patients in routine care via the Systemic Anti-Cancer Therapy (SACT) dataset [9]. The use of this dedicated chemotherapy dataset for research has been limited. Several studies have highlighted possible data issues, for example that older patients and those with comorbidities are not fully represented within the dataset, and that there might be limitations in the accurate recording of chemotherapy cycle numbers, particularly with oral drugs [10–15]. The only study to date that has attempted to validate SACT data was

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carried out in a study using general practice records of only 7 % of the UK population, and no validation of chemotherapy regimens was attempted [15].

This study aimed to validate chemotherapy data in a contemporary national cohort of patients with pathological stage III colon cancer, identified from the National Bowel Cancer Audit (NBOCA), who had undergone potentially curative surgical resection and were candidates for adjuvant chemotherapy (ACT) according to national guidelines [16].

We used a structured four-step framework to compare national chemotherapy data with data available in Hospital Episode Statistics (HES), a national administrative dataset of all hospital admissions in the English NHS. First, we assessed the agreement between the two datasets for chemotherapy receipt in all patients. Second, we compared the chemotherapy regimen and cycle number in both datasets. Regimens were established in hospital administrative data using novel methodology to translate clinical coding guidelines into clinically meaningful information. Third, we identified potential biases that may originate from incomplete capture of chemotherapy in each dataset by exploring the characteristics of patients, regimens, and number of cycles according to which dataset information was obtained from. Lastly, we carried out a sensitivity analysis to evaluate to what extent the observed impact of ACT has on 3-year colon cancer-specific mortality dependent on the type

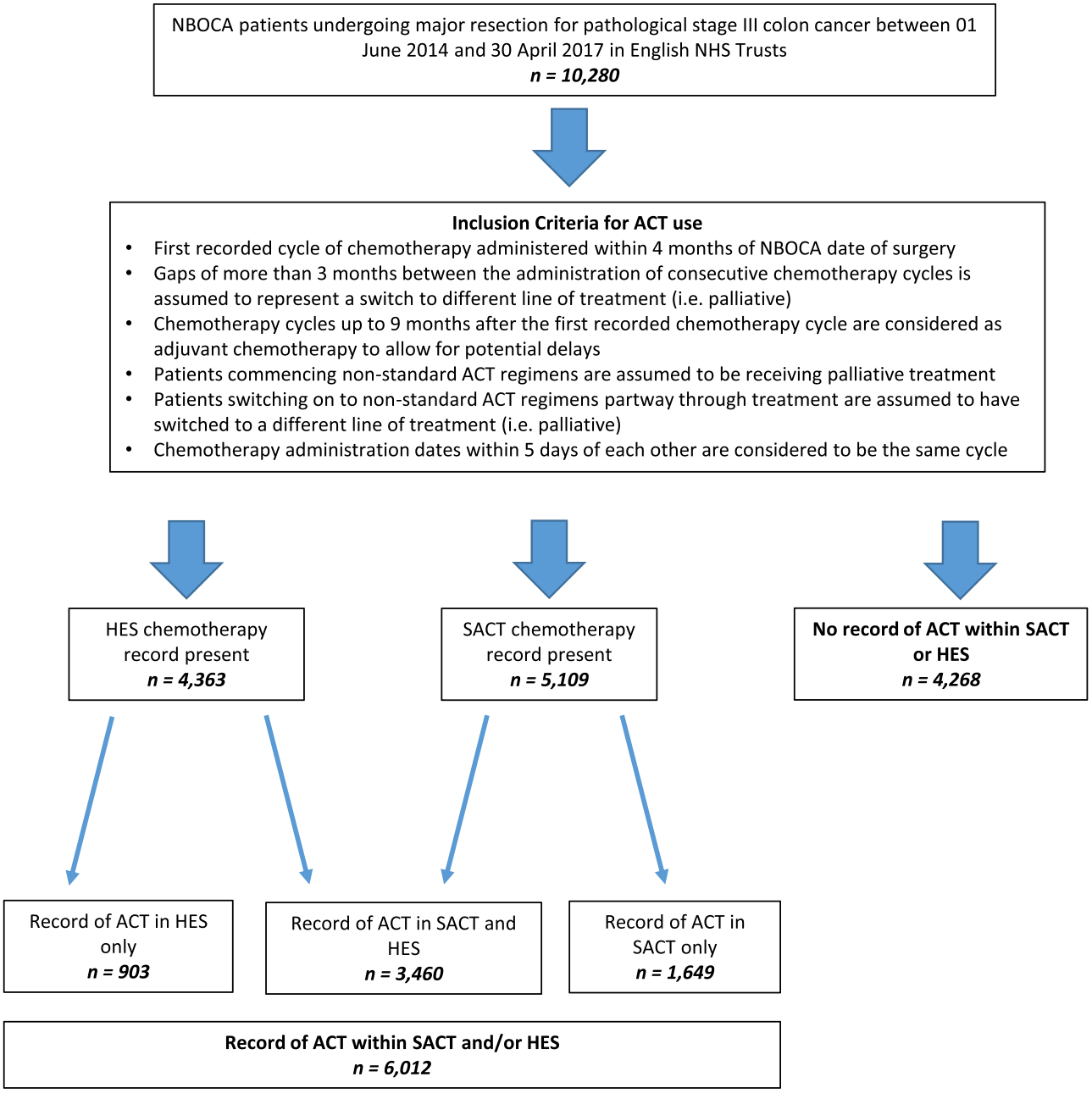

Fig. 1. Algorithms applied to SACT and HES records to establish ACT and resulting final patient cohorts.

Table 1
Numbers of patients identified as commencing ACT within 4 months of surgical resection with pathological stage III colon cancer, according to either SACT or HES datasets.

	ACT according to SACT		
ACT according to HES	Yes	No	Total
Yes	3,460*	903*	4,363
No	1,649*	4,268	5,917
Total	5,109	5,171	10,280

* 6,012 patients (58 %) were identified as receiving ACT according to SACT and/or HES.

Table 2
Numbers of patients receiving each standard ACT regimen according to SACT and HES, for patients with ACT in both datasets (n = 3,460).

	First adjuvant HES regimen			
First adjuvant SACT regimen	5-FU	FOLFOX	Capecitabine	CAPOX
5-FU	**252**	31	1	1
FOLFOX	7	**1,097**	0	18
Capecitabine	6	2	**391**	63
CAPOX	0	8	3	**1,580**

Bold values indicate numbers of patients with matching regimens identified in both datasets.

of dataset that was used to capture ACT information.

2. Methods

2.1. Chemotherapy data sources

2.1.1. Systemic Anti-Cancer Therapy (SACT) dataset

The SACT is a dedicated chemotherapy dataset that includes detailed drug-level information, including administration date, drug name, dose, and administration route [9]. SACT captures chemotherapy administered in any inpatient, daycase, outpatient, or community setting, and in most hospitals the data is collected via electronic prescribing systems [10]. In SACT, the drug name is a mandatory data item which is mapped to a pre-defined list of regimens.

2.1.2. Hospital Episode Statistics (HES)

HES is an administrative dataset of all admissions to English NHS hospitals [17]. Inpatient and daycase chemotherapy use is captured via clinical coding, primarily through dedicated Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures, 4th revision (OPCS-4) codes [18], with chemotherapy-related International Classification of Diseases, 10th revision (ICD-10) codes also available (Appendix A) [19].

2.2. Study population

NBOCA is a prospective mandatory database for all newly diagnosed colorectal cancer patients in the English NHS. Patients aged 18 years and above with a primary diagnosis of colon cancer, according to ICD-10 code C18, undergoing major resection at an English NHS hospital between 1 June 2014 and 30 April 2017 with pathological stage III colon cancer were identified in the NBOCA database. Cancers of the appendix were excluded.

10,280 NBOCA records were identified. These records were linked at patient-level to HES records, and to SACT records containing a colorectal cancer ICD-10 diagnosis code (C18-C20). Only SACT records between 30 June 2014 and 30 April 2018 were used because not all English NHS chemotherapy providers were submitting SACT data before 1 July 2014 [10]. This ensured that all patients were followed up for at least 12 months from the date of surgery, allowing sufficient time for ACT completion. Linkage to SACT included all chemotherapy for each patient regardless of treatment intent (e.g. curative or palliative).

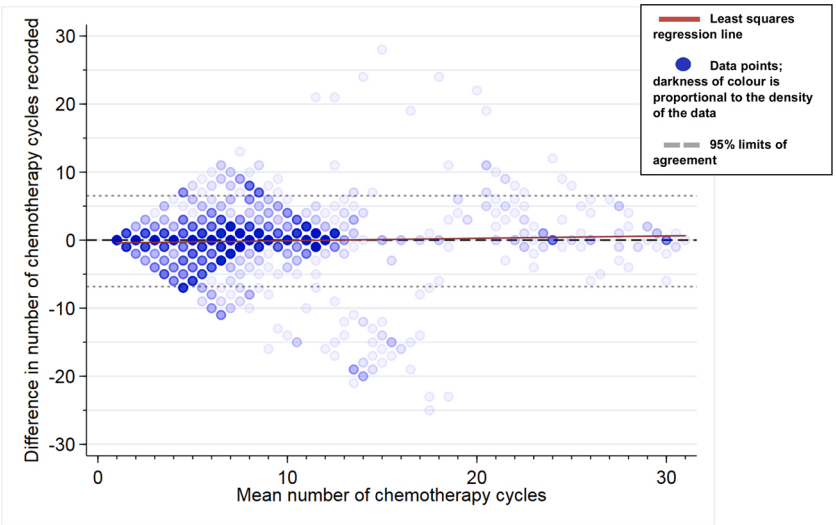

Fig. 2. Bland-Altman plot demonstrating agreement between the mean number of cycles of chemotherapy according to SACT and HES at patient-level, and the difference between the number of cycles recorded in HES and SACT at patient-level, for patients with ACT in both datasets (n = 3,460).

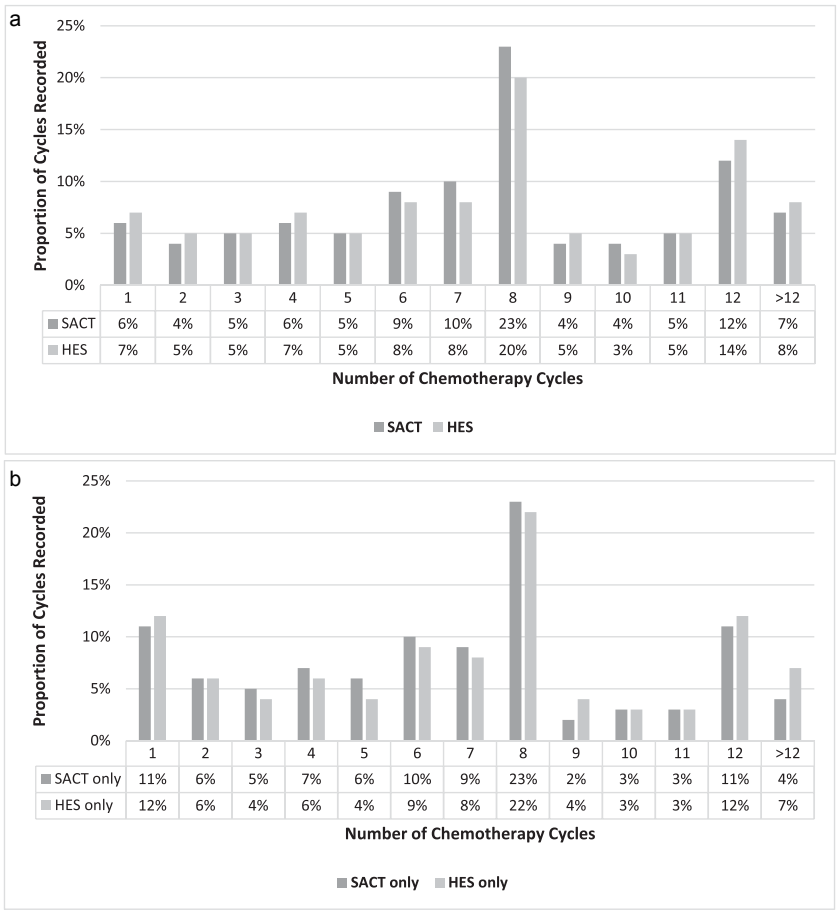

Fig. 3. a Bar chart demonstrating the distribution of total ACT cycles recorded in SACT compared to HES, for patients with ACT in both datasets (n = 3,460). b Bar chart demonstrating the distribution of total ACT cycles recorded in SACT compared to HES for those patients with ACT in SACT only (1,649) and HES only (n = 903).

2.3. Measuring adjuvant chemotherapy

According to clinical guidelines for stage III colon cancer, standard ACT is considered to be fluoropyrimidine monotherapy (5-fluorouracil (5-FU) or capecitabine), or combination therapy as either 5-FU with oxaliplatin (FOLFOX), or capecitabine with oxaliplatin (CAPOX) [16].

For both datasets, the same rules were applied to determine which chemotherapy had been given in the adjuvant setting. First, restriction to the four standard regimens above was applied. Second, chemotherapy needed to have been started within 4 months of the NBOCA date of surgery and completed within 9 months of the first chemotherapy cycle, with gaps no larger than 3 months between consecutive cycles. Third, any patients who switched regimens partway through treatment to a non-standard regimen were assumed to have switched to palliative chemotherapy (Fig. 1).

2.4. Establishing chemotherapy regimens within HES

HES does not provide regimen names. However, the National Tariff Chemotherapy Regimens List provides guidance on which OPCS-4 procurement and delivery codes should be used in HES, according to whether the chemotherapy is recorded as an inpatient or daycase administration, and which regimen is administered (Appendix B) [18]. Chemotherapy regimens were therefore indirectly captured in HES using novel methodology involving these codes.

2.5. Clinical characteristics

Data regarding sex, age, performance status, pathological T- and N-staging, surgical urgency, and surgical access were obtained from NBOCA records. The Royal College of Surgeons' (RCS) Charlson co-morbidity score was derived from ICD-10 codes recorded in HES in the year preceding colon cancer diagnosis [20].

The hospital where the surgery was performed was identified according to NBOCA data. University teaching hospital status was determined according to the hospitals' membership of the University Hospital Association [21]. Information regarding on-site chemotherapy facilities were collected in a national NBOCA survey of colorectal cancer services [22].

Date and cause of death were obtained from linked Office for National Statistics (ONS) mortality data [23].

Table 3
Patient, tumour and hospital-level characteristics according to the dataset capturing ACT use.

	SACT and HES (n = 3,460)		HES alone (n = 903)		SACT alone (n = 1,649)		χ^2 *P* values
	No.	%	No.	%	No.	%	
Sex							0.827
Male	1,832	52.9	483	53.5	862	52.3	
Female	1,628	47.1	420	46.5	787	47.7	
Age							**<0.001**
<60	992	28.7	250	27.7	357	21.6	
60-69	1,250	36.1	296	32.8	463	28.1	
70-79	1,024	29.6	287	31.8	703	42.6	
≥80	194	5.6	70	7.8	126	7.6	
RCS Charlson Score							**0.001**
0	2,242	64.8	549	60.8	996	60.4	
1	944	27.3	276	30.6	475	28.8	
≥2	274	7.9	78	8.6	178	10.8	
Performance Status							**<0.001**
0	1,854	62.8	522	64.3	765	52.5	
1	871	29.5	215	26.5	534	36.7	
≥2	228	7.7	75	9.2	157	10.8	
Missing	507	14.7	91	10.1	193	11.7	
Pathological T-stage							0.072
T1/T2	294	8.5	75	8.3	158	9.6	
T3	1,756	50.8	445	49.3	877	53.2	
T4	1,409	40.7	382	42.4	614	37.2	
Missing	1	0	1	0.1	0	0	
Pathological N-stage							**0.005**
N1	2,158	62.4	534	59.1	1,080	65.5	
N2	1,302	37.6	369	40.9	569	34.5	
Surgical Urgency							**0.001**
Elective/Scheduled	2,802	81.1	680	75.4	1,315	79.9	
Emergency/Urgent	653	18.9	222	24.6	330	20.1	
Missing	5	0.1	1	0.1	4	0.2	
Surgical Access							**0.004**
Open	1,179	34.2	361	40.0	582	35.4	
Laparoscopic converted	258	7.5	71	7.9	148	9.0	
Laparoscopic	2,008	58.3	470	52.1	916	55.7	
Missing	15	0.4	1	0.1	3	0.2	
Chemotherapy on-site							**<0.001**
Yes	3,236	93.5	857	94.9	1,215	73.7	
No	224	6.5	46	5.1	434	26.3	
University Teaching Hospital							**<0.001**
Yes	913	26.4	159	17.6	415	25.2	
No	2,547	73.6	744	82.4	1,234	74.8	

Bold values indicate *p*-values with statistical significance (<0.05).

2.6. Stepwise validation framework

2.6.1. Patient-level agreement of receipt, regimen, and number of cycles of ACT

First, patient-level agreement between SACT and HES with respect to ACT receipt and regimen were explored using contingency tables. Second, in patients who had linked SACT and HES records, agreement between the number of chemotherapy cycles recorded in each dataset was evaluated using Bland-Altman analysis with a line of best fit [24]. The distribution of recorded number of cycles according to each dataset was also compared using bar charts.

2.6.2. Evaluating potential biases from incomplete capture within each dataset

Third, clinical characteristics, regimens, and numbers of cycles were compared between patients with ACT captured in SACT alone, HES alone, or both datasets, using chi-squared tests to calculate *p*-values and 0.05 as the statistical significance level.

2.6.3. Sensitivity of findings to the data source

Fourth, the 3-year colon cancer-specific mortality from the NBOCA date of surgery was estimated separately for patients according to receipt of ACT. This was carried out using a competing risks method in which death from other causes was the competing event [25]. Survival times were censored at 3 years after surgery or, if earlier, on the date of the last available death record, which was 10th February 2020. These mortality estimates were compared between analyses in which ACT receipt was identified in SACT alone, HES alone, or in either SACT or HES.

3. Results

3.1. Patient-level agreement of receipt of ACT

10,280 patients were identified who had undergone surgical resection with pathological stage III colon cancer. 6,012 (58 %) were identified as having received ACT according to either SACT or HES (Table 1). Of these 6,012 patients, 3,460 patients (58 %) had ACT according to both datasets, 1,649 patients (27 %) had ACT according to SACT alone, and 903 patients (15 %) according to HES alone. Overall, there was 75 % agreement between the two datasets (concordant cells / total number of patients). 68 % of patients with ACT identified in SACT had ACT according to HES, and 79 % of patients with ACT identified in HES had ACT according to SACT.

3.2. Patient-level agreement of recorded regimen and cycle number

Of the 3,460 patients with ACT recorded in both datasets, 3,320 (96 %) had matching regimens in HES and SACT (Table 2). The Bland-Altman plot demonstrated reasonable agreement between the numbers of cycles recorded in each dataset for patients with ACT records in both (Fig. 2). The 95 % limits of agreement were -6.84 to 6.52. The line of best fit was very close to a zero mean difference in cycles which demonstrated good overall agreement across the range of mean number of cycles.

For the 3,460 patients with ACT recorded in both datasets, the overall distribution of the number of recorded cycles was similar regardless of data source, including the proportion of patients with a single cycle of chemotherapy recorded (6 % in SACT vs. 7 % in HES) (Fig. 3a). HES captured slightly more patients having more than 8 cycles of chemotherapy (32 % in SACT vs. 35 % in HES).

3.3. Evaluating potential biases from incomplete capture within each dataset

Patients identified as having ACT in only one dataset were significantly more likely to be older, more comorbid, and less fit, compared to patients captured in both datasets (Table 3).

Table 4
Distribution of ACT regimen according to whether the patient has ACT in both HES and SACT, SACT only, or HES only. χ^2 test for association: *P* value=<0.001.

Regimen	SACT and HES (n = 3,640)	SACT only (n = 1,649)	HES only (n = 903)	Overall (n = 6,012)
5-FU	285 (63.1)	76 (16.8)	91 (20.1)	452
(Column %)	*8.2*	*4.6*	*10.1*	*7.5*
FOLFOX	1,122 (63.2)	404 (22.7)	250 (14.1)	1776
(Column %)	*32.4*	*24.5*	*27.7*	*29.5*
Capecitabine	462 (32.7)	854 (60.4)	97 (6.9)	1413
(Column %)	*13.4*	*51.8*	*10.7*	*23.5*
CAPOX	1,591 (67.1)	315 (13.3)	465 (19.6)	2371
(Column %)	*46.0*	*19.1*	*51.5*	*39.4*

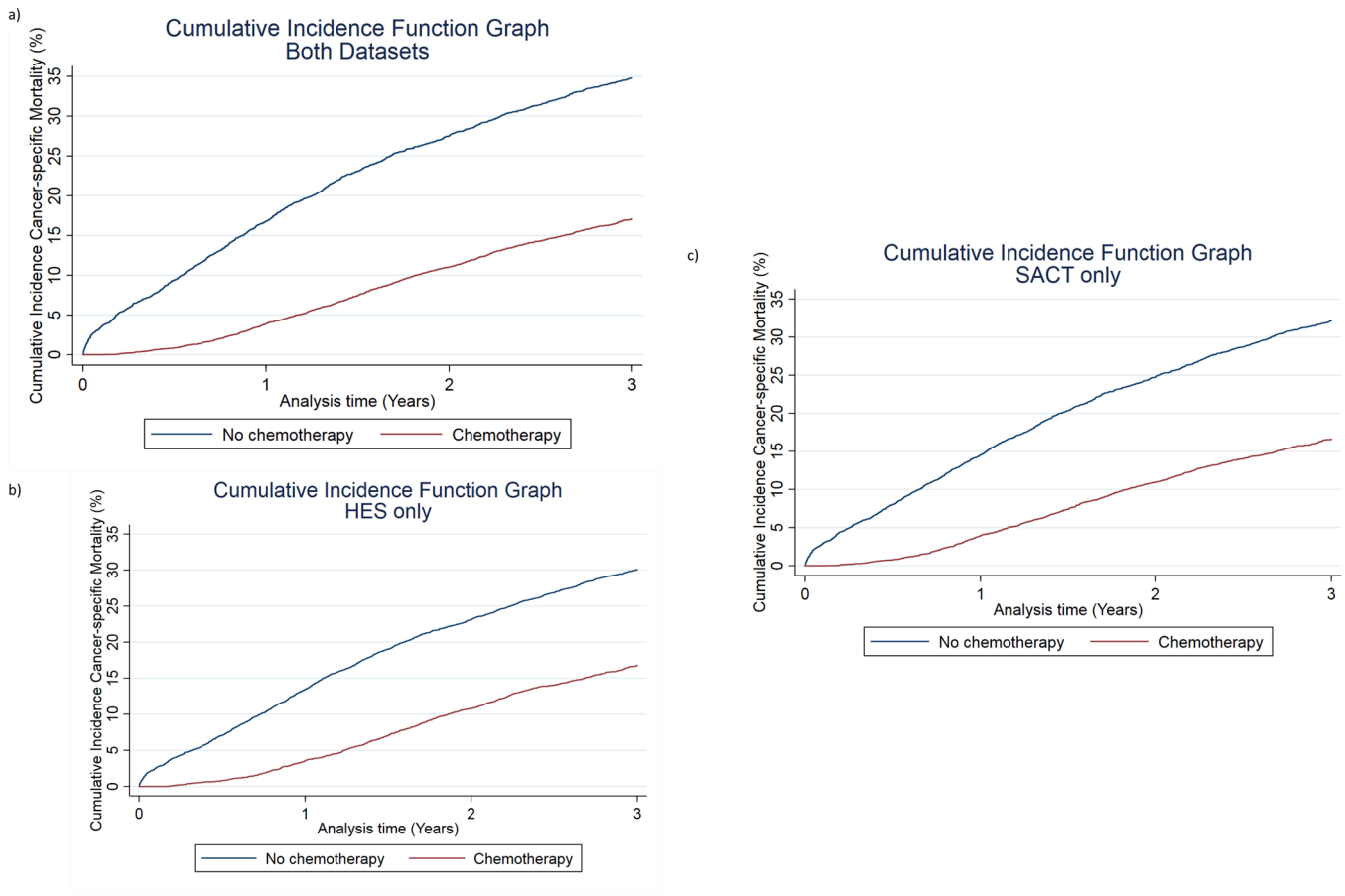

Fig. 4. Cumulative incidence function graphs for 3-year colon cancer-specific mortality with competing risk of other causes of death stratified by receipt of ACT, according to classification within a) both datasets b) HES only and c) SACT only.

Patients identified as having ACT in SACT alone also tended to have less advanced nodal disease, and were more likely to have undergone major resection in a hospital without chemotherapy facilities on-site. Patients identified as having ACT in HES alone were more likely to have undergone major resection in a hospital that was not a university teaching hospital, and which had on-site chemotherapy facilities (Table 3).

There were statistically significant differences in the capture of regimen according to dataset ($P < 0.001$) (Table 4). Patients with ACT recorded in SACT alone were more likely to have received capecitabine, compared to patients in HES alone who were more likely to have received CAPOX.

Patients with ACT identified within a single dataset had a higher proportion of patients with a single cycle of chemotherapy recorded (11 % for SACT alone and 12 % for HES alone compared to 6 % and 7 % for patients with ACT identified in both datasets) (Fig. 3a and b).

3.4. Sensitivity of findings to the data source

For patients classified as receiving ACT in either dataset (n = 6,012), the 3-year colon cancer-specific mortality was 17.1 % (95 % CI: 16.1%–18.0%) (Fig. 4). This was 16.8 % (95 % CI: 15.7%–17.9%) in patients classified as receiving ACT according to HES alone (n = 4,363), and 16.6 % (95 % CI: 15.6%–17.7%) in patients classified as receiving ACT according to SACT alone (n = 5,109).

For patients classified as not receiving ACT in either dataset (n = 4,268), the 3-year colon cancer-specific mortality was 34.8 % (95 % CI: 33.4%–36.2%) (Fig. 4). This was only slightly higher than the 30.1 % (95 % CI: 28.9%–31.2%) observed in patients classified as not receiving ACT according to HES alone (n = 5,917), and the 32.1 % (95 % CI; 30.9%–33.4%) observed in patients classified according to SACT alone (n = 5,171).

4. Discussion

This study used a structured validation framework to examine the capture of ACT receipt and the accuracy of recording of regimen and cycle number in routinely collected national chemotherapy data (SACT) and administrative hospital data within the English NHS [9]. These datasets can be used in isolation or linked together, as well as linked at patient-level to other data sources, in order to inform improvements in service provision, clinical practice, and patient outcomes [10].

Both datasets were found to be accurate in recording regimen type and cycle number. To our knowledge, the use of detailed coding within HES to assign chemotherapy regimens has not previously been explored. National guidelines exist which explicitly instruct on the recording of chemotherapy codes for financial reimbursement within hospital administrative data, meaning that their use should be standardised and this novel methodology transferable to other cancer types [18].

This study did, however, highlight issues of incomplete capture of ACT in both datasets, particularly within hospital administrative data. Differences were demonstrated in clinical characteristics and regimens captured, although mortality rates remained comparable regardless of data source. Ideally, both sources of chemotherapy data should be used together to maximise capture of ACT and, in that way, reduce the potential for bias.

The main limitation of this study was that we did not consider HES outpatient data which might have captured more patients, in particular those receiving oral drugs, although capture of diagnosis and procedure coding within HES outpatient data is known to be very incomplete [26].

Another limitation was that cycles were not matched between the two datasets according to dates. However, the same algorithm for determining ACT was applied to each dataset, and 90 % of patients with ACT records in both datasets had a first chemotherapy date that matched within one week, in line with a previous study [15].

The proportion of patients identified as receiving ACT according to either dataset is similar to a previous population-based study [27]. In addition, the proportion of all patients recorded as receiving ACT according to hospital administrative data alone was 15 %, comparable to previous work showing 12.5 % [15].

Reasons for patients being captured in only one dataset are likely multifactorial. However, the most important reason appears to be differences in the capture of chemotherapy delivered in outpatient and community settings, as demonstrated by 60 % of all capecitabine being captured in the dedicated chemotherapy dataset alone.

Poor submission of SACT data may explain why some ACT is captured in HES alone. SACT case ascertainment has been linked to the availability of electronic prescribing (e-prescribing) [10]. This is supported by our results showing that fewer patients in HES alone were managed in a university teaching hospital. It might be expected that the uptake of e-prescribing is higher in larger, academic oncology units.

The novel methodology used to assign chemotherapy regimens within hospital administrative data is important. First, it reduces overestimation of ACT cycles by limiting the inclusion of chemotherapy given outside the adjuvant setting. Second, it facilitates more clinically meaningful interpretation of hospital administrative data and can be adapted for other cancer types.

This study showed that for patients with records in both datasets, the proportion recorded as having only one cycle was similar in each dataset. In addition, the higher proportion of single cycles recorded when ACT was captured in a single dataset were consistent regardless of data source. This is therefore more likely to reflect clinical characteristics rather than a data quality issue [10]. Older, less fit patients are more likely to discontinue chemotherapy early due to toxicity, and these are the patients more likely to be captured in only one dataset.

Concerns about the capture of oral chemotherapy within SACT have been raised [28]. However, our results showed that reporting of capecitabine was considerably more complete in SACT, and the higher proportion of patients with just one cycle of capecitabine recorded in one dataset alone could again be explained by the older, less fit population.

Patients captured in SACT alone tended to be older, less fit, have less advanced disease, and were more likely to receive fewer than 8 cycles. Capecitabine therapy consisted of 8 cycles as standard practice during the timeframe of this study [29,30]. Capecitabine monotherapy is also often favoured in the elderly, as well as those with low-risk cancer (T1-T3 and N1 disease), due to uncertain survival advantages and neurotoxicity associated with combination therapy [31,32].

Hospital administrative data was more likely to have ACT missing if surgery was performed at a hospital which did not have on-site chemotherapy. This is likely explained by several tertiary oncology centres notably not recording chemotherapy within this dataset. Patients receiving ACT in tertiary centres are usually referred from hospitals which are different to those in which they underwent surgery.

Our findings are in line with those previously reported in lung cancer patients which suggested older, more comorbid patients might be underrepresented in SACT, and raised concerns that mortality in those receiving chemotherapy may then be underestimated [15]. However, our study showed similar survival outcomes for those receiving chemotherapy regardless of which data source was used to classify ACT receipt. A higher mortality and larger absolute difference between those receiving and those not receiving ACT according to both datasets, compared to those classified by one dataset, supports the interpretation that the classification of ACT receipt is more accurate when both datasets are in agreement.

This study highlights the importance of validating routinely collected data, either national chemotherapy or administrative hospital data, on real world chemotherapy practice within specific cancer types. For example, some of the biases demonstrated were due to differential capture of oral chemotherapy which may not be applicable to all cancers. However, the transparent structured validation framework can be applied to other cancer types as well as different lines and types of chemotherapy, such as hormonal and biological agents.

The dedicated chemotherapy dataset is the first national dataset of its kind, relying largely on the capture of data from e-prescribing systems. This data can be linked at patient-level to other national datasets, providing invaluable opportunities for research [12]. Many European countries, the United States, Australia and New Zealand, have been expanding e-prescribing within primary care [33], and this study adds further rationale for implementing e-prescribing in secondary care to reduce data collection burden if not already available.

5. Conclusion

This study has demonstrated the accuracy of data from a national chemotherapy dataset (SACT) and administrative hospital dataset (HES) for patients with stage III colon cancer receiving chemotherapy in the English NHS when records are present from both sources. However, chemotherapy information should ideally be captured from both datasets to avoid under-capture, particularly of oral chemotherapy in administrative hospital data, and to minimise bias.

This methodology should facilitate more accurate and robust national reporting of chemotherapy use and outcomes, with applicability across different cancer types. Other countries should consider the feasibility of e-prescribing for the routine collection of national dedicated chemotherapy data which can be linked to other data sources in order to inform healthcare quality improvement.

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CRediT authorship contribution statement

Jemma M. Boyle: Conceptualization, Methodology, Validation, Formal analysis, Writing - original draft. **Angela Kuryba:** Formal analysis, Writing - review & editing. **Michael S. Braun:** Writing - review & editing. **Ajay Aggarwal:** Writing - review & editing. **Jan van der Meulen:** Methodology, Writing - review & editing, Supervision. **Thomas E. Cowling:** Methodology, Writing - review & editing, Visualization. **Kate Walker:** Conceptualization, Methodology, Validation, Writing - review & editing, Supervision.

Declaration of Competing Interest

None.

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Appendix A. OPCS-4 and ICD-10 codes for chemotherapy use in HES

OPCS-4 code	Classification
X701	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 1
X702	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 2
X703	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 3
X704	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 4
X705	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 5
X708	Other specified procurement of drugs for chemotherapy for neoplasm in Bands 1-5
X709	Unspecified procurement of drugs for chemotherapy for neoplasm in Bands 1-5
X711	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 6
X712	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 7
X713	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 8
X714	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 9
X715	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 10
X718	Other specified procurement of drugs for chemotherapy for neoplasm in Bands 6-10
X719	Unspecified procurement of drugs for chemotherapy for neoplasm in Bands 6-10
X721	Delivery of complex chemotherapy for neoplasm including prolonged infusional treatment at first attendance
X722	Delivery of complex parenteral chemotherapy for neoplasm at first attendance
X723	Delivery of simple parenteral chemotherapy for neoplasm at first attendance
X724	Delivery of subsequent element of cycle of chemotherapy for neoplasm
X728	Other specified delivery of chemotherapy for neoplasm
X729	Unspecified delivery of chemotherapy for neoplasm
X731	Delivery of exclusively oral chemotherapy for neoplasm
X738	Other specified delivery of oral chemotherapy for neoplasm
X739	Unspecified delivery of oral chemotherapy for neoplasm
X748	Other specified other chemotherapy drugs
X749	Unspecified other chemotherapy drugs
X352	Intravenous chemotherapy
X373	Intramuscular chemotherapy
X384	Subcutaneous chemotherapy
ICD-10 code	**Classification**
Z082	Follow-up exam after chemotherapy for malignant neoplasm
Z292	Other prophylactic chemotherapy
Z511	Chemotherapy session for neoplasm
Z512	Other chemotherapy
Z542	Convalescence following chemotherapy

Appendix B. OPCS-4 delivery and procurement codes used to determine ACT regimen within HES according to the National Tariff Chemotherapy Regimens List

	Inpatient chemotherapy	Daycase chemotherapy		
ACT Regimen	Procurement Code	Procurement Code	Delivery Code	Overall Code
5-FU	X701	X701	X721 or X723	X701 and X721/X723
FOLFOX	X704	X704	X721	X704 and X721
Capecitabine	X702	X702	X731	X702 and X731
CAPOX	X711	X711	X722	X711 and X722

The code combinations for other potential colorectal chemotherapy regimens were checked to ensure that the same codes were not being used for other regimens. Inpatient chemotherapy is coded with a procurement code only, in comparison to daycase chemotherapy which has both procurement and delivery codes.

For each of CAPOX and 5-FU, two procurement codes were available which could potentially impact on the recording of their inpatient delivery. For 5-FU, X702 or X701 could be coded, and for CAPOX this could be X704 or X711. However, less than 1 % of HES records had chemotherapy recorded as an inpatient and, when comparing linked SACT-HES data, >80 % of recorded codes were X701 and X711 respectively. These factors meant that the chances of 5-FU and capecitabine, or CAPOX and FOLFOX, being misclassified when recorded as an inpatient were very low.

Similarly, 5-FU had two delivery codes available which were X721 and X723. Any possible combinations of procurement and delivery codes for 5-FU remained unique, and therefore this was not an issue for the coding of daycase 5-FU.

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5. MEASURING SEVERE ACUTE TOXICITY FOLLOWING SACT IN ROUTINELY COLLECTED DATA

5.1 Methodological paper 2

Title: Development and validation of a coding framework to identify severe acute toxicity from systemic anti-cancer therapy using hospital administrative data

The online PDF version can be accessed here.

Supplementary material is contained within the paper.

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SECTION A – Student Details

Student ID Number	1802390	**Title**	Dr
First Name(s)	Jemma Megan		
Surname/Family Name	Boyle		
Thesis Title	Using National Routine Data to Explore the Utilisation and Outcomes of Multimodal Treatment in the Management of Colorectal Cancer		
Primary Supervisor	Dr Kate Walker		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Cancer Epidemiology		
When was the work published?	January 2022		
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For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Designed the work, analysed and interpreted the data, drafted the article, and approved final version for submission.

SECTION E

Student Signature	
Date	15th February 2022

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Development and validation of a coding framework to identify severe acute toxicity from systemic anti-cancer therapy using hospital administrative data

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ABSTRACT

Background: The capture of toxicities from systemic anti-cancer therapy (SACT) in real-world data will complement results from clinical trials. The aim of this study was to develop and validate a comprehensive coding framework to identify severe acute toxicity in hospital administrative data.

Methods: A coding framework was developed to identify diagnostic codes representing severe acute toxicity in hospital administrative data. The coding framework was validated on a sample of 23,265 colon cancer patients treated in the English National Health Service between 1 June 2014 and 31 December 2017. This involved comparing individual toxicities according to the receipt of SACT and according to different SACT regimens, as well as assessing the associations of predictive factors and outcomes with toxicity.

Results: The severe acute toxicities captured by the developed coding framework were shown to vary across clinical groups with an overall rate of 26.4% in the adjuvant cohort, 53.4% in the metastatic cohort, and 12.5% in the comparison group receiving no chemotherapy. Results were in line with regimen-specific findings from clinical trials. For example, patients receiving additional bevacizumab had higher rates of bleeding (12.5% vs. 2.7%), gastrointestinal perforation (5.6% vs. 2.9%) and fistulation (1.4% vs. 0.5%), and allergic drug reactions (1.4% vs. 0.5%). Severe acute toxicity was associated with pre-existing renal ($p = 0.001$) and cardiac disease ($p = 0.038$), and urgency of surgery ($p = 0.004$). Severe toxicity also predicted lower rates of completion of chemotherapy ($p = <0.001$) and an increased likelihood of altered administration route ($p = <0.001$).

Conclusion: These results demonstrate that the developed coding framework captures severe acute toxicities from hospital administrative data of colon cancer patients. A similar approach can be used for patients with other cancer types, receiving different regimens. Toxicity captured in administrative data can be used to compare treatment outcomes, inform clinical decision making, and provide opportunities for benchmarking and provider performance monitoring.

Abbreviations: SACT, Systemic anti-cancer therapy; RCT, Randomised controlled trial; NBOCA, National Bowel Cancer Audit; HES, Hospital Episode Statistics; NHS, National Health Service; CTCAE, Common Terminology Criteria for Adverse Events.

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1. Introduction

Given the widespread use of systemic anti-cancer therapy (SACT), the ability to measure and understand severe acute toxicities is vital for comparing different treatments and informing patient and clinician decision-making, as well as for facilitating the comparative assessment of toxicities across hospital settings to benchmark best practice and stimulate quality improvement.

A study in breast cancer patients showed a hospitalisation rate of 43% in those receiving SACT, with 75% of admissions confirmed as chemotherapy-related adverse events [1]. Despite this significant burden of toxicity on patients and healthcare systems, there remains a lack of data related to real-world practice. Existing evidence usually comes from randomised controlled trials (RCTs) which can be limited in their application to real-world practice [2,3]. First, there is evidence that acute toxicities are more common in real-world practice than in clinical trials [4]. Second, RCTs often underrepresent patients who are older, comorbid, or less fit, and sometimes ethnic and socioeconomic groups too [5]. Third, rare adverse events may be difficult to capture in RCTs with small sample sizes or short study durations.

To date, some studies of real-world practice have used medical note abstraction or diagnostic and procedural codes from insurance claims to identify acute toxicity [6–8]. Medical note abstraction confers considerable time and cost implications and is impractical for ongoing monitoring. Insurance claims have been shown to provide inconsistent information about specific SACT regimens and incomplete data on the occurrence of events related to SACT [9,10].

Many studies of acute SACT toxicity in real-world practice are limited by their lack of generalisability because they only included patients who had a specific toxicity, disease stage, or SACT regimen, or they excluded patients based on age or insurance status [6–8]. In addition, there is often a lack of granularity about SACT details such as administration dates which are important for ascertaining the precise timeframe during which acute toxicities may occur [4].

Most studies that attempted to validate coding frameworks were designed to identify acute toxicity from insurance claims or hospital administrative data in breast cancer patients [1,11,12]. These studies have included only a small selection of toxicities, often not considering biologic therapies which have unique toxicity profiles.

The aim of our study was to develop a broad and comprehensive coding framework of severe acute toxicity (toxicity necessitating an overnight hospital admission) from SACT across a range of organ systems using hospital administrative data, covering different regimens including biologic therapies. The performance of this coding framework was validated in a large national population-based sample of colon cancer patients treated in the English National Health Service (NHS).

2. Methods

2.1. Data sources

This study used National Bowel Cancer Audit (NBOCA) data [13], Hospital Episode Statistics (HES) data [14,15], and Systemic Anti-Cancer Therapy (SACT) data [16] linked at patient level for colon cancer patients in the English National Health Service (NHS).

2.2. National bowel cancer audit

NBOCA is a prospective mandatory database for all newly diagnosed colorectal cancer patients in the English NHS. Data items in NBOCA were used to determine sex, age, Eastern Cooperative Oncology Group performance status [17], staging according to the TNM system, date of surgery, and surgical urgency (elective/scheduled or emergency/urgent).

2.3. Systemic anti-cancer therapy dataset

The SACT dataset is a dedicated national chemotherapy dataset held by the English National Cancer Registration and Analysis Service [18]. Data are largely captured via electronic prescribing systems. The SACT dataset includes detailed drug-level information for chemotherapy administered in any inpatient, day-case, outpatient, or community setting [16]. Data items in SACT were used to determine the first and last chemotherapy cycle administration dates, regimens, cycle completion, and change in administration route.

Adjuvant chemotherapy was defined as the receipt of a standard regimen (fluoropyrimidine monotherapy or combination therapy with oxaliplatin) commenced within the 4-month period following the NBOCA date of surgery [19]. For patients with Stage IV disease, SACT administered as a first treatment within 4 months of diagnosis was included.

2.4. Hospital episode statistics

The HES dataset is a national administrative dataset of all admissions to English NHS hospitals [15,20]. This study used HES Admitted Patient Care data which includes records of day-case or overnight admissions. HES records contain a unique patient identifier that allows for longitudinal follow-up. Diagnoses are coded using the International Classification of Diseases, 10th revision (ICD-10) [21] and procedures are coded using the Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures, 4th revision (OPCS-4) [22].

Data items in HES were used to determine the number of comorbidities, as well as specific markers for cardiac and renal impairment (important considerations for SACT use), according to the RCS Charlson Score [23]. HES was used to supplement chemotherapy capture in SACT, as per previous methodology [24].

2.5. Office for national statistics

If applicable, date of death was obtained from linkage to official death records provided by the Office for National Statistics (ONS) [25].

2.6. Coding framework for severe acute toxicities

Using a combination of previous studies [1,11,12], the CTCAE (Common Terminology Criteria for Adverse Events) dictionary, and adverse events commonly reported for RCTs [26–34], we compiled a comprehensive list of ICD-10 codes likely to represent severe acute toxicities in the context of chemotherapy administration (*'forward coding'*) with expert input (JB & AA). Death was also included.

Toxicities corresponded to Grade 3–5 severe adverse events according to the CTCAE [35]. Grade 3 toxicity includes severe or medically significant adverse events where hospitalisation is required, or adverse events which are disabling or limit activities of daily living. Grade 4 toxicity includes life-threatening consequences or those requiring urgent intervention, and Grade 5 indicates death.

The most frequently occurring diagnosis codes in the records of overnight admissions during and up to 8 weeks after the last date of chemotherapy administration for patients with stage III and IV colon cancer receiving chemotherapy, were also examined and included if they were likely to represent acute toxicity from chemotherapy (*'backward coding'*).

Review of these codes was undertaken independently by two authors (JB & AA) with discrepancies discussed and resolved using clinical expertise (Appendix A). At patient level, diagnostic codes which may reflect chronic conditions were not included if they were recorded within the 12 months preceding administration of the first cycle of chemotherapy to reduce the likelihood of coding pre-existing conditions (Appendix A).

The framework was purposefully kept broad to ensure applicability to most cancer types and chemotherapy regimens, including potential new therapies.

2.7. Validation cohort

Patients aged 18 years and above with a primary diagnosis of colon cancer (ICD-10: C18) were identified in the NBOCA database. Patients undergoing treatments at an English NHS hospital between 1 June 2014 and 30 April 2017 with pathological stage I, II, III and IV disease were identified. This time-period was chosen because not all English NHS chemotherapy providers were submitting SACT data before the end of May 2014 [16]. SACT and HES data from 30 June 2014 until 30 April 2018 were used to capture all chemotherapy episodes.

2.8. Validation and statistical analysis

All admissions requiring an overnight stay, from administration of the first cycle of chemotherapy up until 8 weeks after administration of the last cycle of chemotherapy, were examined to identify diagnosis codes from the coding framework.

A three-step validation process of the coding framework was undertaken. First, the toxicity profiles were compared across the three clinical validation groups: patients receiving adjuvant chemotherapy following major resection for stage III disease; patients receiving chemotherapy for stage IV disease; and a comparison group of patients with stage I and II disease undergoing major resection with no record of chemotherapy receipt. In addition, a multivariable logistic regression model was used to estimate the association between severe acute toxicity and clinical group, adjusting for age, sex, comorbidity, and performance status. Missing values for these patient factors were imputed with multiple imputation using chained equations, creating 10 datasets, and using Rubin's rules to combine the estimated odds ratios across datasets [36].

As the patients with stage I and II disease had not actually received chemotherapy, pseudo start and end times for their chemotherapy were defined. These corresponded to the 10th centile of the time from major resection to administration of the first cycle of chemotherapy (6 weeks) and the 90th centile (7 months) of this timeframe, using data from the stage III patients who received adjuvant chemotherapy.

Second, toxicity profiles were compared across different chemotherapy regimens known to have different toxicity profiles. Stage III patients receiving capecitabine monotherapy were compared with patients receiving capecitabine and oxaliplatin (CAPOX). This is because oxaliplatin combination chemotherapy is expected to have higher rates of haematological, gastrointestinal, and neurological toxicities compared to monotherapy [33,37]. Stage IV patients receiving 5-fluorouracil and oxaliplatin (FOLFOX), or 5-fluorouracil and irinotecan (FOLFIRI), were compared with patients receiving FOLFOX or FOLFIRI in addition to biologic agents in the form of either a vascular endothelial growth factor receptor inhibitor (bevacizumab) or epidermal growth factor receptor inhibitor (cetuximab or panitumumab). These are known to be associated with unique acute toxicities including bleeding, gastrointestinal perforation and fistulation, and skin reactions [27–29].

Third, patient and clinical factors expected to predict acute toxicity were evaluated in patients with stage III disease receiving adjuvant chemotherapy including renal disease, cardiac disease, performance status, and urgency of surgery. Similarly, factors expected to be influenced by severe acute toxicity were evaluated, including completion of chemotherapy and change of administration route.

Chi squared tests were used to compare proportions. Stata® version 15.1 (StataCorp, College Station, Texas, USA) was used for all data management and analysis.

3. Results

3.1. Description of the validation cohort

We included a total of 23,265 patients (Fig. 1). 15,746 patients had stage I or II disease. Of these, 13,573 (86.2%) did not have chemotherapy and were used as a comparison group. 10,680 patients had stage III disease, with 6012 (56.3%) of these receiving adjuvant chemotherapy. 16,846 patients had stage IV disease, with 3680 (21.4%) having records of chemotherapy being administered as the first treatment within 4 months of diagnosis.

Appendix B presents the demographics of each of the clinical cohorts. Of note, patients in the stage I/II comparison group were considerably older (29.1% aged 80 and over, compared to 6.5% of stage III patients and 9.2% of stage IV patients, $p < 0.001$) and more comorbid (19.4% have $\geq$2 comorbidities according to the RCS Charlson Score, compared to 8.8% of stage III patients and 10.4% of stage IV patients, $p < 0.001$).

3.2. Validation across clinical groups

For all 16 organ systems, those receiving chemotherapy for stage IV disease had more toxicities recorded than those receiving chemotherapy for stage III disease and those in the stage I/II comparison group (Table 1). For example, 23.5% of patients with stage IV disease had a gastrointestinal event captured (e.g. diarrhoea), compared to 12.7% of those with stage III disease, and 3.4% of those in the stage I/II comparison group ($p < 0.001$). Similarly, 13.7% of patients with stage IV disease had a haematological event captured (e.g., neutropenia), compared to 4.1% of those with stage III disease, and 1.0% of those in the stage I/II comparison group ($p < 0.001$).

The coding framework captured 54 individual toxicities, and toxicity profiles were in keeping with clinical expectation. For example, when comparing stage III patients who received adjuvant chemotherapy with the stage I/II comparison group, we found the most marked differences in the proportion of patients with neutropenia (4.1% versus 0.1%, $p < 0.001$), neutropenic sepsis (2.5% versus <0.1%, $p < 0.001$), line complications (1.4% versus 0.2%, $p < 0.001$), neuropathy (0.8% versus 0.1%, $p < 0.001$), and diarrhoea (9.3% vs 1.2%, $p < 0.001$).

Overall, 12.5% of patients with stage I/II disease who did not receive chemotherapy had diagnostic codes included in the coding framework for toxicity, which is much lower than the patients with stage III or stage IV disease receiving chemotherapy. However, as discussed, patients with stage I/II disease were considerably older and more comorbid than stage III and IV patients (Appendix B).

The multivariable regression model demonstrated adjusted odds ratios for severe acute toxicity of 2.98 (95% CI: 2.75–3.23) for the stage III chemotherapy group and 8.98 (95% CI: 8.22–9.80) for the stage IV chemotherapy group compared to the comparison group of stage I/II not receiving chemotherapy, despite adjustment for age, sex, comorbidity, and performance status ($p < 0.001$) (Appendix C).

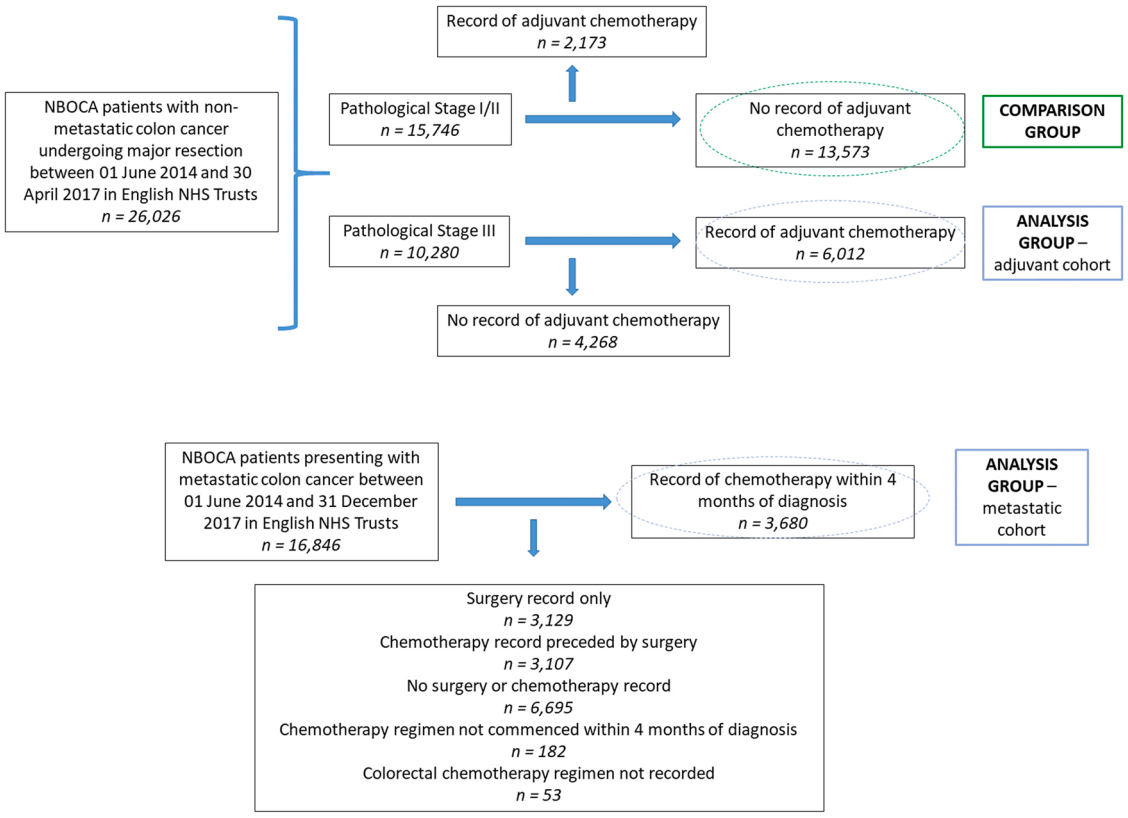

Fig. 1. Flow chart of patients included in the study.

3.3. Validation across chemotherapy regimens

Toxicity profiles for different chemotherapy regimens were in keeping with clinical expectation (Table 2). For example, when comparing stage III patients that received CAPOX with those that received capecitabine monotherapy, there were increased proportions of haematological (4.0% versus 1.6%, $p < 0.001$), gastrointestinal (15.4% versus 9.1%, $p < 0.001$), neurological (2.9% versus 1.0%, $p < 0.001$), infective (10.9% versus 7.1%), and cardiovascular (6.7% versus 5.1%, $p = 0.051$) toxicities.

In addition, patients with stage IV disease that received FOLFOX/FOLFIRI with bevacizumab had higher proportions of bleeding compared to those receiving FOLFOX/FOLFIRI with cetuximab/panitumumab, or FOLFOX/FOLFIRI alone (12.5% versus 3.4% versus 2.7% respectively, $p = <0.001$). Although not statistically significant, patients receiving additional bevacizumab compared to those receiving FOLFOX/FOLFIRI alone also had higher rates of hypertension (4.2% versus 3.6%, $p = 0.98$), gastrointestinal perforation (5.6% versus 2.9%, $p = 0.31$) and fistulation (1.4% versus 0.5%, $p = 0.62$), renal failure (9.7% versus 7.2%, $p = 0.44$), and allergic drug reactions (1.4% versus 0.5%, $p = 0.62$).

Patients with stage IV disease that received FOLFOX/FOLFIRI with cetuximab/panitumumab had higher proportions of dermatological toxicities compared to those receiving FOLFOX/FOLFIRI with bevacizumab, or FOLFOX/FOLFIRI alone (5.4% versus 1.5% versus 1.4% respectively, $p < 0.001$). Similarly, those receiving FOLFOX/FOLFIRI with cetuximab/panitumumab had higher proportions of metabolic toxicities (13.2% versus 8.3% versus 7.8% respectively, $p = 0.003$). Specifically, for patients receiving FOLFOX/FOLFIRI with cetuximab/panitumumab compared to those receiving FOLFOX/FOLFIRI alone there were increased rates of skin reactions (5.2% versus 1.2%, $p < 0.001$), nausea and vomiting (7.8% versus 5.4%, $p = 0.11$), electrolyte disturbances (12.4% versus 7.3%, $p = 0.004$), and ophthalmic disorders (0.8% versus 0.2%, $p = 0.26$).

3.4. Validation according to patient and clinical factors associated with acute toxicity

In stage III patients, factors demonstrated to be associated with an increased risk of acute toxicity were pre-existing renal (35.5% versus 26.0%, $p = 0.001$) and cardiac disease (31.6% versus 26.2%, $p = 0.038$), and presentation requiring emergency/urgent surgery (29.7% versus 25.6%, $p = 0.004$) (Table 3). Acute toxicity was found to be similar across age groups under 80 and lower in those aged 80 and over ($p = 0.011$). Poor performance status was associated with an increased risk of acute toxicity but this was not statistically significant.

Patients who had a severe acute toxicity were less likely to complete standard chemotherapy compared to those that did not have toxicity ($p = <0.001$), and were more likely to have a change in the chemotherapy administration route ($p = <0.001$) (Table 4).

Table 1
Presence of diagnostic codes per patient, by organ system, according to receipt of chemotherapy and clinical group.

	Chemotherapy		No Chemotherapy	
	Stage III (n = 6012)	Stage IV (n = 3680)	Stage I/II (n = 13,573)	p value (χ^2)
Overall	**26.4%**	**53.4%**	**12.5%**	**< 0.001**
Gastrointestinal	**12.7%**	**23.5%**	**3.4%**	**< 0.001**
Diarrhoea	9.3%	11.3%	1.2%	
Nausea or vomiting	3.6%	6.4%	0.8%	
Constipation	1.2%	6.5%	0.8%	
Oral mucositis	1.6%	3.4%	0.2%	
GI ulceration or perforation	0.3%	2.4%	0.2%	
Stoma dysfunction	0.7%	0.5%	0.7%	
Hepatic failure	0.2%	0.7%	< 0.1%	
GI fistulation	0.2%	0.5%	< 0.1%	
Infection	**10.5%**	**24.8%**	**5.5%**	**< 0.001**
Infection	10.5%	24.8%	5.5%	
Additional neutropenia	*2.5%*	*9.3%*	*< 0.1%*	
Cardiovascular	**6.5%**	**14.7%**	**3.9%**	**< 0.001**
Pulmonary Embolism	1.6%	4.9%	0.4%	
Arrhythmia[a]	2.0%	4.7%	1.5%	
Hypotensive episode	1.4%	3.5%	0.9%	
Hypertension[a]	1.1%	3.6%	1.3%	
Thrombophlebitis	0.6%	1.9%	0.2%	
Arterial or venous thromboembolism	0.6%	0.9%	0.1%	
Heart Failure[a]	0.5%	0.7%	0.7%	
Cerebrovascular event[a]	0.5%	0.8%	0.5%	
Angina[a]	0.4%	0.5%	0.3%	
Acute MI	0.5%	0.3%	0.3%	
Pericardial disease	0.2%	0.2%	0.1%	
Cardiomyopathy	0.0%	0.0%	0.1%	
Metabolic & Endocrine	**4.7%**	**8.9%**	**2.3%**	**< 0.001**
Electrolyte abnormalities	4.6%	8.5%	2.1%	
Glucose abnormalities	0.3%	0.7%	0.2%	
Other endocrine	< 0.1%	0.0%	< 0.1%	
Constitutional	**4.4%**	**9.7%**	**1.9%**	**< 0.001**
Hypovolaemia	3.5%	6.1%	1.3%	
Peripheral oedema	0.4%	1.7%	0.2%	
Fatigue	0.5%	1.8%	0.2%	
Anorexia	0.4%	1.4%	0.4%	
Volume overload	0.2%	0.3%	0.1%	
Renal	**4.2%**	**7.7%**	**3.2%**	**< 0.001**
Acute renal failure	4.0%	6.8%	3.0%	
Tubulo-interstitial disease	0.4%	1.3%	0.3%	
Haematology	**4.1%**	**13.7%**	**1.0%**	**< 0.001**
Neutropenia	3.1%	10.5%	0.1%	
Anaemia[a]	1.0%	4.1%	0.9%	
Thrombocytopenia	0.3%	0.7%	0.1%	
Disseminated intravascular coagulation (DIC)	0.0%	0.1%	0.0%	
Pain	**3.8%**	**6.3%**	**1.6%**	**< 0.001**
Respiratory	**1.1%**	**1.9%**	**0.4%**	**< 0.001**
Dyspnoea	0.8%	1.2%	0.2%	
Cough	0.2%	0.6%	0.1%	
Acute Respiratory Distress Syndrome	0.1%	0.1%	< 0.1%	
Pulmonary oedema	< 0.1%	< 0.1%	< 0.1%	
Neurological	**2.3%**	**3.3%**	**0.9%**	**< 0.001**
Dizziness/syncope	0.9%	1.3%	0.4%	
Neuropathy	0.8%	0.8%	0.1%	
Headache	0.4%	0.7%	0.1%	
Seizures[a]	0.2%	0.4%	0.2%	
Other neurological	0.1%	0.3%	0.1%	
Laryngeal spasm	0.1%	0.1%	0.0%	
Line Complications	**1.4%**	**3.3%**	**0.2%**	**< 0.001**
Psychological[a]	**1.4%**	**4.4%**	**1.8%**	**< 0.001**
Bleeding	**1.1%**	**3.0%**	**0.8%**	**< 0.001**
Dermatology & Rheumatology	**1.1%**	**2.0%**	**0.4%**	**< 0.001**
Skin reaction	0.7%	1.6%	0.2%	
Gout[a]	0.4%	0.4%	0.3%	
Ophthalmic[a]	**0.2%**	**0.5%**	**0.3%**	**0.079**
Drug Reaction	**0.2%**	**0.4%**	**< 0.1%**	**< 0.001**
Death	**1.9%**	**14.6%**	**2.3%**	**< 0.001**

[a] Code must not be present in previous 12 months (see Appendix A)

4. Discussion

4.1. Key findings

This is the first study to develop a comprehensive coding framework to identify a broad spectrum of severe acute toxicities after SACT (including traditional cytotoxics and targeted biologic agents). The toxicities are mapped across organ systems using diagnostic codes from hospital administrative data with reference to the established CTCAE dictionary. The validity of this coding framework has been exemplified using a three-step approach demonstrating its ability to distinguish the 'signal' of severe acute toxicity from the 'noise' of background diagnoses in colon cancer patients.

4.2. Comparison with other studies of SACT toxicities

Our finding that stage IV patients receiving chemotherapy had a considerably higher rate of severe acute toxicity than stage III patients receiving adjuvant chemotherapy is in line with a previous study including breast cancer patients [11]. Higher rates in the advanced setting are likely multifactorial and might be explained by more prolonged courses of treatment, and increased use of combination SACT regimens in older patients.

We have demonstrated differences in toxicity profiles as expected from RCTs. First, CAPOX had higher rates of haematological, gastrointestinal, and neurological toxicities compared to capecitabine monotherapy [30,38–40]. Second, the addition of bevacizumab showed increased rates of bleeding, gastrointestinal perforation and fistulation, hypertension, and allergic drug reactions [41,42]. Third, the addition of cetuximab and panitumumab demonstrated increased rates of skin disorders and electrolyte imbalances [28,29].

Our results broadly show higher rates of individual acute toxicities in comparison to RCTs. For example, compared to an RCT for CAPOX, we found a rate of 11.7% versus 8.8% for diarrhoea, 1.9% versus 0.6% for febrile neutropenia, 2.4% versus 11.9% for neutropenia, 4.4% versus 1.3% for vomiting, 1.4% versus 0.9% for mucositis, and 0.6% versus 2.8% for fatigue [43]. Similarly, compared to an RCT for stage IV patients receiving first line FOLFOX or FOLFIRI we found a rate of 11% versus 5.7% for diarrhoea, 5.4% versus 1.6% for vomiting, 3.6% versus 1.6% for mucositis, 12.9% versus 2.1% for febrile neutropenia, and 14.4% versus 42.3% for neutropenia [44].

It is to be expected that we typically found higher toxicity than observed in RCTs given the older and more comorbid population in real-

Table 2
Severe acute toxicities for patients receiving chemotherapy, according to regimen, including biologic therapies.

	Stage III			Stage IV			
	Capecitabine (n = 1413)	CAPOX (n = 2371)	p value (χ^2)	FOLFOX or FOLFIRI (n = 1775)	FOLFOX/FOLFIRI + Bevacizumab (n = 72)	FOLFOX/FOLFIRI + Panitumumab or Cetuximab (n = 386)	p value (χ^2)
Overall	**18.4%**	**27.8%**	**< 0.001**	**54.3%**	**58.3%**	**55.2%**	**0.763**
Gastrointestinal	**9.1%**	**15.4%**	**< 0.001**	**23.3%**	**26.4%**	**23.6%**	**0.826**
Diarrhoea	6.9%	11.7%		11.0%	16.7%	10.6%	
Nausea or vomiting	2.1%	4.4%		5.4%	8.3%	7.8%	
Constipation	0.7%	1.4%		6.3%	6.9%	6.2%	
Oral mucositis	1.3%	1.4%		3.6%	8.3%	3.4%	
GI ulceration or perforation	0.4%	0.5%		2.9%	5.6%	2.9%	
Stoma dysfunction	0.5%	0.5%		0.7%	0.0%	0.5%	
Hepatic failure	0.4%	0.1%		0.8%	1.4%	0.5%	
GI fistulation	< 0.1%	0.0%		0.5%	1.4%	0.3%	
Infection	**7.1%**	**10.9%**	**< 0.001**	**25.6%**	**31.9%**	**28.0%**	**0.330**
Infection	7.1%	10.9%		25.6%	31.9%	28.0%	
Additional neutropenia	1.1%	1.9%		12.9%	9.7%	10.9%	
Cardiovascular	**5.1%**	**6.7%**	**0.051**	**15.1%**	**15.3%**	**18.9%**	**0.175**
Pulmonary Embolism	0.9%	1.9%		5.1%	0.0%	8.0%	
Arrhythmia[a]	1.6%	1.8%		4.9%	9.7%	5.2%	
Hypotensive episode	1.1%	1.5%		3.2%	4.2%	5.7%	
Hypertension[a]	1.1%	0.8%		3.6%	4.2%	3.1%	
Thrombophlebitis	0.2%	0.8%		2.6%	2.8%	1.0%	
Arterial or venous thromboembolism	0.4%	0.3%		1.2%	1.4%	0.8%	
Heart Failure[a]	0.4%	0.3%		0.5%	0.0%	0.8%	
Cerebrovascular event[a]	0.7%	0.4%		1.0%	1.4%	1.0%	
Angina[a]	0.4%	0.6%		0.5%	0.0%	0.3%	
Acute MI	0.6%	0.4%		0.3%	0.0%	0.5%	
Pericardial disease	< 0.1%	< 0.1%		0.0%	0.0%	0.5%	
Cardiomyopathy	0.0%	0.0%		0.0%	0.0%	0.0%	
Metabolic & Endocrine	**4.0%**	**5.6%**	**0.025**	**7.8%**	**8.3%**	**13.2%**	**0.003**
Electrolyte abnormalities	3.9%	5.5%		7.3%	8.3%	12.4%	
Glucose abnormalities	0.1%	0.2%		0.6%	0.0%	1.6%	
Other endocrine	< 0.1%	0.0%		0.0%	0.0%	0.0%	
Constitutional	**3.1%**	**5.2%**	**0.002**	**8.7%**	**12.5%**	**11.4%**	**0.168**
Hypovolaemia	2.4%	3.8%		5.0%	8.3%	6.7%	
Peripheral oedema	0.2%	0.6%		1.8%	1.4%	2.1%	
Fatigue	0.4%	0.6%		1.8%	2.8%	2.1%	
Anorexia	0.2%	0.5%		1.3%	1.4%	2.1%	
Volume overload	< 0.1%	0.3%		0.3%	1.4%	0.5%	
Renal	**2.9%**	**4.0%**	**0.077**	**7.2%**	**9.7%**	**9.3%**	**0.273**
Acute renal failure	2.8%	3.8%		6.3%	9.7%	7.5%	
Tubulo-interstitial disease	0.1%	0.4%		1.2%	1.4%	2.3%	
Haematology	**1.6%**	**4.0%**	**< 0.001**	**17.6%**	**13.9%**	**14.3%**	**0.215**
Neutropenia	1.2%	2.4%		14.4%	11.1%	11.9%	
Anaemia[a]	0.5%	1.3%		4.4%	5.6%	3.6%	
Thrombocytopenia	0.2%	0.4%		0.6%	0.0%	0.5%	
Disseminated intravascular coagulation (DIC)	0.0%	0.0%		0.2%	0.0%	0.3%	
Pain	**3.0%**	**4.1%**	**0.067**	**6.1%**	**9.7%**	**7.3%**	**0.352**
Respiratory	**0.7%**	**0.9%**	**0.474**	**1.6%**	**1.4%**	**2.9%**	**0.261**
Dyspnoea	0.6%	0.7%		1.1%	1.4%	1.3%	
Cough	0.1%	0.0%		0.6%	0.0%	1.0%	
Acute Respiratory Distress Syndrome	< 0.1%	0.2%		0.1%	0.0%	0.5%	
Pulmonary oedema	0.0%	0.0%		0.0%	0.0%	0.0%	
Neurological	**1.0%**	**2.9%**	**< 0.001**	**3.3%**	**4.2%**	**3.4%**	**0.914**
Dizziness/syncope	0.7%	0.8%		1.1%	0.0%	1.6%	
Neuropathy	0.0%	1.4%		0.8%	2.8%	1.3%	
Headache	0.0%	0.3%		0.9%	0.0%	0.5%	
Seizures[a]	< 0.1%	0.2%		0.4%	0.0%	0.5%	
Other neurological	0.2%	< 0.1%		0.3%	1.4%	0.0%	
Laryngeal spasm	0.0%	0.3%		0.1%	0.0%	0.0%	

(*continued on next page*)

Table 2 (*continued*)

	Stage III			Stage IV			
	Capecitabine (n = 1413)	CAPOX (n = 2371)	p value (χ^2)	FOLFOX or FOLFIRI (n = 1775)	FOLFOX/FOLFIRI + Bevacizumab (n = 72)	FOLFOX/FOLFIRI + Panitumumab or Cetuximab (n = 386)	p value (χ^2)
Line Complications	**0.2%**	**0.5%**	**0.218**	**4.2%**	**5.6%**	**8.0%**	**0.006**
Psychological[a]	**1.1%**	**1.4%**	**0.563**	**4.6%**	**1.4%**	**3.9%**	**0.367**
Bleeding	**0.6%**	**1.4%**	**0.032**	**2.7%**	**12.5%**	**3.4%**	**< 0.001**
Dermatology & Rheumatology	**0.9%**	**1.2%**	**0.335**	**1.5%**	**1.4%**	**5.4%**	**< 0.001**
Skin reaction	0.5%	0.7%		1.2%	1.4%	5.2%	
Gout[a]	0.4%	0.5%		0.3%	0.0%	0.3%	
Ophthalmic[a]	**0.2%**	**0.3%**	**0.803**	**0.2%**	**1.4%**	**0.8%**	**0.039**
Drug Reaction	**0.1%**	**0.4%**	**0.188**	**0.5%**	**1.4%**	**0.0%**	**0.182**
Death	**1.6%**	**1.7%**	**0.815**	**13.9%**	**9.7%**	**14.5%**	**0.557**

[a] Code must not be present in previous 12 months (see Appendix A)

Table 3
Patient and clinical characteristics for those with pathological stage III colon cancer receiving adjuvant chemotherapy according to whether or not they have evidence of at least one severe acute toxicity.

Total (n = 6012)	Severe Acute Toxicity		*P* value (χ^2)
	Present (n = 1589)		
	n	%	
Age Category			**0.011**
<60	429	26.8	
60–69	538	26.8	
70–79	547	27.2	
≥80	75	19.2	
Prior renal disease			**0.001**
Yes	89	35.5	
No	1500	26.0	
Prior cardiac disease			**0.038**
Yes	95	31.6	
No	1494	26.2	
Performance Status			0.167
0	813	25.9	
1	437	27.0	
≥ 2	138	30.2	
Missing	*791*		
Surgical urgency			**0.004**
Elective/scheduled	1229	25.6	
Emergency/urgent	358	29.7	

Table 4
Clinical outcomes according to the presence of severe acute toxicity for patients with pathological stage III colon cancer.

	Toxicity Flag		*P* value
	Yes (%)	No (%)	
Completion of chemotherapy (n = 6012)			**<0.001**
Yes	556 (18.8)	2402 (81.2)	
No	1033 (33.8)	2021 (66.2)	
Change of route of administration of CAPOX or FOLFOX (n = 4147)			**<0.001**
Yes	54 (51.4)	51 (48.6)	
No	1165 (28.8)	2877 (71.2)	

world practice [45,46]. The lower rates reported for neutropenia and fatigue are likely explained by RCTs being able to identify these toxicities based on information that we do not have available; namely laboratory results and functional information.

4.3. Relation to existing coding frameworks

Our coding framework for severe acute toxicities includes a large number of diagnostic codes which contrasts with two studies of US insurance claims data which analysed just eight and fourteen toxicities, respectively, in breast and lung cancer patients [9,11]. These studies are also limited by inherent exclusions based on age, geography, and insurance status. This is in contrast to our use of national hospital administrative data which includes more than 95% of patients diagnosed within the English NHS.

A Canadian study of early breast cancer patients used ICD-10 codes within linked hospital administrative data to ascertain emergency department visits and hospitalisation rates related to SACT [1,47]. Reasonable accuracy was demonstrated in the identification of SACT-related visits when validated against medical chart records, especially if hospitalisation had occurred (90% sensitivity and 100% specificity). Our study expands on this by reporting a broader range of toxicities and profiles for specific regimens.

4.4. Strengths and limitations

To date, this study represents the largest observational study in colorectal cancer patients to demonstrate real-world severe acute toxicity profiles in a representative cohort of patients across a spectrum of chemotherapy regimens, including biologic therapies.

First, a key strength of this study is the development of a comprehensive and systematic coding framework which aims to maximise the capture of all severe acute toxicities through 'forwards' and 'backwards' coding techniques. Second, we accounted for pre-existing comorbidities to avoid the misclassification of chronic conditions as toxicity. Third, in order to standardise the severity and clinical relevance of toxicities captured for much needed comparisons of regimens, patients groups, and healthcare providers using hospital administrative data, we restricted the analyses to overnight hospitalisations (a measurable consistent outcome) [35]. Fourth, given the framework's breadth it can be applied to any chemotherapy regimens, including potential new therapies (e.g., immunotherapy), as well as being transferable to other cancer types.

A limitation of this study is the reliance on the accurate coding of diagnoses in hospital administrative data. However, diagnostic codes in HES have been shown to be accurate compared to clinical notes, thereby supporting their use for research [48]. It was not feasible to validate these results using medical notes although this has already been done in previous studies [1,12].

In addition, we found that patients not receiving chemotherapy had diagnostic codes from the coding framework present. However, there were factors present which would have increased the background rate of hospitalisations. First, despite attempting to identify a more homogeneous comparison group by using stage I/II patients not receiving chemotherapy rather than stage III patients not receiving chemotherapy, the cohort remained significantly older and more comorbid (Appendix B). However, a strong association between severe acute toxicity and clinical group persisted despite adjustment for age, sex, comorbidity, and performance status (Appendix C). Second, a pseudo timeframe was used because these patients did not actually receive chemotherapy meaning a fixed 6-month period was used for identification of diagnostic codes.

Whilst absolute rates of toxicity are informative, these are likely to be overestimates given the inability to determine from hospital administrative data whether the overnight hospitalisations truly represent severe acute toxicity, or other clinical confounders or disease burden. However, it has previously been shown that 75% of hospital visits during chemotherapy treatment were due to toxicity [1]. The coding framework is therefore best suited for comparing groups receiving different chemotherapy regimens or being treated by different chemotherapy providers.

4.5. Implications

The medical management of cancer patients is becoming increasingly complex with new combinations of therapies and biologic agents. However, there remains disconnect between RCT and real-world patient populations [49]. This means that the ability to quantify the burden of SACT in terms of toxicities in real-world clinical practice has many implications. First, it will facilitate improved counselling of patients and enhance patient and clinician decision-making processes, particularly for therapies used towards the end of life.

Second, an improved appreciation for the real-world incidence of regimen-specific toxicities may allow the development of interventions for more prompt identification and treatment of these [50]. It may uncover rarer adverse events that might not be picked up within the trial setting and, unlike RCTs, hospital administrative data is free from observer bias [51,52]. This is especially important for the novel biologic therapies for which an understanding of their outcomes in real-world populations remains limited.

Third, by using a coding framework based on hospital administrative data, one can start to provide a more detailed understanding of the cost implications of toxicities of novel therapies across different tumour types.

Fourth, the coding framework for real-world data facilitates comparative provider performance monitoring and quality improvement which is essential given previously demonstrated variation in toxicity across providers [11].

Finally, using hospital administrative data is more cost-efficient and less labour-intensive than medical note abstraction. It is also readily available and population-based, facilitating ongoing monitoring. In comparison to claims data there are no exclusions limiting the generalisability of results and the data is fit for purpose.

5. Conclusion

This study has demonstrated the validity of a coding framework for the identification of severe acute toxicity from SACT using diagnostic codes captured in hospital administrative data, alongside a dedicated national chemotherapy dataset. The breadth of the framework means that it can be readily applied to other chemotherapy regimens and cancer types, following appropriate validation.

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CRediT authorship contribution statement

J.M. Boyle: Conceptualization, Methodology, Validation, Formal analysis, Writing – original draft, Writing – review & editing. **T. Cowling:** Methodology, Writing – review & editing. **A. Kuryba:** Writing – review & editing. **J. van der Meulen:** Methodology, Writing – review & editing, Supervision. **M. Braun:** Methodology, Validation, Writing – review & editing, Supervision. **K. Walker:** Methodology, Writing – original draft, Writing – review & editing, Supervision. **A. Aggarwal:** Conceptualization, Methodology, Validation, Formal analysis, Writing – original draft, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Coding framework used to determine severe acute toxicity

Haematology
D701 D702 D703 D708 D709 D70X D695 D696 D699 M311
R233 D65X D65 D611 D618 D619 D648 D509 * D630 D649 *
Constitutional
R530 R531 R538 R53X R64 R64X R630 R634 R638 E877
E860 E86X E861 E869 R600 R601 R609 R60X
Cardiovascular*
I200 * I201 * I208 * I209 * I210 I211 I212 I213 I214 I219 I220 I221 I228 I229 I230 I231 I232 I233 I234 I235 I236 I238 I500 * I501 * I509 * I440 * I441 * I442 * I443 *
I444 * I445 * I446 * I447 * I471 * I472 * I480 * I483 * I484 * I489 * I48X* I450 * I451 * I452 * I453 * I454 * I455 * I456 * I458 * I459 * I490 * I491 * I492 * I493 * I494 *
I495 * I498 * I499 * R000 R001 R002 R008 I10 * I10X* I110 * I119 * I120 * I129 * I130 * I131 * I132 * I139 * I150 * I151 * I152 * I158 * I159 * I630 * I631 * I632 *
I633 * I634 * I635 * I636 * I638 * I639 * I600 * I601 * I602 * I603 * I604 * I605 * I606 * I607 * I608 * I609 * I64 * I64X* I610 * I611 * I612 * I613 * I614 * I615 * I616 *
I618 * I619 * I620 * I621 * I629 * I690 * I691 * I692 * I693 * I694 * I698 * G450 * G451 * G452 * G453 * G454 * G458 * G459 * G460 * G461 * G462 * G463 * G464 * G465 *
G466 * G467 * G468 * I950 I951 I952 I958 I959 I260 I269 I313 I319 I427 I429 I740 I741 I742 I743 I744 I745 I748 I749 I822 I823 I828 I829 I800 I801 I802
I803 I808 I809
Respiratory
R05X R05 J80X J80 J81 J81X R060
Infection
R502 R508 R509 R680 R650 R651 R659 A410 A411 A412 A413 A414
A415 A418 A419 A020 A021 A022 A028 A029 A040 A041 A042 A043 A044 A045 A046 A047
A048 A049 A050 A051 A052 A053 A054 A058 A059 A070 A071 A072 A073 A078 A079 A080
A081 A082 A083 A084 A085 A150 A151 A152 A153 A154 A155 A156 A157 A158
A159 A170 A171 A178 A179 A180 A181 A182 A183 A184 A185 A186 A187 A188 A190 A191
A192 A198 A199 A38 A38X A390 A391 A392 A394 A395 A398 A399 A400 A401
A402 A403 A408 A409 A420 A421 A422 A427 A428 A429 A46 A46X A480 A481 A482
A483 A484 A488 A490 A491 A492 A493 A498 A499 A810 A811 A812 A818 A819 A850
A852 A858 A86X A86 A870 A871 A872 A878 A879 A880 A881 A888 A89 A89X B001 B002 B003 B004 B005
B007 B008 B009 B010 B011 B012 B018 B019 B020 B021 B022 B023 B027 B028 B029
B07X B07 B080 B081 B082 B083 B084 B085 B088 B09X B150 B159 B160 B161 B162 B169 B170
B171 B172 B178 B179 B190 B199 B250 B251 B252 B258 B259 B270 B271 B278 B279 B300
B301 B302 B303 B308 B309 B330 B331 B332 B333 B334 B338 B340 B341 B342 B343 B344
B348 B349 B371 B372 B373 B374 B375 B376 B377 B378 B379 B440 B441 B442 B447
B448 B449 B450 B451 B452 B453 B457 B458 B459 B49X B59X B950 B951 B952 B953 B954 B955
B956 B957 B958 B960 B961 B962 B963 B964 B965 B966 B967 B968 B970 B971 B972 B973
B974 B975 B976 B977 B978 B99 B99X J200 J201 J202 J203 J204 J205 J206 J207 J208 J209
J120 J121 J122 J123 J128 J129 J13 J14 J13X J14X J150 J151 J152 J153 J154 J155 J156 J157 J158
J159 J160 J168 J170 J171 J172 J173 J178 J180 J181 J182 J188 J189 J09 J100 J101 J22X
J108 J110 J111 J118 J850 J851 J852 J853 J860 J869 N10X N390 N300 N308 N309 N340
N151 N450 N459 N410 N412 N413 L00X L010 L011 L020 L021 L022 L023 L024 L028 L029
L030 L031 L032 L033 L038 L039 L040 L041 L042 L043 L048 L049 L050 L059 L080 L081
L088 L089 N700 N709 N710 N72X N730 N732 N733 N735 N760 N762 N764 N61X T814 G000 G001
G002 G003 G008 G009 G01X G020 G021 G028 G030 G038 G039 G040 G041 G042 G048 G049
G050 G051 G052 G058 G060 G061 G062 G07X G08X A851
M600 I330 I339 I300 I301 I308 I309 I400 I401 I408 I409 I514 I518 H700 K052 K113 J040
J041 J042 H600 H601 H603 H660 J010 J011 J012 J013 J014 J018 J019 J020 J028 J029 J030 J038
J039 M871 K102 M860 M861 M869 M000 M001 M002 M008 M009 K750 K610 K611 K612 K613 K614 K800 K803 K804 K810 K830 K630 K65 K65X
Renal
N170 N171 N172 N178 N179 N19X N19 N10 N10X N12X N12 N130
N131 N132 N133 N134 N135 N136 N137 N138 N139 N141 N142 N144 N158 N159 N280
Line Complications
T825 T827 T828 T829 Z452 T800 T801 T802 T808 T809
Gastrointestinal
K521 K528 K529 A090 A099 R110 R111 R112 R11X R13X K590 K564 K121 K123 B370 K710 K711 K712 K716 K719 K720 K729 R17 R17X K221 K223 K251 K253 K255 K261 K262
K263 K265 K271 K273 K275 K281 K283 K285 K291 K293 K295 K914 K631 N321 N820 N822 N823 N824 K316 K603 K605 K604
Bleeding
R040 R310 R31X N938 N939 R042 J942 K625 I850 K920 K921 K922 K250
K252 K254 K256 K260 K262 K264 K266 K270 K272 K274 K276 K280 K282 K284 K286
K290 K292 K294 K296
Metabolic & Endocrine
E870 E871 E872 E873 E874 E875 E876 E878 E833 E835 E838 E839 E883 E834
R730 R739 E15 E15X E160 E161 E162 E032 E058 E064 E273 E231
Pain
R100 R101 R102 R103 R104 M255 M540 M541 M542 M543 M544 M545
M546 M548 M549 R07 R07X R070 R071 R072 R073 R074 R520 R529 H920 K146 H571 M796
Neurological*
R55X R55 R42 R42X G400 * G401 * G402 * G403 * G404 * G405 * G406 * G407 * G408 * G409 *
G410 * G411 * G412 * G418 * G419 * R56 * R560 * R568 * G620 G628 G629 R200 R201 R202 R203 R208 R209
H910 H931 J385 G250 G251 G252 G253 G258 G259 G240 G254 G256 G711 G720 R270 R260
G430 G431 G432 G433 G438 G439 G440 G441 G442 G443 G444 G448 R51 R51X
Dermatology & Rheumatology*

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R21X R21 L270 L271 L298 L299 L51 L510 L511 L512 L518 L519
L539 R238 R239 M100 * M102 * M104 * M109 *
Drug Reaction
L500 T782 T783 T784 T886 T887 T451
Ophthalmic*
H320 H191 H192 H10 H100 H101 H102 H103 H105 H108
H109 H11 H111 H112 H113 B300 B301 B302 B303 B308 B309 H150 H151 H158 H159 H160
H161 H162 H163 H164 H168 H169 M350 H170 H171 H178 H179 H180 H181 H182 H183
H184 H186 H187 H188 H189 H200 H202 H208 H209 H210 H211 H212 H213 H214 H215
H218 H219 H263 H278 H279 H406 H531 H532 H533 H534 H535 H536 H538 H539 H540 *
H541 * H542 * H543 * H544 * H545 * H546 * H549 * H000 H001 H010 H018 H019 H041 H042 H043
H020 H021 H050 H052 H058 H059 H578 H579 H490 * H491 * H492 * H493 * H494 * H498 *
H499 * H500 * H501 * H502 * H503 * H504 * H505 * H506 * H508 * H509 * H510 * H511 * H512 * H518 * H519 *
H46X* H46 * H470 * H471 * H472 * H473 * H474 * H475 * H476 * H477 * H300 * H301 * H302 * H308 * H309 * H310 *
H311 * H313 * H314 * H318 * H319 * H330 * H332 * H335 * H340 * H341 * H342 * H348 * H349 * H350 * H352 * H353 * H356 * H357 * H358 * H359 * H431 H432 H433
H438 H439 H440 H441 H448 H449
Psychological*
F320 F321 F322 F323 F328 F329 * F410 F411 F412 F413 F418 F419 *

*Codes excluded if present in the 12 months preceding chemotherapy administration

Appendix B. Patient characteristics according to clinical group and receipt of chemotherapy

	Stage I/II MR – no chemo (n = 13,573)		Stage III MR – chemo (n = 6012)		Stage IV – chemo (n = 3680)		P value*
	No.	%	No.	%	No.	%	
Sex							**< 0.001**
Male	7217	53.2	3177	52.8	2119	57.6	
Female	6355	46.8	2835	47.2	1561	42.4	
Age (years)							**< 0.001**
<60	1447	10.7	1599	26.6	1129	30.7	
60–69	3148	23.2	2009	33.4	1113	30.2	
70–79	5023	37	2014	33.5	1100	29.9	
≥80	3955	29.1	390	6.5	338	9.2	
RCS Charlson Score							**< 0.001**
0	6637	48.9	3787	63	2176	60.9	
1	4303	31.7	1695	28.2	1024	28.7	
≥2	2633	19.4	530	8.8	373	10.4	
Missing	0	0	0	0	107	2.9	
Performance Status							**< 0.001**
0	5459	48.3	3141	60.2	1468	45.5	
1	3798	33.6	1620	31	1169	36.2	
≥2	2040	18.1	460	8.8	590	18.3	
Missing	2276	16.8	791	13.2	453	12.3	

*Chi-squared test

Appendix C. Multivariable regression model estimating the association between severe acute toxicity and clinical group, adjusting for age, sex, comorbidity, and performance status

	Adjusted Odds Ratio (aOR)	95% Confidence Intervals	P value*
Age (years)			0.153
< 60	1.0	–	
60–69	0.92	0.84–1.02	
70–79	0.96	0.87–1.06	
≥ 80	1.03	0.92–1.16	
Sex			0.217
Female	1.0	–	
Male	1.04	0.98–1.12	
RCS Charlson Score			**< 0.001**
0	1.0	–	
1	1.24	1.15–1.34	
≥ 2	1.77	1.60–1.95	
Performance Status			**< 0.001**
0	1.0	–	
1	1.18	1.08–1.28	
≥ 2	1.75	1.58–1.94	
Clinical group			
Stage I/II MR* * – no chemo	1.0	–	**< 0.001**
Stage III MR – chemo	2.98	2.75–3.23	
Stage IV – chemo	8.98	8.22–9.80	

*Wald value
* *Major resection

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6. DETERMINANTS OF VARIATION IN ADJUVANT CHEMOTHERAPY USE

6.1 Research paper 1

Title: Determinants of Variation in the Use of Adjuvant Chemotherapy for Stage III Colon Cancer in England

The online PDF version can be accessed here.

Supplementary material can be found in Appendix 13.

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Student ID Number	1802390	**Title**	Dr
First Name(s)	Jemma Megan		
Surname/Family Name	Boyle		
Thesis Title	Using National Routine Data to Explore the Utilisation and Outcomes of Multimodal Treatment in the Management of Colorectal Cancer		
Primary Supervisor	Dr Kate Walker		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

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Original Article

Determinants of Variation in the Use of Adjuvant Chemotherapy for Stage III Colon Cancer in England

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Abstract

Aims: Adjuvant chemotherapy (ACT) for stage III colon cancer is well-established. This study aimed to explore the determinants of ACT use and between-hospital variation within the English National Health Service (NHS).

Materials and methods: In total, 11 932 patients (diagnosed 2014–2017) with pathological stage III colon cancer in the English NHS were identified from the National Bowel Cancer Audit. Records were linked to Systemic Anti-Cancer Therapy and Hospital Episode Statistics databases. Multi-level logistic regression analyses were carried out to estimate independent factors for ACT use, including age, sex, deprivation, comorbidities, performance status, American Society of Anaesthesiologists (ASA) grade, surgical urgency, surgical access, TNM staging, readmission and hospital-level factors (university teaching hospital, on-site chemotherapy and high-volume centre). A random intercept was modelled for each English NHS hospital (n = 142). Between-hospital variation was explored using funnel plot methodology. Fully adjusted random-intercept models were fitted separately in young (<70 years) and elderly (≥70 years) patients and intra-class correlation coefficients estimated.

Results: 60.7% of patients received ACT. Age was the strongest determinant. Compared with patients aged <60 years, those aged 60–64 (adjusted odds ratio [aOR] 0.76, 95% confidence interval 0.63–0.93), 65–69 (aOR 0.63, 95% confidence interval 0.54–0.74), 70–74 (aOR 0.53, 95% confidence interval 0.44–0.62), 75–79 (aOR 0.23, 95% confidence interval 0.19–0.27) and ≥80 years (aOR 0.05, 95% confidence interval 0.04–0.06) were significantly less likely to receive ACT. With adjustment for other factors, ACT use was more likely in patients with higher socioeconomic status, fewer comorbidities, better performance status, lower ASA grade, advanced disease, elective resections, laparoscopic procedures and no unplanned readmissions. Hospital-level factors were non-significant. The observed proportions of ACT administration in the young and elderly were 46–100% (80% of hospitals 74–90%) and 10–81% (80% of hospitals 33–65%), respectively. Risk adjustment did not reduce between-hospital variation. Despite adjustment, age accounted for 9.9% (7.2–13.4%) of between-hospital variation in the elderly compared with 2.7% (1.2–5.7%) in the young.

Conclusions: There is significant between-hospital variation in ACT use for stage III colon cancer, especially for older patients. Advanced age alone seems to be a greater barrier to ACT use in some hospitals.

Key words: Adjuvant; chemotherapy; colonic neoplasms; England

Introduction

In England, approximately about 19 000 cases of colon cancer are diagnosed annually [1]. Of these, 25% present with stage III disease and up to 40% of these develop recurrence after curative resection [2].

The benefits of adjuvant chemotherapy (ACT) for stage III colon cancer are well-established [3]. Current guidelines in

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England recommend ACT in fit patients [4]. A recent audit report suggested that only 57% of patients with stage III colorectal cancer (CRC) received ACT in the English National Health Service (NHS), with variation between regions (41–68%) [1]. ACT has been shown to improve overall 5-year relative survival by up to 33%, meaning under-utilisation is significant [5].

Studies outside the UK have shown similar rates of ACT use for stage III colon cancer [6–8]. Most studies have been conducted in the USA but often include single-state cancer registries or SEER-Medicare data (only insured patients aged 65 years or older), which limits their representativeness. Studies using National Cancer Database data are most representative but still only include one third of inpatient hospitals [9].

Current International Society of Geriatric Oncology (SIOG) consensus recommendations advise fluoropyrimidine monotherapy for patients aged 70 years or older, with oxaliplatin therapy of uncertain benefit [10]. Age has consistently been shown as one of the strongest determinants of ACT use [6–8,11], which is particularly important in the context of an ageing population. There has been a recent focus on the under-treatment of elderly patients with cancer [12,13].

Variation in chemotherapy use between hospitals and regions has been observed but the reasons underlying this are not well understood [14,15]. No previous studies have investigated explanations for between-hospital variation in chemotherapy use. Understanding these reasons is crucial in reducing unwarranted variation, facilitating increased rates of ACT use and potentially improving survival outcomes.

We linked the National Bowel Cancer Audit (NBOCA) [16], a unique resource involving prospective mandatory data collection for all newly diagnosed CRC patients in the English NHS, to chemotherapy and hospital administrative databases. This enabled us to establish current national practice in the use of ACT in stage III colon cancer, explore determinants for use of ACT according to patient and hospital-level characteristics, establish between-hospital variation and investigate possible reasons for this.

Our dataset included all centres providing colon cancer treatment in the English NHS with no exclusions based on insurance status, socioeconomic status or age, and with case ascertainment >95% of all adults diagnosed with primary colon cancer in England. This ‘real-world’ contemporary data from the English NHS, where care is free at the point of need, provides an effective platform for investigating hospital-level variation.

Materials and Methods

Study Population

National Bowel Cancer Audit

Patients aged 18 years or older with a primary diagnosis of colon cancer, according to International Classification of Diseases, 10th revision (ICD-10) codes, between 1 April 2014 and 31 March 2017 who had undergone major resection with pathological stage III disease were identified in the NBOCA database. Cancers of the appendix were excluded. Identified patients were linked to the Admitted Patient Care records in Hospital Episode Statistics (HES-APC), an administrative database of all inpatient admissions to NHS hospitals [17].

The linked NBOCA–HES-APC cohort included 11 932 patients deemed potentially eligible for ACT from 142 English NHS hospitals (Figure 1). Patients diagnosed within a private hospital and undergoing major resection in an NHS hospital were included. Patients diagnosed and treated entirely in the private sector were not captured, but represent a small number of patients.

In total, 604 patients (5%) died within 4 months of surgery. This small proportion was retained in the main analysis because it is unlikely to significantly affect the results and provides a full representation of ACT use, including all patients diagnosed with stage III disease.

Systemic Anti-cancer Therapy (SACT) Database

The SACT database is the world's first comprehensive, dedicated chemotherapy dataset that mandated submission of data by all English NHS providers of chemotherapy in any inpatient, day case, outpatient or community setting, from April 2014 [18]. SACT data were available until 30 September 2017, providing a minimum of 4 months of follow-up from surgery for all patients. SACT provides the regimen start date and regimen name.

Identification of patients receiving adjuvant chemotherapy

Eligible patients were considered to have received ACT if their NBOCA record linked to a SACT record showing use of any potentially curative colonic chemotherapy regimen within 4 months after surgery. The proportion of patients receiving each type of regimen is listed within Supplementary Table S1.

We validated ACT use utilising HES-APC. All inpatient admissions for each patient within 4 months after surgery were searched for relevant chemotherapy codes (Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures, 4th revision and ICD-10) (Supplementary Table S2).

Patient and Hospital Characteristics

Data regarding sex, age, pathological staging (TNM staging), operative date, surgical urgency, performance status [19], American Society of Anaesthesiologists (ASA) grade [20] and surgical access were obtained from NBOCA. Comorbidities, socioeconomic status and 30-day unplanned readmission data were obtained from HES-APC. The Royal College of Surgeons' (RCS) Charlson comorbidity score Charlson comorbidity score was used for diagnostic codes identified in the year preceding colon cancer diagnosis [21].

SIOG recommendations use 70 years as the distinction between elderly and non-elderly; the rationale for our age cut-off [10]. Patients were recorded as having an unplanned

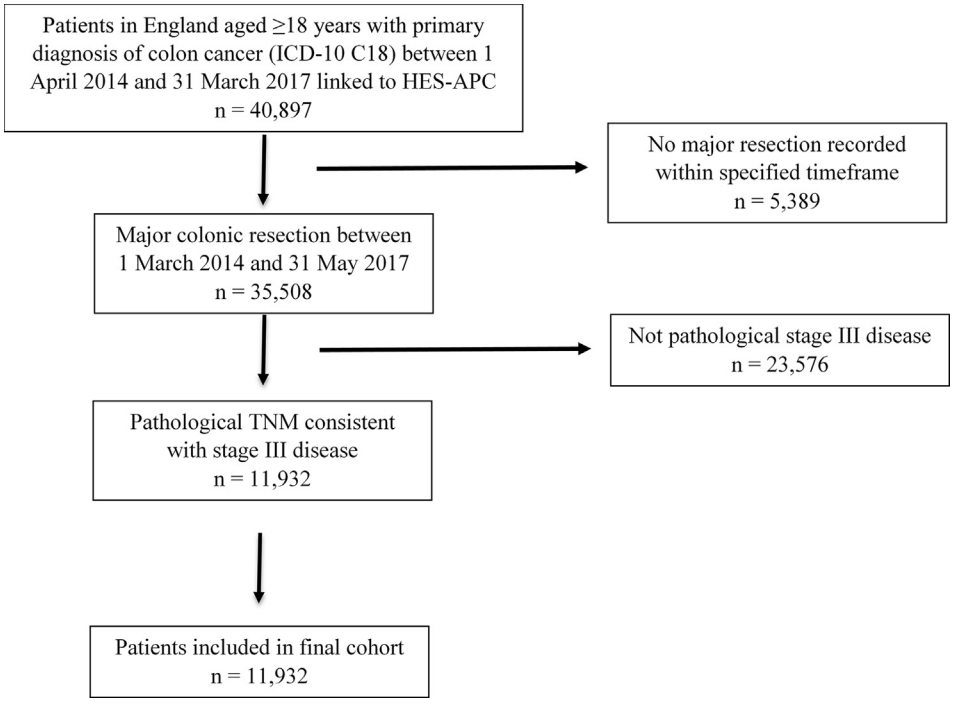

Fig 1. Flow chart showing inclusion of patients in study.

30-day readmission if HES-APC showed an emergency admission within 30 days of surgery.

Socioeconomic status was derived from the Index of Multiple Deprivation, which ranks 32 482 geographical areas of England according to their level of deprivation across seven domains [22]. Patients are allocated to an Index of Multiple Deprivation quintile (IMDQ) based on the national ranking of the area corresponding to their postcode.

In the English NHS, hospital-level care is provided by 'hospital trusts'. These may consist of an individual hospital or several hospitals combined. We use 'hospital' to refer to these hospital trusts. Hospital-level characteristics were derived from the hospital carrying out the surgery according to NBOCA. University teaching hospitals were identified from the University Hospital Association of United Kingdom University Hospitals [23]. On-site chemotherapy presence was collected in an annual national NBOCA survey of CRC services [24]. Hospitals were categorised as high-volume if they carried out on average >100 CRC resections per year, as this represented the median value.

Final Cohort

Table 1 shows the proportion of the 11 932 patients identified in SACT and/or HES-APC as receiving ACT. For the main analysis, 7239 patients with a chemotherapy record in either database were considered to have received ACT; 8.0% (579/7,239) of these were identified from HES-APC alone.

Statistical Analysis

Multivariable random-effects logistic regression was used to estimate associations between ACT use and the patient and hospital characteristics described above. A random intercept was modelled for each hospital to account for possible clustering of results within hospitals. Subgroup analyses were carried out in the same manner to evaluate patient and hospital characteristics separately in the young (<70 years) and elderly (≥70 years).

Missing values for determinants were imputed with multiple imputation using chained equations, creating 10 datasets and using Rubin's rules to combine the estimated odds ratios across the datasets [25]. Multiple imputation was used to impute all missing data for socioeconomic status, RCS Charlson score, performance status, ASA grade, urgency of resection, surgical access and pathological T-stage.

Hospital-level variation in ACT use was explored visually using funnel plots to establish whether the between-hospital variation in the proportion of patients receiving ACT was greater than expected by chance alone [26].

Table 1
Proportion of patients identified as having adjuvant chemotherapy according to the Systemic Anti-Cancer Therapy (SACT) and/or Hospital Episode Statistics – Admitted Patient Care (HES-APC) databases (row and column percentages given)

	Chemotherapy according to SACT		
Chemotherapy according to HES-APC	Yes	No	Total
Yes	4742 (89.1%) (71.2%)	579 (10.9%) (11.0%)	5321
No	1918 (29.0%) (28.8%)	4693 (71.0%) (89%)	6611
Total	6660	5272	11 932

Separate fully adjusted funnel plots were generated for all patients, patients aged below 70 years only and patients aged 70 years or older only, to explore whether between-hospital variation was associated with age. All 142 hospitals had 10 or more patients eligible for ACT overall and were included in the funnel plot for all patients; 135 hospitals had 10 or more patients aged below 70 years and 10 or more patients aged 70 years or older and were included in the young and elderly funnel plots.

The intra-class correlation coefficient (ICC) was used to quantify the between-hospital variation in a fully adjusted random-intercept logistic regression model. The ICC represents the proportion of the total variance that is between hospitals, despite adjustment for all other determinants, with larger values showing greater between-hospital variation.

To identify sources of between-hospital variation, the ICC was estimated in eight strata of the cohort: young (<70 years) versus elderly (≥70 years); non-comorbid (Charlson = 0) versus comorbid (Charlson ≥ 1); performance status 0–1 versus performance status ≥2; and low (IMDQ 1–2) versus high (IMDQ 3–5) socioeconomic status. One risk-adjustment model was estimated in all patients and used for each stratum. We compared the ICC between strata using an independent samples *t*-test to calculate two-tailed *P*-values (0.05 significance level).

All statistical analyses were conducted using STATA® version 15.1 (StataCorp, College Station, Texas, USA).

Results

Determinants of Adjuvant Chemotherapy Use

In total, 7239 patients (60.7%) were identified as having received ACT (Table 2). The strongest predictor for ACT use was age, despite adjustment for all other factors. Compared with 85.3% of patients aged <60 years who received ACT, 80.7%, 76.3%, 71.3%, 50.2% and 18.6% of those aged 60–64 years (adjusted odds ratio [aOR] 0.76, 95% confidence interval 0.63–0.93), 65–69 years (aOR 0.63, 95% confidence interval 0.54–0.74), 70–74 years (aOR 0.53, 95% confidence interval 0.44–0.62), 75–79 years (aOR 0.23, 95% confidence interval 0.19–0.27) and ≥80 years (aOR 0.05, 95% confidence interval 0.04–0.06) received ACT, respectively. Although the use of ACT decreased with age, a substantial proportion of patients aged below 70 years did not receive ACT.

Other patient characteristics associated with increased ACT use included higher socioeconomic status, fewer comorbidities, better performance status and lower ASA grade. ACT use was also more likely in the multivariable model in patients who had had an elective procedure, had undergone laparoscopic resection, had more advanced disease (T3/T4 or N2 disease) and did not have an unplanned readmission.

Subgroup analyses of patient and hospital-level factors were carried out for the young (<70 years) and elderly (≥70 years) (Supplementary Table S3). The multivariable results were largely similar to those of the whole sample, except that women were less likely to receive ACT if they were old, adjusting for other factors.

A further analysis was carried out on patients aged 70 years or older to investigate ACT use in different age strata according to comorbidities, performance status and ASA grade (Supplementary Table S4). A downward trend in ACT use was observed with increasing age for each factor, for example, 75% of 70–74 year olds with performance status 0/1 received ACT versus 25% of those aged 80 years or older also with performance status 0/1.

Variation Between Hospitals

ACT use varied substantially between hospitals. The observed hospital proportion of chemotherapy administered ranged from 26 to 86%. Among patients younger than 70 years old, observed proportions ranged from 46 to 100% (80% of hospitals 74–90%). In comparison, among patients aged 70 years or older, observed proportions ranged from 10 to 81% (80% of hospitals 33–65%).

Adjustment for factors included in the multivariable model did not reduce hospital variation. Assuming differences arise from random errors alone, the expected number of hospitals outside the inner (95%) and outer (99.8%) funnel limits for all analyses is 7 and 0.3, respectively. For patients younger than 70 years old, 10 hospitals lay outside the inner funnel limits and 0 hospitals outside the outer limits, compared with 21 and 5 hospitals for patients aged 70 years or older (Figure 2).

The ICC for patients younger than 70 years old was 2.7% (95% confidence interval 1.2–5.7%) compared with 9.9% (95% confidence interval 7.2–13.4%) for patients aged 70 years or older, which shows a significantly greater proportion of the total variance to be between hospitals in the elderly compared with younger patients ($P < 0.001$). Differences in ICCs by comorbidity, performance status and socioeconomic status were not statistically significant (Figure 3).

Discussion

This large, representative national study has shown significant variation in the use of ACT for patients with stage III colon cancer within the English NHS. It has also shown that age has a significant effect on ACT use, which persists despite risk-adjustment suggesting underuse of ACT in elderly patients. A significantly greater proportion of between-hospital variation was found in the elderly, indicating that age is a greater barrier to ACT use in some hospitals compared with others. We also identified socioeconomic status as a determinant of ACT use, despite case-mix adjustment.

This was the first population-based study evaluating the use of ACT for stage III colon cancer in England. Our finding that 60% of patients received ACT is similar to figures found elsewhere. A recent large US study of 124 008 patients with stage III colon cancer suggested that 66% received ACT between 2003 and 2011 [7]. Two Canadian studies reported

Table 2
Distribution of patient and hospital characteristics and their effect on adjuvant chemotherapy use

	Total (%) $n = 11\,932$	Received adjuvant chemotherapy (%) $n = 7239$	P value (X^2)	Adjusted odds ratios (95% confidence interval)	P value
Sex			0.009		0.368
Male	6227 (52.2)	3847 (61.8)		1.0	
Female	5705 (47.8)	3392 (59.5)		0.96 (0.88–1.05)	
Age (years)			<0.001		<0.001
<60	2267 (19.0)	1933 (85.3)		1.0	
60–64	1320 (11.1)	1065 (80.7)		0.76 (0.63–0.93)	
65–69	1758 (14.7)	1341 (76.3)		0.63 (0.54–0.74)	
70–74	1996 (16.7)	1423 (71.3)		0.53 (0.44–0.62)	
75–79	1976 (16.6)	992 (50.2)		0.23 (0.19–0.27)	
≥80	2615 (21.9)	485 (18.6)		0.05 (0.04–0.06)	
Socioeconomic status (IMDQ)			0.149		0.002
1 (most deprived)	1815 (15.2)	1061 (58.5)		1.0	
2	1990 (16.7)	1193 (60.0)		1.11 (0.93–1.33)	
3	2603 (21.8)	1602 (61.5)		1.29 (1.10–1.50)	
4	2742 (23.0)	1666 (60.8)		1.22 (1.05–1.42)	
5 (least deprived)	2759 (23.1)	1708 (61.9)		1.36 (1.15–1.60)	
Missing*	23	9			
RCS Charlson score			<0.001		<0.001
0	6428 (53.9)	4425 (68.8)		1.0	
1	3344 (28.0)	1913 (57.2)		0.80 (0.72–0.90)	
≥2	1524 (12.8)	570 (37.4)		0.50 (0.44–0.58)	
Missing*	636	331			
Performance status			<0.001		<0.001
0	4989 (41.8)	3724 (74.6)		1.0	
1	3424 (28.7)	1974 (57.7)		0.83 (0.73–0.95)	
2	1319 (11.1)	521 (39.5)		0.54 (0.45–0.65)	
≥3	441 (3.7)	67 (15.2)		0.17 (0.13–0.24)	
Missing*	1759	953			
ASA fitness grade			<0.001		<0.001
I	1469 (12.3)	1182 (80.5)		1.0	
II	6091 (51.1)	4226 (69.4)		0.95 (0.81–1.12)	
III	3272 (27.4)	1339 (40.9)		0.56 (0.50–0.63)	
IV or V	365 (3.1)	72 (19.7)		0.24 (0.18–0.32)	
Missing*	735	420			
Urgency of resection			<0.001		0.001
Elective/scheduled	9005 (75.5)	5668 (62.9)		1.0	
Emergency/urgent	2908 (24.4)	1560 (53.7)		0.80 (0.71–0.91)	
Missing	19	11			
Surgical access			<0.001		<0.001
Open	4885 (40.9)	2689 (55.1)		1.0	
Laparoscopic-converted	971 (8.1)	580 (59.7)		1.0 (0.83–1.19)	
Laparoscopic	6035 (50.6)	3947 (65.4)		1.28 (1.14–1.44)	
Missing*	41	23			
Pathological T-stage			0.001		0.006
T1	241 (2.0)	155 (64.3)		1.0	
T2	706 (5.9)	471 (66.7)		1.35 (0.96–1.88)	
T3	5976 (50.1)	3639 (60.9)		1.47 (1.10–1.95)	
T4	5004 (41.9)	2971 (59.4)		1.61 (1.20–2.17)	
Missing*	5	3			
Pathological N-stage			<0.001		<0.001
N1	7620 (63.9)	4464 (58.6)		1.0	
N2	4312 (36.1)	2775 (64.4)		1.31 (1.18–1.46)	
30-day readmission			0.001		<0.001
No	10 921 (91.5)	6675 (61.1)		1.0	
Yes	1011 (8.5)	564 (55.8)		0.66 (0.56–0.77)	
University teaching hospital			0.595		0.475
No	8880 (74.4)	5375 (60.5)		1.0	
Yes	3052 (25.6)	1864 (61.1)		0.93 (0.75–1.15)	

(*continued on next page*)

Table 2 (*continued*)

	Total (%) $n = 11\ 932$	Received adjuvant chemotherapy (%) $n = 7239$	*P* value (X^2)	Adjusted odds ratios (95% confidence interval)	*P* value
On-site chemotherapy facilities			0.927		0.906
No	1336 (11.2)	809 (60.6)		1.0	
Yes	10 596 (88.8)	6430 (60.7)		0.99 (0.81–1.21)	
High-volume centre			0.232		0.864
No	2643 (22.2)	1577 (59.7)		1.0	
Yes	9289 (77.9)	5662 (61.0)		1.02 (0.81–1.28)	

ASA, American Society of Anaesthesiologists; IMDQ, Index of Multiple Deprivation Quintile; RCS, Royal College of Surgeons.
* Values were missing prior to the use of multiple imputation. There remained no missing data following imputation.

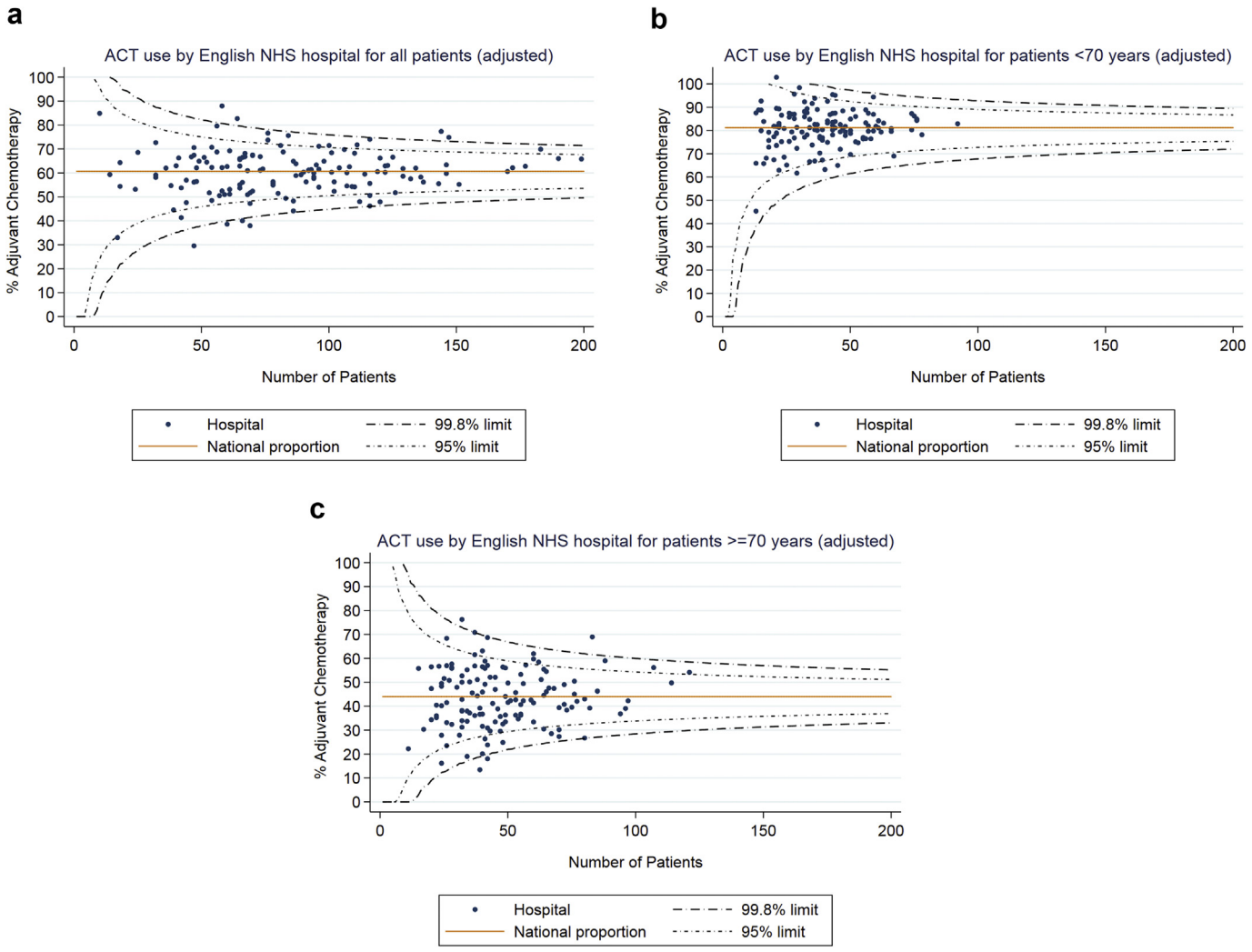

Fig 2. Funnel plots showing the proportion of patients undergoing major resection with pathological stage III colon cancer who received adjuvant chemotherapy at each hospital, adjusted for all patient and hospital factors in Table 2. (a) All patients; (b) young patients (<70 years); (c) elderly patients (≥70 years).

that 50% of patients received chemotherapy, despite a healthcare system where access to treatment is free [27,28]. Within Europe, similar ACT rates have been found in Germany (65%) [29], France (65.1%) [30], Italy (64.6%) [30], Belgium (68%) [2], Sweden (55%) [2] and the Netherlands (61%) [2].

Our multivariable analysis showed findings that are largely consistent with those expected. Although we would expect age to influence ACT use, the magnitude of the effect despite risk-adjustment was marked and most apparent in those aged 75 years or older. The patients included in this study were deemed fit enough to tolerate a major colonic

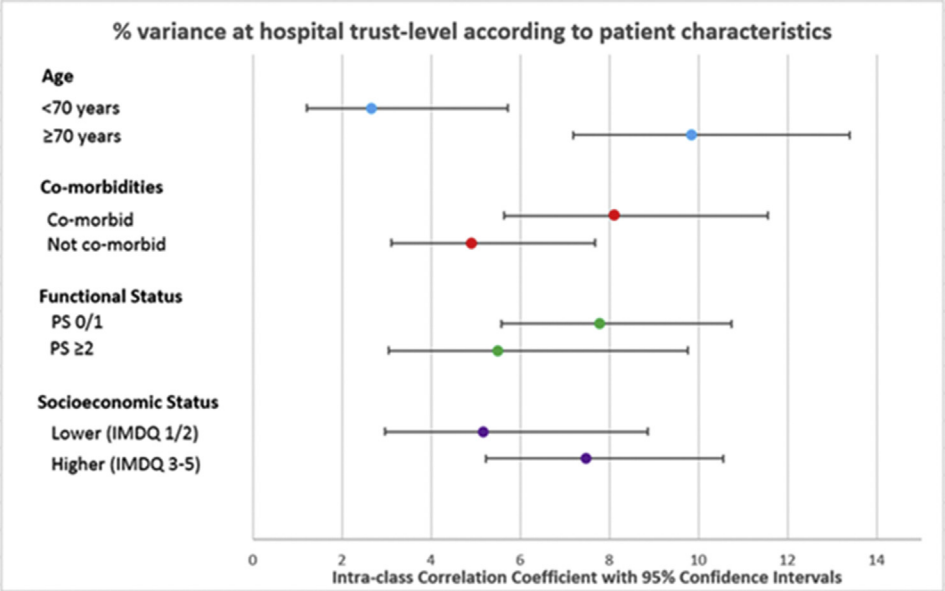

Fig 3. The proportion of the total variation that is between hospitals according to age, comorbidities, performance status and socioeconomic status.

resection, suggesting that many have the potential to be candidates for ACT, although postoperative status and life expectancy also need to be taken into consideration.

Previous studies are in agreement with our finding that socioeconomic status is a determinant of ACT use [31,32]. Suggested explanations include delayed presentation [33], increased comorbidities [32] and reduced health-seeking behaviours [31]. Socioeconomically deprived patients in our cohort tended to be younger and more comorbid, and had more often undergone emergency resection (results not shown). Education and targeted screening may help facilitate ACT use in this group by reducing emergency presentations. However, socioeconomic status was a significant determinant despite risk adjustment suggesting it is a barrier to ACT use in its own right.

Comorbidity has been associated with ACT use [11], but performance status and ASA grade have not previously been reported. These three determinants have been shown to have limited correlation in CRC patients, suggesting that they represent independent measures of patient well-being and supporting their inclusion in our model [34].

As described previously, we have shown that laparoscopic surgery and unplanned readmissions are significant determinants for ACT [2,35–37]. Laparoscopic surgery may increase ACT use because it is associated with fewer complications, faster recovery and reduced inflammatory response. Unplanned readmissions prolong hospital stay, which may make the timely use of ACT more difficult.

Patients undergoing emergency surgery were less likely to receive ACT. Previous studies have shown conflicting evidence [30,38]. An explanation for emergency patients being less likely to receive ACT is that they are at increased risk of experiencing postoperative complications and are more likely to have stomas formed.

Hospital-level characteristics, including being a university teaching hospital or having on-site chemotherapy facilities, were not associated with ACT use. A Scottish study showed the significance of on-site chemotherapy facilities, but its results were limited because of the absence of staging information [39].

Other hospital-level factors that we were unable to measure in this study but may influence between-hospital variation in ACT use include rurality, distance to the nearest chemotherapy centre and oncologist characteristics, such as length of practice and volume of consultations for patients with CRC [37].

A systematic review evaluating geographical variation in access to chemotherapy within the UK suggested that healthcare boundaries, such as which English 'cancer alliance' a hospital lies within rather than 'natural geographic factors', were most important. The influence of commissioners, policy-makers and individual providers are therefore important [14]. Although most marked in the elderly, variation was also present in the young, with up to 55% of patients younger than 70 years old not receiving ACT in some hospitals. The observed variation in ACT use is important because it suggests that not all patients are receiving optimal adjuvant therapy, particularly those aged 70 years or older.

Wennberg [40] described the concept of 'unwarranted variation' whereby variation in the use of healthcare services cannot be explained by variation in patient illness or patient preference. Unwarranted variation may consist of overtreatment or undertreatment. Underlying factors can include clinician and patient preferences and attitudes, availability of particular resources and discrepancies in the treatment of certain patient groups, for example the elderly and those from a lower socioeconomic background, consistent with our study findings [41].

Within this study, we accounted for case-mix differences and it is unlikely that the between-hospital variation after adjustment can be fully explained by patient preferences. This suggests that 'unwarranted variation' exists in the use of ACT and highlights the need for a more consistent use of ACT resources in the English NHS.

Patient choice is an important and complex factor determining the use of chemotherapy. Patient-related factors influencing decision-making for cancer treatments are extensive and can include social, cognitive and psychological issues. Physician-related factors such as poor communication, lack of information or distrust in the patient–clinician relationship are also important. Clinician recommendations have been found to be the most important influence in patient decision-making pathways [42].

Qualitative studies support our suggestion that unwarranted variation (as identified in this study), especially in the elderly, may be attributable to varying clinician practice. One study showed that clinician recommendations varied more widely according to increasing comorbidity in the elderly compared with the young [43]. Other studies have highlighted bias in clinician decision-making related to advancing age [44,45].

Given these findings, clinicians should recognise the importance of their input into shared decision-making and be educated in this process. Patients should also be educated about the benefits and risks of ACT and support provided as necessary to facilitate informed decision-making and overcome potential barriers. Specialist nurses may provide support in this area.

SIOG recommends the use of comprehensive geriatric assessments, which facilitate the formation of individualised treatment plans. There is evidence supporting their use for chemotherapy decision-making [46,47].

Clinical trials need to be enriched through the inclusion of more elderly, frail patients [48]. Real-world data can be used to evaluate outcomes in groups under-represented by trials. Both of these can be used to support the development of elderly-specific guidelines and associated educational resources to aid clinical decision-making and reduce the observed variation in practice.

The NBOCA will be implementing a new process measure pertaining to ACT use for stage III colon cancer. It will report figures for England at a hospital level. Other healthcare providers should consider similar evaluations of practice that highlight 'unwarranted variation', facilitate quality improvement and allow monitoring of ACT rates relative to national benchmarking.

There is robust evidence that ACT improves outcomes. Underuse could therefore be a contributing factor to England having lower survival rates for colon cancer compared with other European countries. A recent study suggested that the survival deficit in England is partly attributable to shortfalls in treatment, with a steep declining age gradient in the probability of receiving colonic resection (particularly those aged 75 years or older) compared with Denmark, Norway and Sweden [49]. Our results indicate that similar patterns may exist for ACT use.

There were several limitations to our study. First, we considered that patients had received ACT if there was evidence of colonic chemotherapy, irrespective of regimen, within the first 4 months after surgery. This approach is supported by the observation that about 96% of observed regimens were in keeping with standard practice (Supplementary Table S1) [4]. The remainder could represent atypical practice or palliative treatment. We were also unable to obtain regimen details for patients captured in HES-APC alone. However, a sensitivity analysis carried out using SACT data alone to identify patients who had received ACT produced similar results (five hospitals were excluded from this analysis as they captured $<$50% of ACT compared with HES-APC).

We could not determine chemotherapy refusal rates, but these have been reported to be around 10% [50] and some studies used an offer of chemotherapy as their numerator, which did not substantially change their results [6]. Refusal is therefore unlikely to completely explain ACT underuse.

Finally, we were unable to capture all factors that may influence ACT use, such as social support, nutrition and cognitive function. Neither could we measure the severity of individual comorbidities, although we captured performance status and ASA grade.

Our study included a large representative cohort of patients with stage III colon cancer identified in all hospitals providing colon cancer care in the English NHS. SACT provides a unique data source, with data captured directly by chemotherapy providers. Linkage of multiple national datasets facilitated further validation of the data.

Conclusions

Our study represents an evaluation of current practice in the use of ACT for stage III colon cancer in the English NHS. We found considerable variation in ACT use between hospitals, most prominently in elderly patients. We also showed that, despite case-mix adjustment, there is an association between socioeconomic status and ACT use, suggesting possible inequalities in access to ACT. Finally, we highlighted the importance of postoperative recovery in the use of ACT.

We envisage that these findings will be applicable to healthcare settings outside of the UK. A more considered use of ACT, particularly in elderly patients, may improve outcomes.

Conflict of Interest

T.E. Cowling is supported by the Medical Research Council (MR/S020470/1). This study was undertaken alongside the National Bowel Cancer Audit. The audit is commissioned by the Healthcare Quality Improvement Partnership (HQIP) as part of the National Clinical Audit and Patient Outcomes Programme and funded by NHS England and the Welsh Government (www.hqip.org.uk/national-

programmes). Neither HQIP nor the funders had any involvement in the study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication. The researchers had full independence from HQIP.

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This study was based on data collected by the National Bowel Cancer Audit linked to the Systemic Anti-cancer Therapy database (https://www.chemodataset.nhs.uk/home) made available by the National Cancer Analysis and Registration Service and Hospital Episode Statistics made available by NHS Digital (https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2019.12.008.

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7. IMPACT OF ADJUVANT CHEMOTHERAPY COMPLETION & TREATMENT MODIFICATION ON SURVIVAL

7.1 Research paper 2

Title: Survival outcomes associated with completion of adjuvant oxaliplatin-based chemotherapy for stage III colon cancer: A national population-based study

The online PDF version can be accessed here.

Supplementary material can be found in Appendix 14.

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SECTION A – Student Details

Student ID Number	1802390	**Title**	Dr
First Name(s)	Jemma Megan		
Surname/Family Name	Boyle		
Thesis Title	Using National Routine Data to Explore the Utilisation and Outcomes of Multimodal Treatment in the Management of Colorectal Cancer		
Primary Supervisor	Dr Kate Walker		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	International Journal of Cancer		
When was the work published?	September 2021		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	N/a		
Have you retained the copyright for the work?*	Choose an item. No	Was the work subject to academic peer review?	Choose an item. Yes

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For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Designed the work, analysed and interpreted the data, drafted the article, and approved final version for submission.

SECTION E

Student Signature	
Date	15th February 2022

Supervisor Signature	K. Walker
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CANCER THERAPY AND PREVENTION

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Survival outcomes associated with completion of adjuvant oxaliplatin-based chemotherapy for stage III colon cancer: A national population-based study

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Abstract

The impact of cycle completion rates of oxaliplatin-based adjuvant chemotherapy for stage III colon cancer in real-world practice is unknown. We assessed its impact, and that of treatment modification, on 3-year cancer-specific mortality. Four thousand one hundred and forty-seven patients with pathological stage III colon cancer undergoing major resection from 2014 to 2017 in the English National Health Service were included. Chemotherapy data came from linked national administrative datasets. Competing risk regression analysis for 3-year cancer-specific mortality was performed according to completion of <6, 6-11, or 12 5-fluoropyrimidine and oxaliplatin (FOLFOX) cycles, or <4, 4-7, or 8 capecitabine and oxaliplatin (CAPOX) cycles, adjusted for patient, tumour and hospital-level characteristics. Median age was 64 years. Thirty-two per cent of patients had at least one comorbidity. Forty-two per cent of patients had T4 disease, and 40% had N2 disease. Compared to completion of 12 FOLFOX cycles, cancer-specific mortality was higher in patients completing <6 cycles [subdistribution hazard ratios (sHR) 2.17; 95% CI 1.56-3.03] or 6-11 cycles (sHR 1.40; 95% CI 1.09-1.78) ($P < .001$). Compared to completion of 8 CAPOX cycles, cancer-specific mortality was higher in patients completing <4 cycles (sHR 2.02; 95% CI 1.53-2.67) or 4-7 cycles (sHR 1.63; 95% CI 1.27-2.10) ($P < .001$). Dose reduction and early oxaliplatin discontinuation did not impact mortality in patients completing all cycles. Completion of all cycles of chemotherapy was associated with improved cancer-specific survival in real-world practice. Poor prognostic factors may have affected findings, however, patients completing <50% of cycles had poor outcomes. Clinicians may wish to facilitate completion with treatment modification in those able to tolerate it.

Abbreviations: CAPOX, capecitabine and oxaliplatin; CI, confidence interval; FOLFOX, 5-fluoropyrimidine and oxaliplatin; HES-APC, Hospital Episode Statistics Admitted Patient Care; ICD-10, International Classification of Diseases 10th edition; IMD, Index of Multiple Deprivation; IMDQ, Index of Multiple Deprivation Quintile; NBOCA, National Bowel Cancer Audit; NHS, National Health Service; ONS, Office for National Statistics; OPCS-4, Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures, fourth revision; RCT, randomised controlled trial; SACT, systemic anticancer therapy; sHR, subdistribution hazard ratios.

Kate Walker, Michael S. Braun and Ajay Aggarwal are joint senior authors.

KEYWORDS
adjuvant chemotherapy, colon cancer, completion of treatment, epidemiology, stage III, survival

What's new?

Adjuvant chemotherapy following curative surgical resection is an established treatment for stage III colon cancer. However, many patients do not complete the planned duration of chemotherapy. This is the largest cohort study in real-world practice to evaluate cancer-specific survival according to the cycle completion rate of oxaliplatin-based adjuvant chemotherapy in stage III colon cancer patients, and the first to assess the impact of treatment modification strategies. The results show that patients who do not complete their planned cycles have significantly poorer outcomes. In the absence of demonstrated negative impacts, clinicians could use treatment modifications to facilitate completion of adjuvant chemotherapy.

1 | INTRODUCTION

Adjuvant chemotherapy after a planned curative surgical resection for stage III colon cancer is an established treatment.[1,2] However, many patients do not complete the planned duration of chemotherapy, even in clinical trials, and in real-world practice this proportion is even higher with non-completion rates reported as high as 45%.[3,4] The impact of not completing adjuvant oxaliplatin-based chemotherapy on patient outcomes in real-world practice is unknown.

FOLFOX and CAPOX have been shown in RCTs to improve outcomes compared to fluoropyrimidines alone.[5-7] After publication of this data, standard practice involved 6 months of adjuvant chemotherapy (8 cycles of CAPOX or 12 cycles of FOLFOX). However, long-term morbidity, in particular cumulative neurotoxicity associated with oxaliplatin-based chemotherapy, is concerning.[5]

The recent IDEA collaborative study sought to establish the impact of reducing treatment duration by comparing 6 months treatment to 3 months (4 cycles of CAPOX or 6 cycles of FOLFOX).[8,9] Although the study failed to demonstrate overall noninferiority of a reduced target of 3 months of oxaliplatin-based chemotherapy, subgroup analysis suggested that 3 months of CAPOX, particularly in patients with low-risk disease, may be as effective as 6 months with reduced toxicity. The study found that those prescribed FOLFOX, or with high-risk disease, may still benefit from longer target durations.[8-10]

Evidence comparing the efficacy of different target durations of adjuvant chemotherapy comes from high quality, large RCTs.[5,11,12] RCTs, however, include highly selected patient populations under rigorously controlled conditions, generally underrepresenting elderly, frail and comorbid patients. One study showed that 59% of stage II or III colon cancer patients in a real-world setting would not be eligible for RCT inclusion.[13] Population-based studies, using data such as electronic healthcare records, are needed to assess the effectiveness of actual durations of adjuvant chemotherapy on outcomes in diverse non-selected populations under routine clinical conditions to complement trial findings.[14-18]

To date, observational studies evaluating the impact of cycle completion rates for oxaliplatin-based adjuvant chemotherapy on survival for colon cancer have been limited by a lack of accountability for important confounders, and their small sample size (most have fewer than 500 patients).[19] In addition, previous studies have not evaluated the survival impacts of treatment modifications (eg, dose reductions) which aim to reduce toxicity and support completion of the target duration of therapy.

In this national population-based study using linked administrative datasets, we assessed the impact of the cycle completion rate of oxaliplatin-based adjuvant chemotherapy on cancer-specific survival for stage III colon cancer patients treated in the English NHS, accounting for important confounders in the largest observational study to date. In addition, the effects of treatment modification on cancer-specific survival, namely dose reduction and early discontinuation of oxaliplatin, were analysed.

2 | METHODS

2.1 | Study population

Our study used NBOCA data,[20] HES-APC[21] and SACT data[22] linked at patient-level.

2.1.1 | National Bowel Cancer Audit

NBOCA is a prospective mandatory database for all newly diagnosed colorectal cancer patients in the English NHS. Patients aged 18 years and above with a primary diagnosis of colon cancer, according to ICD-10 code C18, undergoing major resection between June 1, 2014 and April 30, 2017 with pathological stage III colon cancer were identified in the NBOCA database. Cancers of the appendix were excluded.

2.1.2 | Hospital episode statistics admitted patient care

HES-APC is an administrative dataset of all admissions to English NHS hospitals. Inpatient and day case chemotherapy use is captured via clinical coding, primarily through dedicated OPCS-4 codes,[23] with chemotherapy-related ICD-10 codes also available.[24]

2.1.3 | Systemic anticancer therapy database

SACT is a dedicated chemotherapy dataset held by the National Cancer Registry and Analysis Service.[25] Data collection is largely done via electronic prescribing systems. It includes the capture of detailed drug-level information such as administration date, drug name, dose, and administration route for each cycle of chemotherapy. SACT records chemotherapy administered in any inpatient, day case, outpatient, or community setting.[22]

SACT and HES-APC data from June 30, 2014 until April 30, 2018 were used because not all English NHS chemotherapy providers were submitting SACT data before that period.[22] This ensured that all patients had a minimum of 12 months SACT and HES-APC follow-up data from the NBOCA date of surgery to allow adequate time for adjuvant chemotherapy completion, accounting for potential delays.

Previously established methods were used to ascertain adjuvant chemotherapy receipt, regimen, and number of recorded cycles making use of the information in both SACT and HES-APC.[26] Patients receiving oxaliplatin-based adjuvant chemotherapy according to either SACT or HES-APC were included in the analysis (Figure 1).

2.2 | Study outcome and comparison groups

The primary outcome was colorectal cancer-specific death within 3 years from the date of the first cycle of adjuvant chemotherapy. Date and underlying cause of death were obtained from linkage to official death records provided by the ONS.[27] The date of the latest available death record was 10th February 2020, at which point follow-up times were censored.

Levels of completion of chemotherapy cycles were compared, separately for each regimen. Completion was compared in the groups <50%, 50%-92%, and 100% (<6 cycles, 6-11 cycles, 12 cycles FOLFOX and <4 cycles, 4-7 cycles, 8 cycles CAPOX).

Separate subanalyses were undertaken to evaluate two common treatment modification strategies: dose reduction and early discontinuation of oxaliplatin, both stratified by regimen. For these analyses, only patients completing 12 cycles of FOLFOX or 8 cycles of CAPOX, and with linked SACT records were included (3375 patients). Dose reduction is a binary (yes/no) variable within SACT which refers to dose reduction of "any anti-cancer drug administered at any point in the regimen after commencement of the regimen".[22] Discontinuation of oxaliplatin was derived from drug-level information.

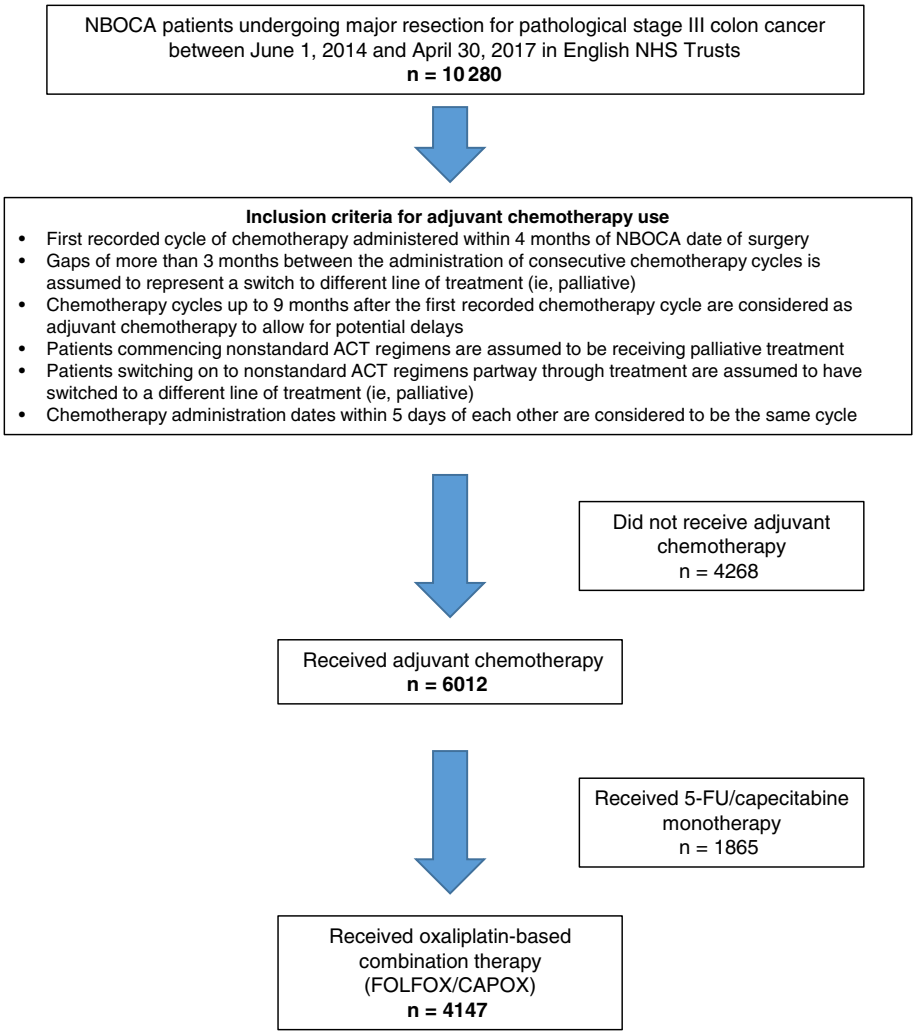

FIGURE 1 Flow chart showing inclusion of patients [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Patient, tumour, and hospital-level characteristics according to level of completion of adjuvant chemotherapy (n = 4147)

	FOLFOX (n = 1776)					CAPOX (n = 2371)				
	<50% (n = 236)	50%-92% (n = 659)	100% (n = 881)	Total		<50% (n = 381)	50%-92% (n = 824)	100% (n = 1166)	Total	
	No. (%)	No. (%)	No. (%)	No. (%)	*P* value (X^2)	No. (%)	No. (%)	No. (%)	No. (%)	*P* value (X^2)
Sex					**<.001**					.125
Male	110 (46.6)	318 (48.3)	503 (57.1)	931 (52.4)		191 (50.1)	446 (54.1)	654 (56.1)	1291 (54.4)	
Female	126 (53.4)	341 (51.7)	378 (42.9)	845 (47.6)		190 (49.9)	378 (45.9)	512 (43.9)	1080 (45.6)	
Age, years					.318					**<.001**
<60	72 (30.5)	218 (33.1)	320 (36.3)	610 (34.3)		100 (26.2)	284 (34.5)	430 (36.9)	814 (34.3)	
60-69	86 (36.4)	264 (40.1)	336 (38.1)	686 (38.6)		162 (42.5)	321 (39.0)	493 (42.3)	976 (41.2)	
70-79	72 (30.5)	165 (25.0)	210 (23.8)	447 (25.2)		114 (29.9)	208 (25.2)	231 (19.8)	553 (23.3)	
≥80	6 (2.5)	12 (1.8)	15 (1.7)	33 (1.9)		5 (1.3)	11 (1.3)	12 (1.0)	28 (1.2)	
IMDQ					.073					.693
1 (most deprived)	31 (13.1)	96 (14.6)	112 (12.7)	239 (13.5)		56 (14.7)	110 (13.4)	140 (12.0)	306 (12.9)	
2	35 (14.8)	114 (17.4)	158 (18.0)	307 (17.3)		68 (17.8)	137 (16.6)	203 (17.4)	408 (17.2)	
3	55 (23.3)	105 (16.0)	168 (19.1)	328 (18.5)		85 (22.3)	200 (24.3)	280 (24.0)	565 (23.8)	
4	62 (26.3)	172 (26.2)	190 (21.6)	424 (23.9)		87 (22.8)	165 (20.0)	264 (22.7)	516 (21.8)	
5 (least deprived)	53 (22.5)	170 (25.9)	252 (28.6)	475 (26.7)		85 (22.3)	211 (25.6)	278 (23.9)	574 (24.2)	
Missing	0	2 (0.3)	1 (0.1)	3 (0.2)		0	1 (0.1)	1 (0.1)	2 (<0.1)	
RCS Charlson Score					.179					.226
0	147 (62.3)	441 (66.9)	605 (68.7)	1193 (67.2)		248 (65.1)	549 (66.6)	819 (70.2)	1616 (68.2)	
1	65 (27.5)	177 (26.9)	218 (24.7)	460 (25.9)		106 (27.8)	227 (27.5)	288 (24.7)	621 (26.2)	
≥2	24 (10.2)	41 (6.2)	58 (6.6)	123 (6.9)		27 (7.1)	48 (5.8)	59 (5.1)	134 (5.7)	
Cardiac history					**.012**					.493
Yes	19 (8.1)	27 (4.1)	32 (3.6)	78 (4.4)		16 (4.2)	24 (2.9)	37 (3.2)	77 (3.2)	
No	217 (91.9)	632 (95.9)	849 (96.4)	1698 (95.6)		365 (95.8)	800 (97.1)	1129 (96.8)	2294 (96.8)	
Liver disease					.826					.076
Yes	10 (4.2)	25 (3.8)	39 (4.4)	74 (4.2)		19 (5.0)	25 (3.0)	31 (2.7)	75 (3.2)	
No	226 (95.8)	634 (96.2)	842 (95.6)	1702 (95.8)		362 (95.0)	799 (97.0)	1135 (97.3)	2296 (96.8)	
Renal disease					**.042**					.300
Yes	12 (5.1)	24 (3.6)	19 (2.2)	55 (3.1)		14 (3.7)	23 (2.8)	26 (2.2)	63 (2.7)	
No	224 (94.9)	635 (96.4)	862 (97.8)	1721 (96.9)		367 (96.3)	801 (97.2)	1140 (97.8)	2308 (97.3)	

TABLE 1 (Continued)

	FOLFOX (n = 1776)					CAPOX (n = 2371)				
	<50% (n = 236)	50%-92% (n = 659)	100% (n = 881)	Total		<50% (n = 381)	50%-92% (n = 824)	100% (n = 1166)	Total	
	No. (%)	No. (%)	No. (%)	No. (%)	*P* value (X^2)	No. (%)	No. (%)	No. (%)	No. (%)	*P* value (X^2)
Performance status					.172					.320
0	123 (61.8)	371 (65.5)	515 (64.9)	1009 (56.8)		218 (66.3)	465 (65.9)	695 (68.3)	1378 (58.1)	
1	59 (29.6)	151 (26.7)	237 (29.9)	447 (25.2)		88 (26.7)	184 (26.1)	266 (26.2)	538 (22.7)	
≥2	17 (8.5)	44 (7.8)	41 (5.2)	102 (5.7)		23 (7.0)	57 (8.1)	56 (5.5)	136 (5.7)	
Missing	37 (15.7)	93 (14.1)	88 (10.0)	218 (12.3)		52 (13.6)	118 (14.3)	149 (12.8)	319 (13.5)	
Pathological T-stage					.972					.887
T1/T2	16 (6.8)	45 (6.8)	63 (7.2)	124 (7.0)		34 (8.9)	87 (10.6)	111 (9.5)	232 (9.8)	
T3	118 (50.0)	343 (52.0)	445 (50.6)	906 (51.0)		187 (49.1)	404 (49.1)	570 (48.9)	1161 (49.0)	
T4	102 (43.2)	271 (41.1)	372 (42.3)	745 (41.9)		160 (42.0)	332 (40.3)	485 (41.6)	977 (41.2)	
Missing	0	0	1 (0.1)	1 (<0.1)		0	1 (0.1)	0	1 (<0.1)	
Pathological N-stage					.778					**.027**
N1	143 (60.6)	382 (58.0)	515 (58.5)	1040 (58.6)		254 (66.7)	492 (59.7)	689 (59.1)	1435 (60.5)	
N2	93 (39.4)	277 (42.0)	366 (41.5)	736 (41.4)		127 (33.3)	332 (40.3)	477 (40.9)	936 (39.5)	
Surgical urgency					**.035**					.203
Elective/scheduled	166 (70.3)	517 (78.7)	673 (76.5)	1356 (76.4)		317 (83.2)	677 (82.3)	930 (79.8)	1924 (81.1)	
Emergency/urgent	70 (29.7)	140 (21.3)	207 (23.5)	417 (23.5)		64 (16.8)	146 (17.7)	236 (20.2)	446 (18.8)	
Missing	0	2 (0.3)	1 (0.1)	3 (0.2)		0	1 (0.1)	0	1 (<0.1)	
Unplanned readmission					.314					.821
Yes	22 (9.3)	44 (6.7)	74 (8.4)	140 (7.9)		28 (7.3)	65 (7.9)	97 (8.3)	190 (8.0)	
No	214 (90.7)	615 (93.3)	807 (91.6)	1636 (92.1)		353 (92.7)	759 (92.1)	1069 (91.7)	2181 (92.0)	
Surgical access					.191					.270
Open	95 (40.4)	242 (36.9)	333 (37.9)	670 (37.7)		115 (30.2)	264 (32.2)	393 (33.9)	772 (32.6)	
Laparoscopic converted	28 (11.9)	50 (7.6)	79 (9.0)	157 (8.8)		33 (8.7)	75 (9.1)	79 (6.8)	187 (7.9)	
Laparoscopic	112 (47.7)	363 (55.4)	467 (53.1)	942 (53.0)		233 (61.2)	482 (58.7)	689 (59.3)	1404 (59.2)	
Missing	1 (0.4)	4 (0.6)	2 (0.2)	7 (0.4)		0	3 (0.4)	5 (0.4)	8 (0.3)	
Time from surgery					**.025**					.123
<8 weeks	124 (52.5)	299 (45.4)	376 (42.7)	799 (45.0)		166 (43.6)	355 (43.1)	456 (39.1)	977 (41.2)	
≥8 weeks	112 (47.5)	360 (54.6)	505 (57.3)	977 (55.0)		215 (56.4)	469 (56.9)	710 (60.9)	1394 (58.8)	

(Continues)

TABLE 1 (Continued)

	FOLFOX (n = 1776)					CAPOX (n = 2371)				
	<50% (n = 236)	50%-92% (n = 659)	100% (n = 881)	Total		<50% (n = 381)	50%-92% (n = 824)	100% (n = 1166)	Total	
	No. (%)	No. (%)	No. (%)	No. (%)	*P* value (X^2)	No. (%)	No. (%)	No. (%)	No. (%)	*P* value (X^2)
Chemotherapy on-site					.039					.047
Yes	219 (92.8)	571 (86.6)	781 (88.6)	1571 (88.5)		336 (88.2)	723 (87.7)	1061 (91.0)	2120 (89.4)	
No	17 (7.2)	88 (13.4)	100 (11.4)	205 (11.5)		45 (11.8)	101 (12.3)	105 (9.0)	251 (10.6)	
University hospital					.529					.004
Yes	53 (22.5)	170 (25.8)	211 (24.0)	434 (24.4)		117 (30.7)	229 (27.8)	269 (23.1)	615 (25.9)	
No	183 (77.5)	489 (74.2)	670 (76.0)	1342 (75.6)		264 (69.3)	595 (72.2)	897 (76.9)	1756 (74.1)	

Note: Bold values denote *P* values <.05 and deemed statistically significant.

2.3 | Patient, tumour and hospital-level characteristics

Data regarding sex, age, pathological staging (TNM staging), operative date, surgical urgency, performance status,[28] and surgical access were obtained from NBOCA. Comorbidities, socioeconomic status, and 30-day unplanned readmission data were obtained from HES-APC.

The Royal College of Surgeons' Charlson comorbidity score was derived from ICD-10 codes recorded in the HES-APC dataset in any hospital admissions in the year preceding colon cancer diagnosis. Individual records for liver, renal, or cardiac disease were obtained for the same timeframe.[29] Patients were recorded as having an unplanned 30-day readmission if HES-APC showed an emergency admission within 30 days of surgery.

Socioeconomic status was derived from the IMD which ranks 32 482 geographical areas of England according to their level of deprivation across seven domains.[30] Patients were allocated to an IMDQ based on the national ranking of the area corresponding to their postcode.

Hospital-level characteristics were derived from the hospital performing the surgery according to NBOCA. University teaching hospitals were identified from the Association of United Kingdom University Hospitals.[31] Onsite chemotherapy presence was collected in an annual national NBOCA survey of colorectal cancer services.[32]

2.4 | Statistical analysis

Patient, tumour and hospital-level characteristics were compared using X^2 tests stratified by chemotherapy regimen alone, and then by regimen and level of completion. The proportion of patients with a dose reduction and the proportion of patients discontinuing oxaliplatin early were reported according to regimen type and level of completion.

As our study evaluates survival outcomes in relation to the completion of chemotherapy, starting the analysis from initiation of chemotherapy may introduce bias as patients who die are unable to receive further cycles of chemotherapy. To account for this, a landmark analysis was undertaken.[33] This involved the designation of a period of time, a priori, from a baseline date (initiation of chemotherapy) to the study start date (the landmark date) known as the exposure period. Patients who died during the exposure period (6 months after chemotherapy initiation) were excluded from the analysis. A sensitivity analysis was undertaken to include those who died within this 6-month period.

The crude 3-year cumulative incidence of cancer-specific death was calculated for each regimen, according to the level of completion, using a competing risks analysis in which other-cause death was the competing event.[34] Fine and Gray[35] competing risk regression models were used to estimate adjusted subdistribution hazard ratios (sHRs) between levels of completion for each regimen, adjusting for all patient, tumour, and hospital-level characteristics.

The same methodology was used to calculate unadjusted and adjusted sHRs for the risk of 3-year cancer-specific death in just those patients completing 100% of cycles, according to whether or not dose reduction occurred. This was then repeated for early discontinuation of oxaliplatin.

Missing values for risk-adjustment variables were imputed with multiple imputation using chained equations, creating 10 datasets and using Rubin's rules to combine the sHRs across the datasets.[36] Wald tests were used to calculate *P* values with the significance level set at .05.

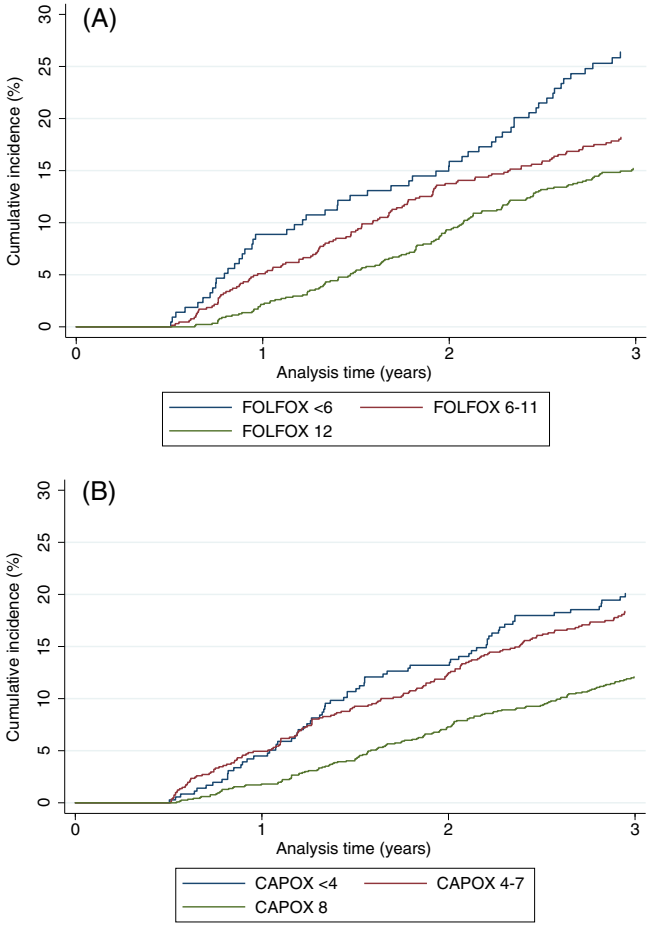

FIGURE 2 Cumulative incidence curves for colon cancer-specific death with competing risk of other-cause death according to level of completion of (A) FOLFOX (n = 1741) and (B) CAPOX (n = 2331) [Color figure can be viewed at wileyonlinelibrary.com]

3 | RESULTS

Of the 10 280 patients undergoing major resection with pathological stage III colon cancer between June 1, 2014 and April 30, 2017, 6012 (58%) went on to receive adjuvant chemotherapy (Figure 1). Of these, 4147 patients received an oxaliplatin-based regimen. The remaining 1865 patients received 5-FU/capecitabine monotherapy and were excluded from further analyses.

Two thousand three hundred and seventy-one patients (57%) received CAPOX and 1776 patients (43%) received FOLFOX (Table 1). The median age for both regimens was 64 years (interquartile range 56-70 years). The cumulative incidence for 3-year cancer-specific mortality for all patients included in the study was 16.4% (95% CI 15.3%-17.6%).

3.1 | Levels of completion

3.1.1 | FOLFOX

Fifty per cent of patients completed 12 cycles (100%) of FOLFOX, 37% completed 6-11 cycles (50%-92%), and 13% of patients completed <6 cycles (<50%) (Table 1). Patients completing the least FOLFOX chemotherapy were more likely to be female ($P < .001$), have a history of cardiac ($P = .012$) or renal disease ($P = .042$), undergo emergency surgery ($P = .035$), and commence chemotherapy within 8 weeks of surgery ($P = .025$). There was also a suggestion that patients who were from more deprived areas were less likely to complete chemotherapy, although this was not statistically significant ($P = .073$).

The 3-year cumulative incidence of cancer-specific death in patients receiving FOLFOX and completing 12 cycles was 15.1% (95% confidence interval [CI], 12.8%-17.6%), completing 6-11 cycles was 18.2% (95% CI 15.3%-21.3%), and completing <6 cycles was 26.4% (95% CI 20.6%-32.5%) (Figure 2a).

TABLE 2 Three-year cancer-specific death according to level of completion of FOLFOX or CAPOX

Recorded cycles	Number of patients	Cumulative 3-year incidence (%) (95% CI)	Unadjusted sHR (95% CI)	*P* value	Adjusted sHR (95% CI)	*P* value
FOLFOX	**1741**			**<.001**		**<.001**
12 (100%)	880	15.1 (12.8-17.6)	1.0		1.0	
6–11 (50%-92%)	647	18.2 (15.3-21.3)	1.24 (0.99-1.55)		1.40 (1.09-1.78)	
<6 (<50%)	214	26.4 (20.6-32.5)	1.87 (1.38-2.54)		2.18 (1.56-3.03)	
CAPOX	**2331**			**<.001**		**<.001**
8 (100%)	1166	12.0 (10.2-14.0)	1.0		1.0	
4-7 (50%-92%)	809	18.2 (15.6-21.0)	1.60 (1.25-2.06)		1.63 (1.27-2.10)	
<4 (<50%)	356	19.8 (15.8-24.1)	1.77 (1.33-2.34)		2.02 (1.53-2.67)	

Note: Bold values denote *P* values .05 and deemed statistically significant.

TABLE 3 Three-year cancer-specific death according to dose reduction and early discontinuation of oxaliplatin for those completing 100% of FOLFOX (12 cycles) or CAPOX (8 cycles)

Treatment modification	Number of patients	Cumulative 3-year incidence (%) (95% CI)	Unadjusted sHR (95% CI)	*P* value	Adjusted sHR (95% CI)	*P* value
FOLFOX						
Dose reduction				.142		.096
No	396	15.5 (12.1-19.3)	1.0		1.0	
Yes	351	11.8 (8.6-15.5)	0.75 (0.50-1.10)		0.70 (0.46-1.07)	
Oxaliplatin discontinued				.074		.120
No	303	14.0 (10.3-18.3)	1.0		1.0	
Yes	455	11.7 (8.9-15.0)	0.71 (0.48-1.03)		0.72 (0.48-1.09)	
CAPOX						
Dose reduction				.330		.651
No	489	11.1 (8.5-14.1)	1.0		1.0	
Yes	452	10.5 (7.9-13.6)	0.83 (0.57-1.21)		0.92 (0.62-1.34)	
Oxaliplatin discontinued				.248		.414
No	608	11.4 (9.0-14.2)	1.0		1.0	
Yes	364	9.1 (6.4-12.4)	0.79 (0.54-1.17)		0.84 (0.55-1.28)	

The adjusted competing risk regression analysis showed that the risk of 3-year cancer-specific death in patients completing <6 cycles or 6-11 cycles of FOLFOX was up to twice as high ($P < .001$) as those completing 12 cycles (Tables 2 and S1).

3.1.2 | CAPOX

Forty-nine per cent of patients completed 8 cycles (100%) of CAPOX, 35% completed 4-7 cycles (50%-92%), and 16% of patients completed <4 cycles (<50%) (Table 1). Patients completing the least CAPOX chemotherapy were more likely to be older ($P < .001$) and have less advanced N-stage disease ($P = .027$). There was also a suggestion that patients with a history of liver disease were less likely to complete CAPOX chemotherapy, although this was not statistically significant ($P = .073$).

The 3-year cumulative incidence of cancer-specific death in those receiving CAPOX and completing 8 cycles was 12.0% (95% CI 10.2%-14.0%), completing 4-7 cycles was 18.2% (95% CI 15.6%-21.0%), and completing <4 cycles was 19.8% (95% CI 15.8%-24.1%) (Figure 2b).

After adjustment, the risk of 3-year cancer-specific death in those completing <4 cycles or 4-7 cycles was up to twice as high ($P < .001$) as those completing 8 cycles (Tables 2 and S2).

3.2 | Treatment modification

3.2.1 | FOLFOX

In the 747 patients completing all cycles of FOLFOX, 47% had a dose reduction and 60% discontinued oxaliplatin early (Table S3). The adjusted risk of 3-year cancer-specific death in patients with dose reduction showed a trend towards lower mortality rates compared to those receiving the full dose; however, this was not statistically significant (sHR 0.70; 95% CI 0.46-1.07; $P = .096$) (Table 3). Similar findings were observed for the adjusted 3-year cancer-specific death in patients discontinuing oxaliplatin early compared to those completing the oxaliplatin component (sHR 0.72; 95% CI 0.48-1.09; $P = .120$) (Table 3).

3.2.2 | CAPOX

In the 941 patients completing all cycles of CAPOX who had linked SACT data, 48% had a dose reduction and 37% discontinued oxaliplatin early (Table S3). The adjusted risk of 3-year cancer-specific death in those receiving a reduced dose was similar to those receiving the full dose, although the confidence interval was wide (sHR 0.92; 95% CI 0.62-1.34; $P = .651$) (Table 3). The adjusted risk of 3-year cancer-specific death in those discontinuing oxaliplatin early was similar to those completing it although, again, the confidence interval was wide (sHR 0.84; 95% CI 0.55-1.28; $P = .414$) (Table 3).

The sensitivity analyses including those patients who died within 6 months of their first chemotherapy dose did not show any significant differences in results (not presented).

4 | DISCUSSION

This is the largest cohort study of real-world practice to date evaluating cancer-specific survival according to the cycle completion rates of oxaliplatin-based adjuvant chemotherapy in stage III colon cancer patients, and the first to assess the impact of treatment modification strategies.

In real-world practice, patients who completed 100% of adjuvant chemotherapy cycles (12 cycles FOLFOX or 8 cycles CAPOX) had significantly improved cancer-specific survival outcomes compared to those completing fewer cycles. However, in our cohort only half of patients completed 100% of standard cycles for the timeframe studied.

Of those completing all cycles, half had a dose reduction, and a substantial proportion discontinued oxaliplatin early (a third of those completing all CAPOX cycles and two thirds of those completing all FOLFOX cycles). However, cancer-specific survival remained similar in patients completing all cycles, irrespective of any modifications to their chemotherapy regimen. Patients completing <50% of cycles (<6 cycles FOLFOX or <4 cycles CAPOX) had much poorer outcomes. This suggests that completion of adjuvant chemotherapy with treatment modifications rather than early cessation may confer survival advantages.

4.1 | Strengths and limitations

The main limitation of our study is that, although we found that the completion of adjuvant chemotherapy is associated with improved cancer-specific survival, we cannot simply assume a causal relationship. The factors which make patients less likely to complete their chemotherapy, for example, age and comorbidity, can also make them less likely to survive. However, the use of cancer-specific survival reduces the impact that these factors have on survival differences.

Whilst we have adjusted for many confounders (eg, age, comorbidity, performance status), we were unable to account for other causes of chemotherapy discontinuation, for example, patient preference, psychosocial support, and health behaviours. Despite this, the effect sizes seen are large and unlikely to be fully explained by residual confounding.

Second, duration of follow-up was limited by the availability of SACT data from 2014 onwards and cancer recurrence data was not available. The implications of this were that we reported 3-year cancer-specific survival. However, given our early event rate and the survival differences observed within this shorter timeframe, longer follow-up is only expected to accentuate our findings. In addition, approximately 80% of recurrences occur within the first 3 years after major resection.[37]

The strengths of our study include using a large, contemporary and highly representative cohort of patients, which includes all centres providing colon cancer treatment in the English NHS (UK) without exclusions, and 95% of eligible patients.[20] The patient and clinical characteristics of our study are comparable to other observational studies with regards to staging, performance status, surgical urgency, and time from surgery to adjuvant chemotherapy initiation.[38-42] We have also overcome the biases present in previous observational studies by performing extensive risk-adjustment for important confounders.[19]

The study period did not include SCOT trial patients and preceded publication of the IDEA collaborative results, meaning treatment duration reflects toxicity or intolerance, rather than patient or clinician choice informed by these results.[8,43] A landmark analysis was used to exclude patients who died within 6 months of their first chemotherapy dose ($n = 75$, 2%).[44] This was intended to account for immortal time bias; patients who died during the time they should have received chemotherapy would have been unable to complete treatment. Finally, patients within our cohort were analysed by the recorded number of chemotherapy cycles in a validated national curated chemotherapy dataset[26] rather than, for example, insurance or claims data. This has the advantage of using known individual chemotherapy administration dates compared to, for example, estimating completion based on the duration between the first and last claims for chemotherapy without taking account of individual cycles.[45]

4.2 | Completion and survival

Our adjuvant chemotherapy completion rates of approximately 50% for FOLFOX and CAPOX are comparable to those from previous observational studies.[3,4] They are also plausible compared to the completion rates of 59% within the SCOT trial for both regimens, given that adherence rates within trial settings are known to be higher.[43] Of interest, completion of the least FOLFOX was associated with being female. There has been ongoing debate as to whether an underlying difference in toxicities exists with 5-FU due to gender.[46] Clinicians should consider this for their own practice through regimen choice and adequate toxicity prevention measures, for example, antiemetics. Our study predated the widespread use of DPYD testing.

High early discontinuation rates were observed in older patients with around 15%-20% of patients aged 70-79 years completing <50% of CAPOX or FOLFOX cycles. Based on our study, we are unable to comment as to whether early stoppage reflects greater toxicity in older patients, patient preference, or clinician choice. This is because the completeness of the data item capturing this information in the SACT dataset was very poor (<20% complete). Given the importance of completing the target duration, consideration should be made as to whether monotherapy may be more suitable for elderly patients if this might support improved compliance.

Several observational studies have demonstrated that patients who do not complete fluoropyrimidine adjuvant chemotherapy in real-world practice have less favourable survival outcomes.[3,47-49] A recent systematic review and meta-analysis including 20 observational studies concluded that shortened durations of combination chemotherapy with CAPOX or FOLFOX may not adversely affect survival.[19] However, the findings of this review were limited by the majority of studies failing to address important confounders such as chemotherapy regimen, age, sex, tumour site, and stage. We have systematically addressed these potential confounders in the current study.[19] In addition, many of the studies used outdated data and small sample sizes with the largest study available in abstract format only.[50]

The IDEA collaborative study used intention-to-treat analyses to assess efficacy of two different target durations of adjuvant

chemotherapy, whereas our study sought to evaluate the impact of actual completion rates on survival in real-world practice.[8] Therefore, a direct comparison of the two is not appropriate. There is more relevance to comparing our findings to the per-protocol results in, for example, the SCOT trial which failed to demonstrate equivalence in survival (hazard ratio 1.158; 95% CI 1.018-1.317; $P = .64$) between patients who actually received 3 vs 6 months of FOLFOX or CAPOX.[43] However, even this is not comparable with our findings because the national patient cohort included in our study receiving adjuvant chemotherapy has poorer prognostic factors than those in trials. For example, patients in our national cohort are less fit [one-third have a performance status ≥1 (not fully active) compared to one-fifth within the IDEA study) and have more advanced disease (41.2% have T4 disease compared to 24.6% in the IDEA study, and 39.5% have N2 disease compared to 28.6% in the IDEA study).

Further subanalyses to stratify our findings by low- and high-risk disease were not possible due to small numbers. After the publication of the IDEA/SCOT results, surveys have highlighted the ongoing variation in clinical practice with regards to choice and duration of combination adjuvant chemotherapy with shifts towards the use of 3 months of treatment for high-risk disease, particularly in the UK.[51,52] We recommend that additional research into the outcomes and optimal treatment of patients, particularly those with high-risk disease, is needed.

4.3 | Treatment modification and survival

For patients completing 100% of target cycles, we found that dose reductions or early discontinuation of oxaliplatin was not associated with any difference in cancer-specific survival. This has been observed in other studies, which have demonstrated that reduced dose intensity may not negatively influence survival.[53,54] This may reflect the relative importance of the fluoropyrimdine component of treatment and the uncertain effect in patients aged 70 and above who constitute a quarter of our cohort.[55,56] We found that between 40%-60% of patients discontinued their oxaliplatin (depending on regimen), but continued on a single agent fluoropyrimidine for the rest of their cycles.

Further analysis of the impact of dose reductions or oxaliplatin discontinuation in low- and high-risk prognostic groups was limited by small numbers (reflected in the wide confidence intervals), and an inability to quantify exact dose reductions.

4.4 | Implications for policy and practice

Current recommendations advise 12 cycles of FOLFOX and suggest that 4 cycles of CAPOX can be used dependent on other risk factors, particularly staging.[57] Our findings suggest that in real world practice, once combination chemotherapy has been commenced, completion of at least 4 cycles of CAPOX or 6 cycles of FOLFOX confers a survival advantage over early discontinuation.

Unless toxicities are very severe, our data suggests that patients may benefit from attempting to complete adjuvant chemotherapy with treatment modifications. Improved strategies to support completion of chemotherapy might include prompt identification and management of chemotherapy-related adverse effects, clear clinician-patient communication and education, and provision of adequate support to overcome any physical or psychosocial barriers.

5 | CONCLUSION

Our study demonstrated that in real-world clinical practice only half of stage III colon cancer patients completed all cycles of their adjuvant chemotherapy. Patients who do not complete their cycles were shown to have significantly poorer outcomes. Given that no negative impacts on survival were demonstrated with treatment modifications, clinicians may want to use these to facilitate and encourage completion of adjuvant chemotherapy in those patients able to tolerate it.

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CONFLICT OF INTEREST

The authors have declared no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of our study are available from the corresponding author upon reasonable request after permission of HQIP.

ETHICS STATEMENT

All patient data used are fully anonymised and are therefore exempt from United Kingdom National Research Ethics Committee approval.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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8. DEVELOPMENT OF SEVERE ACUTE TOXICITY AS A HOSPITAL-LEVEL PERFORMANCE INDICATOR

8.1 Research paper 3

Title: Severe acute toxicity as a hospital-level performance indicator for systemic anti-cancer therapy (SACT) delivery: a national population-based evaluation.

This is the manuscript which was submitted to a peer-reviewed journal at the time of thesis submission. Supplementary material can be found in Appendix 15.

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Surname/Family Name	Boyle		
Thesis Title	Using National Routine Data to Explore the Utilisation and Outcomes of Multimodal Treatment in the Management of Colorectal Cancer		
Primary Supervisor	Dr Kate Walker		

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	JAMA Oncology
Please list the paper's authors in the intended authorship order:	J. M. Boyle, J. van der Meulen, A. Kuryba, T.E. Cowling, N.S. Fearnhead, M.S. Braun, K. Walker & A. Aggarwal.
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SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Designed the work, analysed and interpreted the data, drafted the article, and approved final version for submission.

SECTION E

Student Signature	
Date	15th February 2022

Supervisor Signature	K. Walker
Date	15th February 2022

Severe acute toxicity as a hospital-level performance indicator for systemic anti-cancer therapy (SACT) delivery: a national population-based evaluation.

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ABSTRACT

Importance: Systemic anti-cancer therapy (SACT) is a complex treatment that may vary in quality across hospitals. To date, there is little systematic assessment of the quality of SACT delivery within routine practice at a national level.

Objective: We evaluated the rates of severe acute toxicity during SACT treatment derived from hospital administrative data as a hospital-level performance indicator within the English National Health Service (NHS).

Design: Cohort study. Colorectal cancer (CRC) patients treated in all 106 English NHS hospitals delivering SACT between April 2016 and March 2019.

Setting: Population-based.

Participants: CRC patients receiving SACT in the adjuvant (n=8,173) or metastatic (n=7,683) setting.

Exposure: Severe acute toxicity from SACT.

Main outcomes: Hospital-level severe acute toxicity rates following SACT administration were determined based on a validated coding framework using specific ICD-10 diagnostic codes. The "statistical power" of the indicator to detect a 50%-increase in the toxicity rate compared to the national average was assessed. The "fairness" of the indicator was evaluated by determining to what extent hospital-level toxicity rates could be adjusted for important case-mix factors using logistic regression.

Results: Between April 2016 and March 2019, between-hospital severe acute toxicity rates varied from 11% to 49% for stage III patients, and from 25% to 67% for stage IV patients. This was following adjustment for relevant case-mix factors, using regression models which were found to be well calibrated with reasonable discrimination for stage III and IV cohorts respectively (HL-test $p = 0.711$ and $p = 0.952$, and C-statistic 0.58 (95% CI: 0.57 to 0.59) and 0.64 (95% CI: 0.62 to 0.66)).

Overall, we identified 12 hospitals (12%) with rates of severe acute toxicity more than 2 standard deviations above the national average (low performers), and 11 with rates less than 2 standard deviations below the national average (high performers).

Conclusions and Relevance: Severe acute toxicity levels derived from administrative hospital data provide a powerful and fair performance indicator to compare hospitals providing SACT. Routine use of this performance indicator can guide quality improvement initiatives to reduce SACT toxicity.

INTRODUCTION

The delivery of systemic anti-cancer therapy (SACT) is a complex care process which includes appropriate patient selection and optimisation, tailoring treatment doses, and the monitoring and management of toxicities.[124] Whilst randomised controlled trials (RCTs) have established the efficacy of SACT, there has been little or no systematic assessment of the quality of SACT delivery within routine care. Much of the available literature on the quality of SACT delivery focuses on access to treatments rather than on outcome measures.[119 131 133]

The only performance indicator currently reported and monitored at hospital level is 30-day mortality after the final SACT treatment, which is more a proxy for the appropriate selection of patients for SACT treatment than a measure of quality of care.[7] Several studies have suggested that the rate of unplanned hospital admissions during SACT could be used as a potential measure of quality.[122 133] A study in breast cancer patients showed a hospitalisation rate of 43% in patients during SACT with about three quarters of the admissions confirmed as SACT-related events.[110]

We have previously validated an indicator of severe acute toxicity (at least Grade 3 according to the Common Terminology Criteria for Adverse Events (CTCAE)) derived from hospital administrative data in colorectal cancer (CRC).[160] The indicator uses a coding framework to identify specific diagnostic codes during the timeframe of chemotherapy administration which are likely to represent SACT-related severe acute toxicity. As part of this work, we found variations in toxicity rates across different SACT regimens in line with those seen in RCTs. In addition, the rates of toxicity were associated with anticipated risk factors, for example higher rates in those with comorbidities.

In the current study, we evaluate the use of this indicator as a national-level performance measure to assess hospital variation in severe acute toxicity rates for colorectal cancer (CRC) patients receiving SACT. The indicator will be used to identify outlying hospital performance and benchmark best practice to support quality improvement processes in SACT delivery.

METHODS

Data sources

In this national population-based evaluation we used National Bowel Cancer Audit (NBOCA) data[3], Hospital Episode Statistics (HES) data[16], Systemic Anti-Cancer Therapy (SACT) data[148], and Office for National Statistics (ONS) mortality data[15] linked at patient level for CRC patients diagnosed and treated in the English National Health Service (NHS). SACT and HES data were available up until 31 March 2020.

NBOCA is a prospective mandatory database for all newly diagnosed CRC patients in the English NHS. Data items in NBOCA were used to determine sex, age, Eastern Cooperative Oncology Group performance status[161], tumour site, staging (TNM), date of diagnosis, and date of surgery.

HES is a routinely collected administrative dataset of all admissions to English NHS hospitals.[16 58] Diagnoses are coded using the International Classification of Diseases, 10th revision (ICD-10)[11] and procedures are coded using the Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures, 4th revision (OPCS-4).[162] Data from HES were used to identify admissions for severe acute toxicity (see below), to determine the number of comorbidities according to the RCS Charlson comorbidity score[149] and as one of the sources of SACT information (see below).

The SACT dataset captures detailed drug-level information for SACT administered in any inpatient, day case, outpatient, or community setting, including individual administration dates.[148] The SACT dataset was also used to determine the NHS hospital trust (the organisational unit of NHS hospitals in England that can be located on one or more sites) that delivered SACT. Data submission is mandatory for all chemotherapy providers within the English NHS, excluding a small proportion of privately treated patients. 106 hospitals were identified as delivering SACT. These hospitals needed to have treated at least 10 patients during the inclusion period (see below) to be included in further analyses.

Study Population

We defined two distinct cohorts of patients aged 18 years and above with a primary diagnosis of CRC (ICD-10: C18, C19 and C20) identified in the NBOCA database and undergoing treatments at an English NHS hospital during the inclusion period which ranged from 1 April 2016 to 31 March 2019. These cohorts define the "denominator" of the performance indicator.

The first cohort included patients with pathological stage III CRC who had received adjuvant SACT according to SACT or HES within the 4-month period after major resection, as per previous work.[163] Patients in the stage III cohort were restricted to those receiving capecitabine and oxaliplatin (CAPOX), 5-fluorouracil (5-FU) and oxaliplatin (FOLFOX), or single agent fluoropyrimidine (capecitabine or 5-FU alone), as per national guidelines.[41]

The second cohort included patients who were diagnosed with stage IV CRC and had commenced SACT within the 4-month period after diagnosis, according to SACT or HES. Of the 6,810 patients (89%) with SACT records and therefore drug-level information, approximately 46% of patients received an oxaliplatin-based regimen, 26% an irinotecan-based regimen, 15% single agent fluoropyrimidine, 8% irinotecan with a targeted therapy (e.g., bevacizumab, cetuximab), 5% fluoropyrimidine with a targeted therapy, less than 1% a targeted therapy alone, and less than 1% other agents (e.g., raltitrexed). For stage IV patients, SACT was restricted to treatments given continuously (gaps of no more than 8 weeks between cycles), and for a maximum of 12 months.

The pooled reporting of stage III and IV patients was deemed inappropriate given the heterogeneity of the groups in terms of disease burden, underlying fitness, differences in chemotherapy regimens used, and reported differences in overall toxicity rates reported by our prior research.[160]

Definition of the performance indicator

The coding framework defined patients who had experienced severe acute toxicity (the "numerator" of the performance indicator) according to the presence of pre-defined ICD-10 diagnostic codes in HES indicative of a SACT-related toxicity (eTable 1).[160] Severe toxicity was defined as those patients with a selected ICD-10 diagnostic code who required an overnight hospital admission between the administration of the first cycle of SACT and up until 8 weeks after the administration of the last cycle of SACT. For the small proportion of patients undergoing a surgical procedure during this timeframe, the date of this surgery was used as the cut-off for identifying toxicities to ensure that post-operative complications were not captured.

The indicator captures all admissions to any English NHS hospital, regardless of whether or not the hospital provides chemotherapy. Toxicities were attributed to the hospital providing the chemotherapy.

Statistical power

We calculated the statistical power to detect an important difference (defined as a 50% increase in the toxicity rate compared to the overall national rate) in the rate of severe acute toxicity in a typical hospital and the overall national rate in England, for each cohort. We calculated the median number of patients per year receiving SACT at each hospital over the 3-year study period and used this to calculate the statistical power for reporting periods of 1-, 3- and 5-years. The definition of an important difference is arbitrary but was chosen because it has been used in previous work and represents a substantial absolute increase in the rate of toxicity.[164] A 5% significance level was used for testing differences between the hospital-level and national rates because it corresponds to the commonly used 95%-control limits of funnel plots (see below).

Fairness

We determined to what extent we could adjust for the case-mix factors that are likely to affect the risk of severe acute toxicity, based on a combination of review of existing literature and expert clinical input. We assessed the data completeness of these factors. Missing values for case-mix factors were imputed with multiple imputation.[158] We carried out indirect risk-adjustment, using multivariable logistic regression modelling to obtain expected numbers of severe acute toxicity events per hospital.[157] Calibration of the risk-adjustment model across deciles of predicted risk was assessed using the Hosmer-Lemeshow test, constructing an F-statistic to carry out the test in multiply imputed data. The C-statistic was used to assess model discrimination, combining estimates across imputed datasets using Rubin's rules.[158 165]

Variation between hospitals

Within our cohort of 106 hospitals, we used funnel plots to identify outlying hospitals defined as those with results more than 2 standard deviations (2SD) (corresponding to 95%-control, or inner, funnel limits), or 3 standard deviations (3SD) (corresponding to 99.8%-control, or outer, funnel limits) below or above the overall national rate. This is equivalent to carrying out statistical tests comparing a specific hospital's result with the

overall national rate using a two-sided 5% or 0.02% significance level, respectively.[125 157 166] Fully-adjusted funnel plots were generated for each cohort.

RESULTS

Study cohorts

Between 1 April 2016 and 31 March 2019, 8,173 patients received adjuvant SACT for stage III CRC. Of these 8,173 patients, 2,074 (25%) had a severe acute toxicity identified according to the indicator. In addition, 7,683 patients received SACT within 4 months of a diagnosis of stage IV CRC. Of these 7,683 patients, 3,625 (47%) had a severe acute toxicity identified. Table 1 summarises the different types of toxicity identified from the coding framework, according to organ system.

Statistical power

For the stage III cohort, 97 out of 106 English NHS hospitals had treated more than 10 patients over the 3-year inclusion period and were included in further analyses. The annual volumes of patients who received adjuvant SACT in each hospital varied considerably with a median value of 24 (range 5 to 132, interquartile range 15 to 33). Similarly, 98 hospitals were included for the stage IV cohort, with a median annual volume of 22 (range 5 to 142, interquartile range 13 to 32).

The statistical power to detect an increase of 50% compared to the overall national average rate for different reporting periods (1-, 3-, and 5-year) are presented in eTable 2. These power calculations demonstrate that a 3-year reporting period achieves approximately 70% power in the stage III and 99% power in the stage IV cohort to detect a 50% increase compared to the overall national rate. A 1-year reporting period could have been chosen for the stage IV cohort but, for consistency, the same reporting period was used for both.

Fairness

For risk-adjustment, the following case-mix factors were identified within the literature and from clinical expertise: age, sex, number of comorbidities, performance status, tumour site, staging and socioeconomic status.[7 167] All of these case-mix factors are typically accessible from routinely collected datasets. We found that their completeness rate is high in the English NHS (Table 2a and 2b).

Tables 2a and 2b summarise for the stage III and stage IV cohorts the results of the logistic regression models that capture the associations between the case-mix factors and risk of severe acute toxicity. In both cohorts, severe acute toxicity was increased for female sex, those with more than 2 comorbidities, and advanced T- and N-stage disease at time of diagnosis. In the stage III cohort, rectal cancer was associated with increased toxicity whereas in the stage IV cohort it was associated with reduced toxicity. In the stage IV cohort, rectal cancer patients were significantly younger and fitter (according to performance status) than those patients with colon cancer. In the stage IV cohort, poor performance status was associated with increased toxicity but this association was not statistically significant in the stage III cohort.

Following this analysis, we included age, sex, RCS Charlson comorbidity score, performance status, tumour site, T-stage, and N-stage in the logistic regression models used to adjust for case-mix factors when assessing between-hospital variation in rates of severe acute toxicity. Due to the debate around its appropriateness in case-mix adjustment, and the fact it was not associated with increased toxicity, socioeconomic status was included in the model as a sensitivity analysis.

There was no evidence of a lack of calibration for either the stage III cohort (p = 0.711) or the stage IV cohort (p=0.952), according to the Hosmer-Lemeshow test. The C-statistic of discrimination was 0.58 (95% CI: 0.57 to 0.59) for the stage III cohort and 0.64 (95% CI: 0.62 to 0.66) for the stage IV cohort.

Variation between hospitals

The unadjusted rates of severe acute toxicity after adjuvant SACT in stage III CRC patients varied significantly between the 97 included hospitals, ranging from 11% to 47% with 10 hospitals outside the 95%-funnel limits, including one outside the 99.8%-funnel limits (Figure 1). Adjusting for case-mix factors had little effect on the variation in severe acute toxicity rates. Adjusted severe acute toxicity rates ranged from 11% to 49% with the same outlying hospitals. This corresponded to one hospital being 3SD above, five hospitals being 2SD above, and four hospitals being 2SD below, the national average toxicity rate. A sensitivity analysis including socioeconomic status in the risk-adjustment did not change the outlying hospitals (results not presented).

The unadjusted rates of severe acute toxicity after SACT for stage IV CRC also varied significantly between the included 98 English NHS hospitals, ranging from 26% to 65% with 12 hospitals outside the 95%-funnel limits (Figure 2). Adjusting for case-mix factors had little effect on the variation in severe acute toxicity rates (25% to 67%) and outlying hospitals, with 13 hospitals outside the 95%-funnel limits. This corresponded to six hospitals being 2SD above, and seven hospitals being 2SD below, the national average toxicity rate. A sensitivity analysis including socioeconomic status in the risk-adjustment removed generated two new outlying hospitals (results not presented).

Across both cohorts, 22 different hospitals were identified as having rates of severe acute toxicity more than 2SD from the national average toxicity rate (only 1 hospital had rates more than 2SD for both cohorts). The Pearson correlation coefficient comparing the adjuvant and metastatic rates of toxicity for each hospital was 0.2 (p=0.090).

DISCUSSION

This study demonstrates how diagnostic coding in hospital administrative data can be used to derive a hospital-level performance indicator of SACT toxicity across hospitals treating CRC patients. We used a previously validated coding framework based on a pre-defined set of specific ICD-10 codes and found considerable variation in severe acute toxicity rates between hospitals in both the adjuvant and metastatic setting. We found that hospital rates of severe acute toxicity requiring an overnight hospital admission

(equivalent to at least grade 3 CTCAE) varied between 11% and 49% in stage III patients receiving adjuvant chemotherapy, and were even higher for stage IV patients with rates varying between 25% and 67%. We identified 22 potentially outlying hospitals, with 12 (12%) having rates of severe acute toxicity more than 2 standard deviations above the national average, even after adjustment for important case-mix factors.

This hospital performance indicator will be used as part of a publicly reported outlier program in the UK from 2022. Within the national outlier process, poor performing hospitals are grouped as "alerts" (greater than 2SD above the national average) or "alarms" (greater than 3SD above the national average).[168] "Alarm" hospitals are contacted to acknowledge the potential outlier status and start by corroborating the data completeness and quality.[169] Once the data is verified, hospitals are expected to formulate a formal response and action plan to understand which factors might be driving unwarranted variation (Figure 3).[122 125 170] "Alert" hospitals are monitored and become potential outliers if they underperform in consecutive years. The outlier process is entirely publicly reported. High performing hospitals offer the opportunity to identify and support the dissemination of best practice.

These results show that this performance indicator can be used to trigger and guide initiatives to improve the quality of SACT delivery on a national scale. As the performance indicator is derived from administrative diagnostic coding, the risk of information bias or clinical data manipulation is reduced. The linked datasets included patient and tumour characteristics that allowed the development of a case-mix adjustment model with good calibration and adequate discriminatory power. The relatively modest C-statistic of the risk-adjustment model, and the fact that there was similar between-hospital variation in the unadjusted and risk-adjusted rates of severe acute toxicity, suggest that hospital factors are more important determinants of the variation in this adverse outcome than patient and tumour characteristics.

The use of ICD-10 codes in the coding framework makes it internationally applicable as it can be applied in different health systems that use ICD-10 codes within their hospital administrative data. In addition, whilst this study has focused on CRC, the coding framework can be applied across different tumour types and regimens, including targeted therapies and immunotherapy.

Differences in hospital-level severe acute SACT toxicity

The higher rates of toxicity in patients with advanced disease has been previously observed.[116] This is likely due to differences in baseline characteristics, for example, poorer performance status in those with stage IV disease, and the wider range of SACT drugs used within this cohort. Figure 3 also considers the points along the SACT care pathway that may contribute to the between-hospital variation in toxicity rates.

Higher rates of severe acute toxicity may reflect differences in the assessment of patients regarding fitness or appropriateness of treatment. Toxicity rates may be reduced, for example, through comprehensive risk-stratification and discussion within the multidisciplinary team, and having access to specialist geriatrician and

prehabilitation services so that patients with a high risk of severe acute toxicity can be identified.[171-173] In addition, patients should be appropriately counselled and consented for SACT treatments by a sufficiently experienced clinician, including the potential short- and long-term side effects.

Furthermore, increased rates of toxicity may represent the inappropriate regimen use and dosing, inadequate or outdated protocols, insufficient monitoring, or failure to recognise and address early signs of toxicity. Finally, the available infrastructure and clinical pathways within hospitals may play a role, for example, access to acute oncology services, emergency services, and the availability of specialist on-site advice out of hours, as well as more generalised disparities in the clinical expertise, availability, and training.[174] For example, acute oncology services have been shown to improve outcomes.[175] However, substantial variation remains as to whether hospitals have this service.

Only one hospital was identified as a low outlier for both cohorts of patients. When comparing both cohorts, there was some evidence of an association between the rates of toxicity in the adjuvant and metastatic cohorts within each hospital. However, we would not necessarily expect these to align as the two cohorts are very different as evidenced by their average toxicity rates. It may also reflect the reduced fitness of patients in the stage IV cohort which means that poor treatment, patient selection, and supportive care, are more likely to be exposed.

Strengths and Limitations

The strengths of this study include ensuring that the performance indicator meets a pre-defined set of essential criteria ("validity", "statistical power", and "fairness" as detailed in the Methods).[176] The validity of the indicator was demonstrated in an earlier study comparing toxicity across SACT regimens.[160] Although within this study we have reported the overall incidence of severe toxicity after SACT at each hospital, we are also able to detail specific individual toxicities according using our indicator (e.g., neutropenic sepsis, diarrhoea, and line complications – see Table 1). This is hugely important for providing detailed feedback to hospitals to facilitate quality improvement.

In addition, routinely available national clinical cancer data linked to SACT data and hospital administrative data provided over 95% case ascertainment across all English NHS hospitals with good recording of comorbidities, performance status, staging, and detailed SACT information. This also allowed the capture of all hospital admissions, regardless of whether the hospital provided chemotherapy, but we assigned the toxicity to the hospital delivering the chemotherapy. [177]

This, and the good calibration of the risk-adjustment model, meant that toxicity rates between hospitals could be adjusted for important case-mix factors known to influence toxicity, enhancing the fairness of hospital-specific reporting.[178] There is a debate surrounding the complexities of the inclusion of deprivation in risk-adjustment, with varying practice between different reporting programmes.[179] A sensitivity analysis showed

minor changes in results for the stage IV cohort which need to be considered. Finally, an overview of potentially actionable areas have been identified as a starting point for targeted local quality improvement (Figure 3).

The first limitation of this study is the reliance on ICD-10 diagnostic codes in hospital administrative data. However, these diagnostic codes in HES have been shown to be accurate compared to clinical notes, thereby supporting its use for healthcare performance assessment and research.[17] In addition, we used two independent data sources to capture information about the use of SACT. Our previous validation work has shown excellent agreement between the two data sources (SACT and HES data).[163] Second, there is a possibility that some of the variation between hospitals is due to chance alone. However, we would only expect 5 hospitals to lie more than 2 standard deviations from the national average by chance.

Third, the coding framework is best suited for studying differences between groups of patients (e.g., those treated in different hospitals or receiving different SACT regimens) rather than estimating absolute rates of toxicity which may be over-estimated. However, to limit the likelihood of overestimation we restricted the indicator to only those diagnoses likely to reflect SACT toxicity and to the time period of chemotherapy administration (excluding any post-operative period in a small proportion of patients). In addition, previous studies have suggested the vast majority of hospital admissions during SACT treatment are SACT-related.[110]

Finally, previous studies have demonstrated that mental health status, nutritional status, and laboratory values (e.g., blood tests) were also important predictors for SACT toxicity in older patients.[178 180] However, this information is not routinely included in hospital administrative data and so could not be included as part of the risk-adjustment. As a result, a certain level of "residual confounding" will need to be accepted, irrespective of which patient groups are being compared.

Implications

There are several implications of using this performance indicator for a national assessment of the delivery of SACT. First, our study shows that the performance indicator can be used to compare SACT toxicity between hospitals.[125] In the English NHS, similar hospital-level toxicity rates are already routinely available for patients who had surgery or radiotherapy for prostate, bowel, and oesophageal cancer as part of a programme of national clinical audits.[3 181 182] Outcome reporting programmes are also being established internationally.[121] Second, the performance indicator allows ongoing monitoring of severe acute toxicity events within hospitals which will inform continuous local quality improvement processes. Evidence has shown that quality improvement initiatives are more likely to produce positive effects if continuous monitoring and feedback is undertaken.[125 167] As per previous work, the indicator allows specific individual toxicities to be described in detail which can further inform quality improvement processes.[160]

Third, an improved understanding of the risks of SACT will inform the counselling of patients and strengthen the process of "shared decision making" in day-to-day practice, particularly for novel SACT drugs.

In addition to supporting direct patient care, public reporting of severe acute toxicity rates can also provide transparency around best practice through benchmarking to guide patients in making informed choices about the hospital in which they will receive their SACT treatment.[183 184] This avoids the reliance on surrogate markers of care quality (e.g. presence of robotic surgery), and further stimulates quality improvement through competitive mechanisms or regulation by reducing information asymmetry regarding care quality.[185-187] This transparency can also guide investments, with outcomes considered as part of pay-for-performance schemes in order to support greater value in care delivery.[188]

Finally, the coding framework developed to identify severe acute toxicity was designed to be broad in order to make it applicable to all types of SACT, including traditional cytotoxics, immunotherapy, and targeted agents.[160] This means that the performance indicator can be used in a wide range of clinical settings and expanded across most cancer types, following appropriate validation.

Conclusion

We have evaluated the use of a national performance indicator derived from linked clinical and hospital administrative datasets to assess hospital variation in severe acute toxicity rates for hospitals providing SACT for CRC patients in order to stimulate and support quality improvement. This approach can be applied across different cancer types and in many different countries where similar regional or national clinical and administrative hospital datasets are available.

Table 1 – Distribution of types of toxicities following SACT administration for stage III and IV cohorts, stratified according to CTCAE criteria[96]

Toxicity type	Stage III (n=8,173) (%)	Stage IV (n=7,683) (%)
Gastrointestinal	13.2	23.1
Infection	10.4	24.2
Cardiovascular	6.2	14.1
Metabolic & Endocrine	5.2	10.4
Constitutional	5.0	10.0
Renal	4.9	9.1
Haematology	4.1	12.0
Pain	3.7	6.5
Neurological	2.6	3.9
Neutropenic sepsis	2.4	7.6
Respiratory	1.2	1.6
Line complications	1.2	3.5
Bleeding	1.1	3.0
Dermatology & Rheumatology	0.8	2.3

Table 2a – Patient and tumour characteristics and associated severe acute toxicity for patients with stage III disease

	Stage III (adjuvant) cohort (n=8,173)				
Patient Characteristics	**Number (%)**	**Severe acute toxicity (%)**	**Unadjusted odds ratio**	**Adjusted odds ratio* (95% CI)**	**P value****
Age (years)					**0.010**
<60	2,369 (29)	566 (24)	1.0	1.0	
60-69	2,720 (33)	692 (25)	1.09	1.09 (0.96 to 1.24)	
70-79	2,631 (32)	721 (27)	1.20	1.14 (1.00 to 1.31)	
≥80	453 (6)	95 (21)	0.85	0.78 (0.61 to 1.01)	
Sex					**<0.001**
Male	4,647 (57)	1,072 (23)	1.0	1.0	
Female	3,526 (43)	1,002 (28)	1.32	1.35 (1.22 to 1.49)	
Socioeconomic status (IMDQ)					0.969
1 (most deprived)	1,159 (14)	293 (25)	1.0	1.0	
2	1,460 (18)	374 (26)	1.02	1.02 (0.85 to 1.22)	
3	1,691 (21)	427 (25)	1.00	1.02 (0.85 to 1.21)	
4	1,958 (24)	489 (25)	0.98	1.01 (0.85 to 1.20)	
5 (least deprived)	1,896 (23)	489 (26)	1.03	1.05 (0.89 to 1.25)	
Missing	*9 (0.1)*	-	-		
RCS Charlson score					**<0.001**
0	4,985 (61)	1,181 (24)	1.0	1.0	
1	2,377 (29)	640 (27)	1.19	1.19 (1.07 to 1.34)	
≥2	811 (10)	253 (31)	1.46	1.48 (1.25 to 1.75)	
Performance status					0.546
0	4,925 (67)	1,217 (25)	1.0	1.0	
1	1,946 (27)	526 (27)	1.12	1.06 (0.94 to 1.20)	
≥2	472 (6)	130 (28)	1.15	1.08 (0.87 to 1.36)	
Missing	*830 (10)*	-	-	-	
Tumour Characteristics					
Site					**0.004**
Colon	6,147 (75)	1,540 (25)	1.0	1.0	
Rectosigmoid	524 (6)	139 (27)	1.08	1.17 (0.95 to 1.44)	
Rectum	1,502 (18)	395 (26)	1.07	1.25 (1.09 to 1.44)	
Pathological T-stage					**<0.001**
T1	215 (3)	50 (23)	1.0	1.0	
T2	760 (9)	168 (22)	0.94	0.91 (0.63 to 1.30)	
T3	4,565 (56)	1,083 (24)	1.03	1.00 (0.72 to 1.39)	
T4	2,631 (32)	773 (29)	1.37	1.34 (0.96 to 1.88)	
Missing	*2 (<0.1)*	-	-	-	
Pathological N-stage					**0.002**
N1	5,338 (65)	1,280 (24)	1.0	1.0	
N2	2,835 (35)	794 (28)	1.23	1.18 (1.06 to 1.31)	

*Adjustment for all other variables in the table

**Wald test from multivariable model

Table 2b – Patient and tumour characteristics and associated severe acute toxicity for patients with stage IV disease

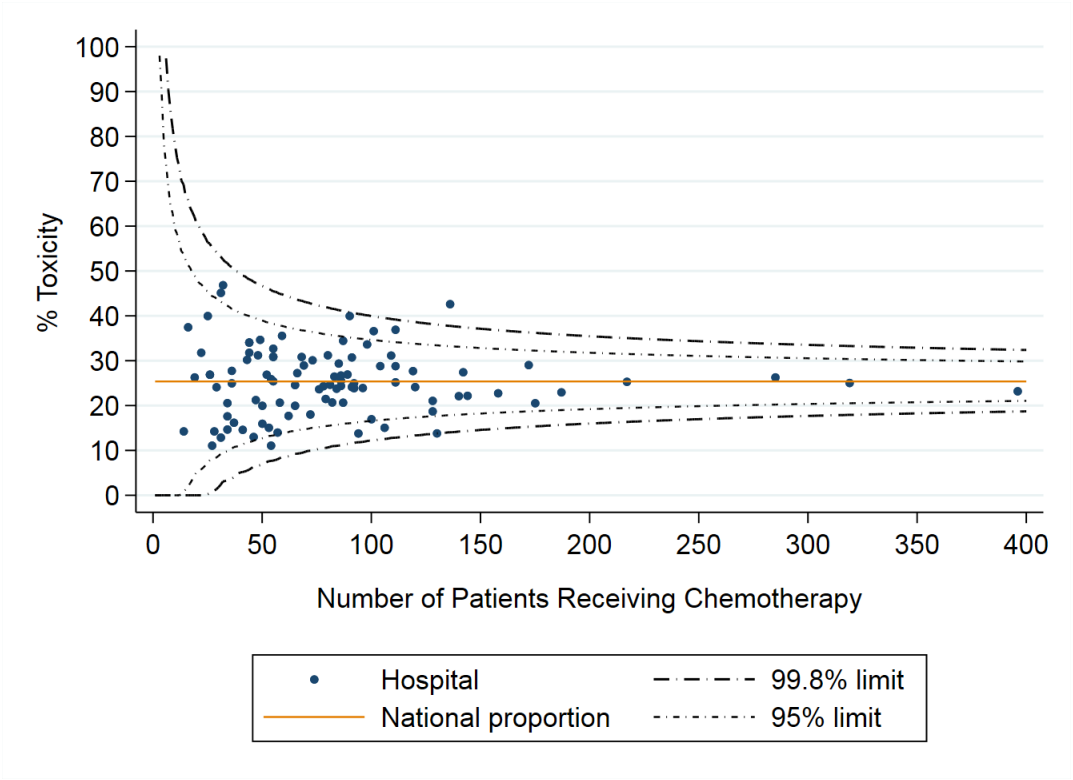
	Stage IV (metastatic) cohort (n=7,683)				
Patient Characteristics	**Number (%)**	**Severe acute toxicity (%)**	**Unadjusted odds ratio**	**Adjusted odds ratio*(95% CI)**	**P value****
Age (years)					**0.026**
<60	2,630 (34)	1,249 (47)	1.0	1.0	
60-69	2,331 (30)	1,073 (46)	0.94	0.92 (0.82 to 1.03)	
70-79	2,189 (28)	1,071 (49)	1.06	0.96 (0.85 to 1.09)	
≥80	533 (7)	232 (44)	0.85	0.74 (0.61 to 0.90)	
Sex					**0.017**
Male	4,640 (60)	2,111 (46)	1.0	1.0	
Female	3,043 (40)	1,514 (50)	1.19	1.12 (1.02 to 1.23)	
Socioeconomic status (IMDQ)					
1 (most deprived)	1,206 (16)	615 (51)	1.0	1.0	0.069
2	1,399 (18)	683 (49)	0.92	0.93 (0.80 to 1.09)	
3	1,602 (21)	727 (45)	0.80	0.82 (0.71 to 0.96)	
4	1,732 (23)	803 (46)	0.83	0.86 (0.74 to 0.96)	
5 (least deprived)	1,732 (23)	793 (46)	0.81	0.83 (0.72 to 0.97)	
Missing	*12 (0.2)*	-	-		
RCS Charlson score					
0	4,674 (62)	2,146 (46)	1.0	1.0	**0.021**
1	2,076 (28)	998 (48)	1.09	1.07 (0.97 to 1.19)	
≥2	759 (10)	395 (52)	1.29	1.24 (1.06 to 1.45)	
Missing	174 (2)	-	-	-	
Performance status					
0	3,730 (54)	1,616 (43)	1.0	1.0	**<0.001**
1	2,255 (33)	1,135 (50)	1.32	1.31 (1.18 to 1.46)	
≥2	902 (13)	500 (55)	1.65	1.61 (1.38 to 1.87)	
Missing	*796 (10)*	-	-	-	
Tumour Characteristics					
Site					**<0.001**
Colon	4,929 (64)	2,505 (51)	1.0	1.0	
Rectosigmoid	510 (7)	235 (46)	0.83	0.83 (0.69 to 1.00)	
Rectum	2,244 (29)	885 (39)	0.63	0.65 (0.58 to 0.72)	
Pre-treatment T-stage					**0.004**
T1	14 (0.2)	6 (43)	1.0	1.0	
T2	369 (6)	157 (43)	1.04	0.96 (0.34 to 2.74)	
T3	3,619 (54)	1,566 (43)	1.07	0.97 (0.34 to 2.72)	
T4	2,699 (40)	1,372 (51)	1.43	1.17 (0.42 to 3.31)	
Missing	*982 (13)*	-	-	-	
Pre-treatment N-stage					**0.001**
N0	1,186 (18)	516 (44)	1.0	1.0	
N1	2,935 (44)	1,319 (45)	1.07	1.09 (0.96 to 1.25)	
N2	2,610 (39)	1,274 (49)	1.26	1.30 (1.12 to 1.50)	
Missing	*952 (12)*	-	-	-	

*Adjustment for all other variables in the table

**Wald test from multivariable model

Figure 1 – Funnel plot showing a) unadjusted and b) adjusted rates of severe acute toxicity by English NHS hospital for patients receiving SACT for stage III colorectal cancer

a)



b)

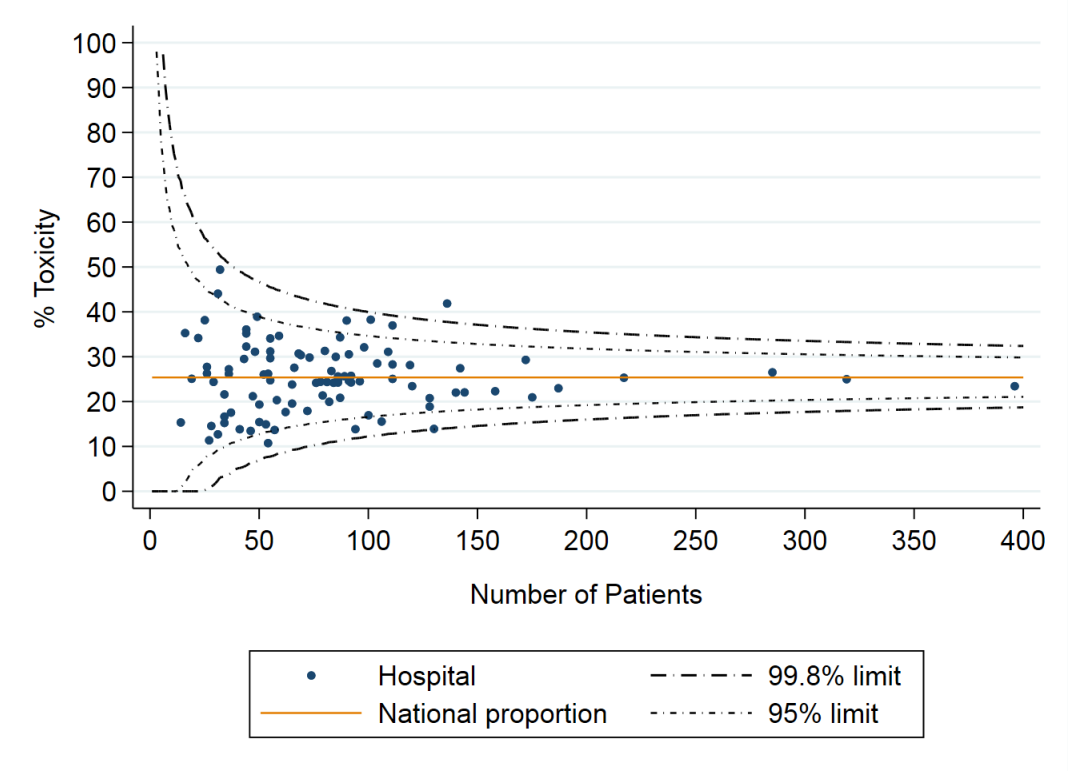
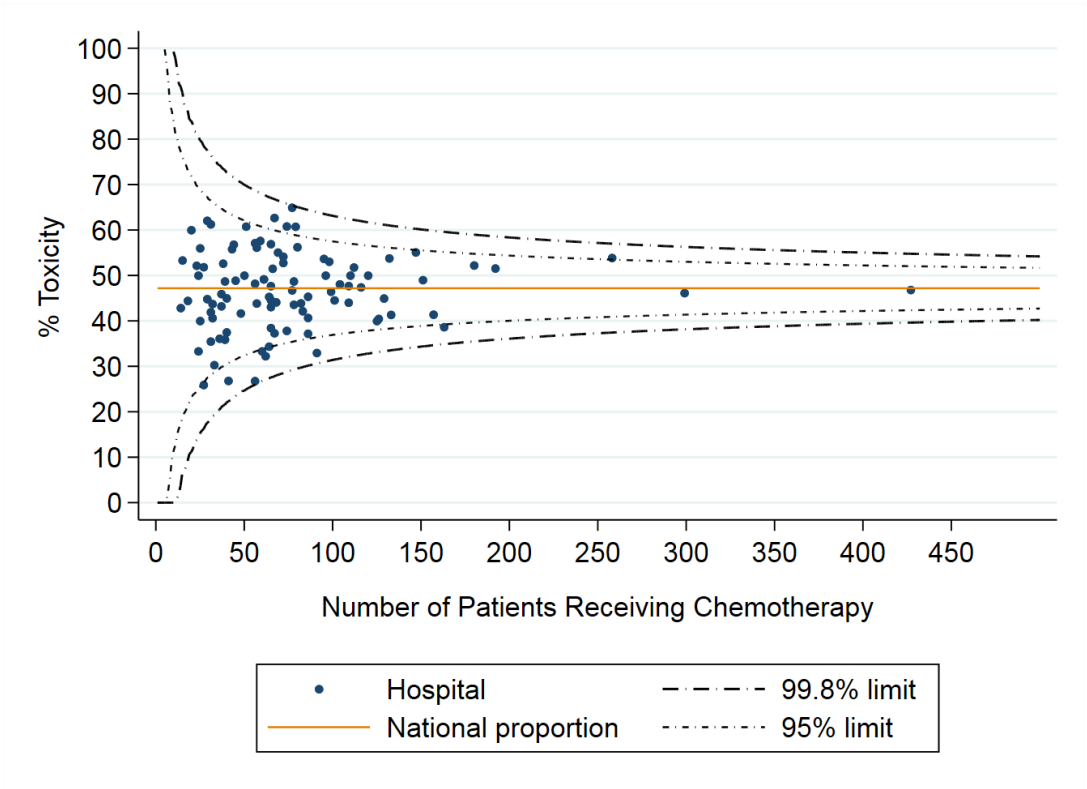


Figure 2 – Funnel plots showing a) unadjusted and b) adjusted rates of severe acute toxicity by English NHS hospital for patients receiving SACT for stage IV colorectal cancer

a)



b)

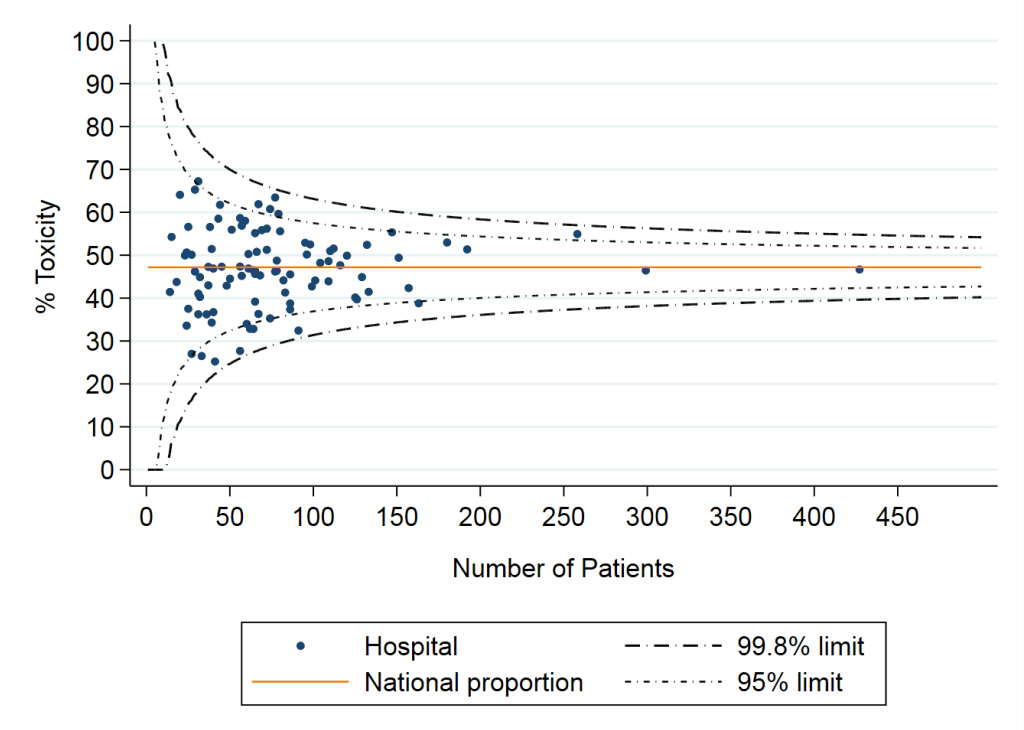


Figure 3 – Quality improvement conceptual framework highlighting potential areas within the SACT care pathway that may represent sources of variation in care

9. VOLUME-OUTCOME RELATIONSHIP FOR RECTAL CANCER SURGERY

9.1 Research paper 4

Title: What is the impact of hospital and surgeon volumes on outcomes in rectal cancer surgery?

This is the manuscript which was submitted to a peer-reviewed journal at the time of thesis submission.

Supplementary material can be found in Appendix 16.

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1802390	**Title**	Dr
First Name(s)	Jemma Megan		
Surname/Family Name	Boyle		
Thesis Title	Using National Routine Data to Explore the Utilisation and Outcomes of Multimodal Treatment in the Management of Colorectal Cancer		
Primary Supervisor	Dr Kate Walker		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	British Journal of Surgery
Please list the paper's authors in the intended authorship order:	J. M. Boyle, J. van der Meulen, A. Kuryba, T.E. Cowling, M.S. Braun, A. Aggarwal, N.S. Fearnhead & K. Walker.
Stage of publication	Choose an item. Ready to be Submitted.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Designed the work, analysed and interpreted the data, drafted the article, and approved final version for submission.

SECTION E

Student Signature	
Date	15th February 2022

Supervisor Signature	K. Walker
Date	15th February 2022

What is the impact of hospital and surgeon volumes on outcomes in rectal cancer surgery?

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***joint senior author**

ABSTRACT

Background: Recent NICE guidelines have recommended minimum annual volumes at hospital and surgeon level for rectal cancer surgery. However, the evidence for a volume-outcome relationship is low quality and this large national study aims to address this existing gap.

Methods: Patients undergoing a major resection for rectal cancer (including anterior resection, abdominoperineal resection (APR), low Hartmann's procedure, panproctocolectomy, and pelvic exenteration) were identified from the National Bowel Cancer Audit database.

Mean annual hospital and surgeon volumes were calculated using Hospital Episode Statistics to maximise capture of procedures. Patient, tumour, and treatment characteristics were compared according to tertiles of mean hospital and surgeon volumes using chi-squared tests.

Multivariable regression was used to model a continuous relationship between each outcome (90-day mortality, 30-day unplanned readmission, unplanned return to theatre, stoma at 18 months following anterior resection, positive CRM, length of stay, and 2-year all-cause mortality rate) and hospital and surgeon volumes, using a linear plus a quadratic term for volume. Extensive risk-adjustment for patient, tumour, and treatment characteristics was undertaken.

Results: 13,858 patients undergoing rectal cancer surgery in 166 English NHS hospitals by 846 surgeons between 2015 and 2019 were included. Compared to current national guidelines, 6 hospitals (3.6%) performed less than 10 rectal cancer resections per year, and 381 surgeons (45.0%) performed less than 5 rectal cancer resections per year.

Both high volume hospitals and surgeons were less likely than low volume hospitals and surgeons to treat ethnic minority groups, and more likely to treat affluent patients. Low volume hospitals were more likely to perform sphincter-sparing procedures, and less likely to perform robotic surgery. High volume surgeons were more likely to perform elective surgery, sphincter-sparing procedures, and robotic surgery.

High volume surgeons had a reduced length of stay (p value for linear plus quadratic term = 0.0162). However, no volume-outcome relationship was demonstrated for any other outcomes at hospital or surgeon level.

Conclusion: Almost half of colorectal surgeons in England are not meeting the NICE standard for rectal cancer surgery volume. However, our results suggest that centralising rectal cancer surgery with the main focus of increasing operative volume will have a limited impact on surgical outcomes. Therefore, quality improvement initiatives should address a wider range of evidence-based process measures, across the whole multidisciplinary care pathway, to enhance rectal cancer surgery outcomes.

INTRODUCTION

An increasing body of evidence has shown improved post-operative and long-term oncological outcomes for hospitals and surgeons performing higher volumes of 'more complex' surgical procedures including oesophagectomy, gastrectomy, pancreatectomy, and hepatectomy.[134-136 140] As a result, in many countries specialisation of these surgical procedures to selected hospitals (also referred to as "centralisation") has occurred in order to increase case volumes.[138 189] The specialisation of oesophago-gastric cancer in England via a "hub-and-spoke" model coincided with a reduction in post-operative mortality from 7.4% to 2.5%, although this could not be explained by hospital volume increases alone.[139]

The management of rectal cancer is becoming increasingly challenging due to complexity of available treatment options and need for multidisciplinary team (MDT) input regarding evidence-based best practice decisions about neo-adjuvant and adjuvant therapies, local excision, "watch-and-wait" strategies, surgical approach (including robotic access), surgical procedure (appropriateness of sphincter-sparing surgery), and the use of temporary stomas. However, the evidence for a volume-outcome relationship for rectal cancer remains conflicting.[142]

To date, there have been significant methodological limitations with studies evaluating the volume-outcome relationship for rectal cancer.[143] This includes dichotomisation of volumes into arbitrary categories which leads to an inability to pool results due to heterogeneity in the definition of what constitutes a high volume hospital or surgeon, as well as a reduction in the statistical power to detect a volume-outcome relationship. There is significant heterogeneity in study populations (e.g., inclusion of colon cancer, particular operations or staging, elective versus emergency), factors used in risk-adjustment models, and outcomes explored. In addition, analyses often use data from the 1990s and early 2000s, precluding widespread use of laparoscopic surgery.

As a result of the lack of clear evidence on a volume-outcome relationship, national guidelines vary between countries on the minimum annual volume of rectal cancer resections per hospital (e.g., 10 in England, 20 in Germany and the Netherlands, and 21 in the US) and per surgeon (e.g., 5 in England, and 10 in Germany).[41 190]

This large national study aims to address the existing gap in the availability of high quality evidence for the volume-outcome relationship in rectal cancer surgery. The study uses contemporary linked national clinical datasets including all hospitals providing rectal cancer surgery in the English National Health Service (NHS), with no exclusions, and case ascertainment beyond 95% of all diagnosed cases. Using this rich and complete data, we aim to overcome prior methodological limitations by performing comprehensive risk-adjustment, using an extensive panel of outcome measures, modelling volume as a continuous variable, and ensuring surgeon-level information is robust through cross-validation of information between data sources.

METHODS

Data sources

This study used National Bowel Cancer Audit (NBOCA) data[3], Hospital Episode Statistics (HES) data[16], Radiotherapy Dataset (RTDS) data[14], and Office for National Statistics (ONS) mortality data[15] linked at patient-level for patients with a primary diagnosis of rectal cancer in the English NHS (International Classification of Diseases, 10th edition (ICD-10) code - C20).

National Bowel Cancer Audit (NBOCA)

NBOCA is a prospective mandatory database for all patients newly diagnosed with colorectal cancer in the English NHS. Data items from NBOCA were used to determine sex, age, Eastern Cooperative Oncology Group (ECOG) performance status[161], pathological staging according to the TNM system, American Society of Anaesthesiologists (ASA) score, date of surgery, surgical procedure, surgical urgency (elective/scheduled or emergency/urgent), and surgical access.

Hospital Episode Statistics (HES)

The HES dataset is a national administrative dataset of all admissions to English NHS hospitals.[16 58] HES provided information on the number of comorbidities according to the Royal College of Surgeons of England Comorbidity score[149], socioeconomic deprivation reported as quintiles of the national distribution of the Index of Multiple Deprivation (IMD)[3], and ethnicity.

Radiotherapy Dataset (RTDS)

Radiotherapy information was obtained from linkage to RTDS and included whether the patient received radiotherapy, and whether this was short- or long-course based on prior methodology using the number of fractionations and time between radiotherapy and surgery.[150]

Study population

Patients undergoing a major resection for rectal cancer between 1 April 2015 and 31 March 2019 according to NBOCA were identified (Figure 1). Procedures included were anterior resection, abdominoperineal resection (APR), low Hartmann's procedure, panproctocolectomy, and pelvic exenteration.

Hospital-level volumes

Using previously developed methodology, mean annual hospital-level volumes were calculated from HES, in order to maximise the capture of procedures.[153] Hospital refers to individual English NHS hospital sites performing rectal cancer surgery (multiple hospital sites can make up a hospital trust). All 166 hospitals performed rectal cancer surgery across all years of the included timeframe.

Surgeon-level volumes

Similarly, using previously developed methodology, mean annual surgeon-level volumes were calculated.[153] This made use of NBOCA, HES, and General Medical Council (GMC) data to maximise the capture of procedures and restrict surgeon-level analyses to active General Surgeons. For records where there was a discrepancy between NBOCA and HES on the responsible surgeon, the information recorded in NBOCA was deemed to be the more accurate source of information. This is because NBOCA data is used for the NHS Clinical Outcomes Publication scheme (individual surgeon outcomes are published in the public domain) and so it would be expected that this information was more accurate.[123]

The mean annual volume was calculated as the number of rectal cancer procedures performed during the surgeon's active period divided by the duration of the active period. The duration of the active period was defined as the number of years in which the surgeon had procedures recorded and was deemed to be actively operating.

Outcomes

90-day mortality

Patient records linked to ONS mortality data were used to ascertain patients who died within 90 days of their rectal cancer surgery.

30-day unplanned readmission

HES records were used to identify any unplanned admission for any cause and to any English NHS hospital within 30 days of the date of discharge.

30-day unplanned return to theatre

HES records were used to identify patients who returned to theatre following their primary rectal cancer surgery using a pre-existing validated coding algorithm based on Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures, 4th revision (OPCS-4) codes.[191]

Stoma at 18 months following anterior resection

This is defined as the proportion of patients who still have a stoma 18 months after an anterior resection for rectal cancer. The vast majority of stomas formed during an anterior resection are temporary and expected to be reversed. OPCS-4 codes within HES records were used to identify patients undergoing reversal procedures.

Patients needed to have at least 18 months follow-up after their rectal cancer surgery to be included within this analysis (includes patients undergoing major resection until 30 September 2018).

Positive circumferential resection margin (CRM)

NBOCA records provided information on CRM status which reflects a key determinant of rectal surgery quality.

Length of stay

HES records were used to calculate the length of inpatient stay from the date of rectal cancer surgery. A binary outcome was generated based on whether the hospital stay was greater than 14 days in order to try to capture those patients with a significant delay in post-operative recovery, likely due to immediate complications.

2-year all-cause mortality rate

NBOCA-HES records linked to ONS mortality records were used to identify patients who died within 2 years of the date of rectal cancer surgery from any cause. Follow-up time was censored at 16 April 2020 or two years, whichever was earliest. Approximately two-thirds of patients were recorded in ONS as dying from colorectal cancer.

Statistical analysis

Patient, tumour and treatment characteristics were compared using chi-squared tests according to tertiles of mean annual hospital and surgeon volumes.

Multivariable regression was used to model a continuous relationship between each outcome and hospital and surgeon volumes, using a linear plus a quadratic term for volume. For binary outcomes, multivariable logistic regression was used with a random intercept at hospital or surgeon level to account for clustering. For the 2-year all-cause mortality rate, multivariable Poisson regression was used with a random intercept at hospital or surgeon level to account for clustering.

Several sensitivity analyses were performed. This included modelling volume as a categorical variable (according to tertiles and quintiles), and also estimating models one-by-one excluding emergency patients, those having pelvic exenteration, and those having robotic surgery.

Risk-adjustment for age, sex, socioeconomic status, RCS Charlson comorbidity score, ECOG performance status, ASA grade, surgical urgency (emergency/urgent versus elective/scheduled), surgical procedure (pelvic exenteration versus other procedure), pathological TNM staging, and radiotherapy use (long-course, short-course or none) was undertaken. Risk-adjustment factors included were based on those suggested by the NICE review of evidence.[143]

The adequacy of a linear plus quadratic relationship between volume and each binary outcome was assessed by superimposing the fitted line onto a graph of the predicted outcome with 95% confidence intervals, in 6 equally sized categories of volume, setting the value of all other covariates to the mean value.

Patients with missing data on outcomes (CRM status and length of stay) were excluded from those analyses (Figure 1). Missing values for risk-adjustment variables were imputed with multiple imputation using chained equations, creating 20 datasets and using Rubin's rules to combine the estimated odds ratios across the datasets.[158]. All statistical analyses were undertaken using Stata version 15.

RESULTS

Hospital and surgeon level volumes

13,858 patients undergoing rectal cancer surgery at 166 English NHS hospitals between 1 April 2015 and 31 March 2019 in the English NHS were included. 13,841 patients were included in the surgeon analyses with 846 active General Surgeons identified (patients were excluded if the GMC number in neither data source corresponded to a General Surgeon).

At hospital level, the median annual number of procedures was 26 (interquartile range (IQR) 19 to 36, and range 1 to 74). 6 hospitals (3.6%) performed less than 10 resections, and 43 hospitals (25.9%) performed less than 20 resections. At surgeon level, the median annual number of procedures was 5 (interquartile range (IQR) 3 to 7, and range 1 to 31). 75 surgeons (8.9%) performed only 1 resection, 381 (45.0%) performed less than 5 resections, and 756 (89.3%) performed less than 10 resections.

High volume surgeons were more likely to work in high volume hospitals ($p<0.001$), although 13% of high volume surgeons worked in the lowest volume hospitals and 34% of low volume surgeons worked in the highest volume hospitals (Appendix 1).

Patient characteristics according to hospital- and surgeon-level volumes

Both high volume hospitals and surgeons were less likely than low volume hospitals and surgeons to treat ethnic minority groups, and more likely to treat affluent patients (Table 1). Low volume hospitals were more likely to perform sphincter-sparing procedures, and less likely to perform robotic surgery. High volume surgeons were more likely to perform elective surgery, sphincter-sparing procedures, and robotic surgery.

Although statistically significant, many of the other observed differences in characteristics at hospital- and surgeon-level are unlikely to be clinically significant.

Outcomes

For the whole cohort, the overall outcomes were as follows: 253 patients (1.8%) died within 90 days of their rectal cancer resection, 1,920 patients (13.9%) had an unplanned 30-day readmission, 1,595 (11.5%) had a 30-day unplanned return to theatre, and 2-year all-cause mortality was 9.4%.

Of the 5,710 patients who underwent an anterior resection with sufficient follow-up, 2,051 (35.9%) had a stoma at 18 months. Of the 11,519 patients with CRM information, 1,021 (8.9%) had positive margins. Of the 13,822 patients with length of stay information, 2,941 (21.3%) had a stay beyond 14 days.

Volume-outcome relationship

The linear-quadratic model was a good fit to the data for each outcome. There was no demonstrable volume-outcome relationship at hospital level for any outcomes (Figure 2). High volume surgeons had a significantly shorter length of stay (p value for linear plus quadratic term = 0.016) than low volume surgeons (Figure 3). There was no demonstrable volume-outcome relationship for any of the other outcomes at surgeon level.

Sensitivity analyses performed to model volume as a categorical variable (tertiles and quintiles) did not change the results. Similarly, sensitivity analyses modelling outcomes excluding emergency patients, those having pelvic exenterations, and those having robotic procedures did not yield any significant volume-outcome relationships (results not presented).

DISCUSSION

This large national study explores the relationship between hospital and surgeon rectal cancer volumes and a comprehensive set of outcome measures available from routinely collected data within the English NHS. It demonstrates that over half of surgeons are falling short of the recently recommended national quality standard of 5 rectal cancer resections per year.[41] Within this study, a volume-outcome relationship was demonstrated for reduced length of stay for high volume surgeons. However, we were not able to demonstrate a volume-outcome relationship for any of the other outcomes (including post-operative mortality, complications, and resection margins) at hospital or surgeon level.

Strengths and Limitations

The main limitation of this study is that, although national high-quality data was used, this data was not captured for the purpose of evaluating a volume-outcome relationship. Case ascertainment is high and validation of surgeon information was undertaken using two data sources with 92% agreement on surgeon-level information, and further verification through linkage to GMC data.[153] However, the datasets only capture the responsible Consultant surgeon meaning we could not definitively attribute the surgery to this surgeon which may attenuate our findings, for example, if a trainee performed the procedure. Ideally, every case would be captured and allocated to the correct surgeon (including grade).

It was not possible to fully capture the complexity of each procedure from the available data. Tumour height and body mass index are captured but are currently too poorly completed to be included in any risk-adjustment. A previous study found that high volume surgeons tend to remove lower tumours, which would tend to bias positive associations between volume and outcomes towards the null.[76] However, for the 6,947 patients (50.1%) with this information available in our study, there was little association between volume and tumour height, with the proportion of tumours below 5cm at 23%, 22% and 25% for low, middle, and high volume surgeons, respectively, and missing data not differing between groups. It therefore seems unlikely that risk-adjustment for tumour height would significantly alter the findings.

There are several strengths of this study. Volume was modelled as a continuous variable to overcome the limitations associated with arbitrary cut-offs which make the interpretation and pooling of results across studies troublesome. A review of 403 studies showed that only 4.3% used volume as a continuous variable.[192] Random intercepts were used to account for the clustering of outcomes in hospitals and surgeons. Ideally, we would want to simultaneously account for the clustering of patients within surgeons, and the clustering of surgeons within hospitals. However, the multilevel models would not converge with multiply imputed data.

The use of contemporary national linked datasets allowed comprehensive risk-adjustment to be undertaken in line with most risk factors suggested by NICE and is reflective of current practice (e.g., robotic surgery).[143] Finally, reporting was undertaken for individual hospital sites which is important given the potential for differences in infrastructure between geographically separate hospitals within the same trust (see Methods).

Interpretation of findings

Low volume hospitals and high volume surgeons tended to perform more sphincter-sparing surgery. The decision as to whether to perform an anterior resection or APR largely depends on tumour height and involvement of the sphincter-complex. It also takes into consideration the patient's likely functional outcome and preference (not captured in routinely collected data). High-volume surgeons may have increased confidence to perform anterior resections for lower tumours, including prior experience of hand-sewn colo-anal anastomoses. The lower number of patients with permanent stomas in low volume hospitals may be explained by a reduced complexity of cases due to pre-existing referral patterns to specialist centres.

Reduced length of stay for high volume surgeons has been found previously, although prior studies included colon cancer patients.[77 144] This finding is likely explained by high volume surgeons having an increased use of laparoscopic and robotic techniques which are associated with a faster recovery.[193] This is supported by the loss of statistical significance when surgical access was added to the risk-adjustment model (results not shown).

To date, the evidence for a volume-outcome relationship in rectal cancer surgery has been conflicting. However, significant results are always in favour of high volume hospitals and surgeons. Studies showing a

relationship between high hospital and surgeon volumes and overall survival, CRM rate, peri-operative complications, local recurrence, permanent stoma rate, and perioperative mortality have been identified, although there are equal numbers of studies that fail to identify a relationship.[143 192]

A prior study conducted in England for elective colorectal cancer cases examined hospital and surgeon volumes from HES in relation to 30-day post-operative mortality, 28-day readmission, reoperation, and length of stay, and found hospital and surgeon volume-outcome relationships for length of stay alone (having adjusted for surgical access).[144]

There are several explanations as to why a volume-outcome relationship may not have been demonstrated for outcomes in this study. The first is residual confounding. Although we performed extensive risk-adjustment, it is possible that we have not fully adjusted for complexity of surgery. It is possible that high volume hospitals and surgeons are operating on more complex cases due to selective referral (providers with better reputations attracting more referrals).[41] These same high volume providers may practice less risk averse behaviour due to their experience, as well as taking referrals for patients requiring specialist expertise in the peri-operative phase (e.g., patients requiring access to dialysis) who have increased baseline morbidity. Alternatively, the most experienced surgeons may actually be performing fewer complex cases, supported by one third of the lowest volume surgeons working in high volume hospitals (Appendix 1). All of these factors have the potential to dilute the volume-outcome relationship.

Some of the analyses are likely to be underpowered due to low event rates or reduced cohorts due to missing outcome data. Statistical power was more of an issue for surgeon volumes due to the low number of surgeons with high volumes (median 5 rectal resections per year, IQR 3-7). Positive CRM (the most surgical outcome in this study) and stoma at 18 months following anterior resection, both appeared in our data to be lower for higher volume surgeons. It may be that in a larger cohort evidence of a relationship would be found. It is possible that a volume-outcome relationship only exists for the most complex cases but, even in a national study, numbers are not large enough to assess this.

Some of the measures used, for example unplanned return to theatre, are more difficult to define within routinely collected data. It is also difficult to capture the nuances in the quality of shared decision-making and care that is undertaken within the MDT setting from this data. For example, appropriate decisions about the suitability for oncological therapies, “watch-and-wait” strategies, choice of surgical procedure, surgical approach, and need for a temporary stoma will each influence the outcomes in this study to a greater or lesser degree.[194]

Finally, these results might simply reflect a true lack of volume-outcome relationship. A previous study demonstrated wide variation in elective colorectal surgery outcomes in the English NHS, even amongst the

very highest volume surgeons (e.g., mortality rates ranging from 0% to 7.7%).[144] Other studies have also demonstrated variation in outcomes across the whole spectrum of caseload.[195 196]

Implications

Volume-based policies are based on the assumption that increased patient volumes enable greater specialisation of staff, and greater experience and expertise; the "practice makes perfect" hypothesis.[197] The potential benefits of specialisation have been well cited within the literature: team critical mass and back-up with well-defined care processes and protocols enhancing decision-making, accessibility to a full range of facilities (e.g., radiotherapy on-site), access to advanced surgical and innovative techniques (e.g. less invasive procedures, liver resections[198], and HIPEC), active salvage in the event of post-operative complications (requiring interventional radiology and endoscopy support), high volume training opportunities and exposure to salvage surgery, better institutional infrastructure, and potential cost-benefit implications due to optimisation of resource utilisation.

The main disadvantage of specialisation is the additional travel distances incurred by patients which may pose a barrier to accessing cancer care. We have shown that high volume hospitals are less likely to treat more deprived patients. Travel time has been shown to be more of a limiting factor to accessing cancer care for those living in socioeconomically deprived areas.[199] However, patients have previously expressed a willingness to travel for high quality care.[200] Other issues might include capacity problems, and deskilling of surgeons for emergency procedures (less problematic for rectal cancer given low emergency numbers). An alternative solution to specialisation between hospitals, might be to restrict the number of surgeons performing rectal cancer surgery within each hospital.

This study has provided additional evidence regarding the volume-outcome relationship within the English NHS. It has demonstrated that a significant proportion of surgeons are performing fewer rectal cancer resections per year than national recommendations and this needs to be addressed.[41] Despite a definite "signal" for improved outcomes with high volumes in the wider literature, we were not able to demonstrate a significant volume-outcome relationship within this study. Prior to any specialisation that might occur, it appears critical that commissioners ascertain which providers specialisation should involve, as this study suggests that volume alone does not differentiate high quality care.[201]

Conclusion

This study has provided additional evidence regarding the volume-outcome relationship within the English NHS. We found a substantial number of surgeons are not currently performing the national recommended annual volume of rectal cancer resections. However, apart from a reduced length of stay for higher-volume surgeons, we were not able to demonstrate significant volume-outcome relationships within this study at hospital or surgeon level.

Given that current evidence is lacking for increasing operative volume in isolation, all essential aspects of high-quality care should be balanced in the event of specialisation of multidisciplinary rectal cancer services. A wide range of evidence-based process measures across the whole care pathway, including those important to patients, should be evaluated to enhance rectal cancer surgery outcomes and ensure that patients are appropriately directed.

Table 1 – Characteristics according to tertiles of hospital- and surgeon-level mean annual volumes

	Hospital-level volume				Surgeon-level volume			
	Low volume (<22) 60 hospitals	**Mid volume (22-31) 51 hospitals**	**High volume (32-74) 55 hospitals**	**p value**	**Low volume (1-3) 268 surgeons**	**Mid volume (4-6) 322 surgeons**	**High volume (>6) 256 surgeons**	**p value**
	No. (%) N=2,701	**No. (%) N=4,066**	**No. (%) N=7,091**		**No. (%) N=1,414**	**No. (%) N=4,747**	**No. (%) N=7,680**	
Age				0.021*				0.265
<50	225 (8.3)	273 (6.7)	515 (7.3)		98 (6.9)	354 (7.5)	558 (7.3)	
50-59	512 (19.0)	726 (17.9)	1,265 (17.8)		237 (16.8)	831 (17.5)	1,432 (18.6)	
60-74	1,259 (46.6)	2,091 (51.4)	3,528 (49.8)		740 (52.3)	2,380 (50.1)	3,753 (48.9)	
75-84	622 (23.0)	857 (21.1)	1,574 (22.2)		291 (20.6)	1,048 (22.1)	1,710 (22.3)	
≥85	83 (3.1)	119 (2.9)	209 (2.9)		48 (3.4)	134 (2.8)	227 (3.0)	
Sex				0.452				0.082
Male	1,787 (66.2)	2,639 (64.9)	4,599 (64.9)		948 (67.0)	3,041 (64.1)	5,026 (65.4)	
Female	914 (33.8)	1,427 (35.1)	2,492 (35.1)		466 (33.0)	1,706 (35.9)	2,654 (34.6)	
Ethnicity				<0.001*				<0.001*
White	2,383 (92.1)	3,709 (95.8)	6,418 (95.8)		1,253 (92.2)	4,328 (95.3)	6,913 (95.5)	
Other	205 (7.9)	161 (4.2)	280 (4.2)		106 (7.8)	214 (4.7)	326 (4.5)	
Missing	113 (4.2)	196 (4.8)	393 (5.5)		55 (3.9)	205 (4.3)	441 (5.7)	
IMDQ				<0.001*				<0.001*
1 (most deprived)	411 (15.2)	697 (17.2)	977 (13.8)		241 (17.1)	771 (16.3)	1,069 (13.9)	

2	543 (20.1)	725 (17.9)	1,164 (16.4)		262 (18.5)	861 (18.2)	1,304 (17.0)	
3	603 (22.4)	856 (21.1)	1,501 (21.2)		298 (21.1)	1,016 (21.4)	1,644 (21.5)	
4	601 (22.3)	913 (22.5)	1,631 (23.0)		326 (23.1)	1,028 (21.7)	1,788 (23.3)	
5 (least deprived)	539 (20.0)	864 (21.3)	1,806 (25.5)		286 (20.2)	1,061 (22.4)	1,859 (24.3)	
Missing	4 (0.1)	11 (0.3)	12 (0.2)		1 (0.1)	10 (0.2)	16 (0.2)	
RCS Charlson score				0.004*				0.357
0	1,543 (57.1)	2,366 (58.2)	4,243 (59.8)		805 (56.9)	2,771 (58.4)	4,570 (59.5)	
1	829 (30.7)	1,132 (27.8)	1,948 (27.5)		416 (29.4)	1,365 (28.8)	2,122 (27.6)	
≥2	329 (12.2)	568 (14.0)	900 (12.7)		193 (13.6)	611 (12.9)	988 (12.9)	
Performance status				<0.001*				0.002*
0	1,550 (60.6)	2,370 (65.2)	3,884 (64.9)		804 (62.5)	2,635 (62.6)	4,362 (65.4)	
1	732 (28.6)	1,026 (28.2)	1,608 (26.9)		350 (27.2)	1,229 (29.2)	1,779 (26.7)	
≥2	276 (10.8)	237 (6.5)	495 (8.3)		133 (10.3)	343 (8.2)	529 (7.9)	
Missing	143 (5.3)	433 (10.6)	1,104 (15.6)		127 (9.0)	540 (11.4)	1,010 (13.2)	
ASA grade				0.04*				0.893
1	405 (15.7)	597 (15.5)	1,004 (14.9)		209 (15.5)	708 (15.6)	1,087 (15.0)	
2	1,524 (59.0)	2,408 (62.3)	4,128 (61.3)		816 (60.5)	2,768 (60.8)	4,468 (61.5)	
≥3	652 (25.3)	859 (22.2)	1,606 (23.8)		323 (24.0)	1,074 (23.6)	1,713 (23.6)	
Missing	120 (4.4)	202 (5.0)	353 (5.0)					
Surgical access				<0.001*				<0.001

Open	580 (21.6)	1,058 (26.1)	1,952 (27.6)		430 (30.6)	1,500 (31.7)	1,646 (21.5)	
Laparoscopic	2,052 (76.3)	2,758 (68.0)	4,654 (65.8)		959 (68.2)	3,110 (65.7)	5,392 (70.4)	
Robotic	56 (2.1)	238 (5.9)	463 (6.5)		18 (1.3)	122 (2.6)	617 (8.1)	
Missing	13 (0.5)	12 (0.3)	22 (0.3)					
Surgical urgency				<0.001*				<0.001*
Elective/scheduled	2,582 (95.8)	3,858 (95.3)	6,894 (97.6)		1,307 (92.7)	4,574 (96.6)	7,447 (97.4)	
Emergency/urgent	113 (4.2)	191 (4.7)	173 (2.5)		103 (7.3)	161 (3.4)	202 (2.6)	
Missing	6 (0.2)	17 (0.4)	24 (0.3)		4 (0.3)	12 (0.3)	31 (0.4)	
Surgical procedure				<0.001*				<0.001*
Anterior resection	1,759 (65.1)	2,554 (62.8)	4,468 (63.0)		883 (62.4)	2,977 (62.7)	4,917 (64.0)	
APR	629 (23.3)	1,038 (25.5)	1,778 (25.1)		315 (22.3)	1,202 (25.3)	1,925 (25.1)	
Hartmann's	279 (10.3)	402 (9.9)	663 (9.3)		181 (12.8)	490 (10.3)	664 (8.6)	
Pelvic Exenteration	4 (0.1)	22 (0.5)	88 (1.2)		8 (0.6)	16 (0.3)	90 (1.2)	
Panproctocolectomy	30 (1.1)	50 (1.2)	94 (1.3)		27 (1.9)	62 (1.3)	84 (1.1)	
Pathological T-stage				0.211				0.05
T1	320 (12.7)	465 (12.3)	914 (14.0)		140 (10.8)	582 (13.1)	976 (13.8)	
T2	715 (28.5)	1,130 (29.8)	1,866 (28.5)		361 (27.7)	1,308 (29.4)	2,038 (28.8)	
T3	1,278 (50.9)	1,910 (50.4)	3,259 (49.8)		689 (53.0)	2,213 (49.8)	3,543 (50.0)	
T4	200 (8.0)	282 (7.4)	502 (7.7)		111 (8.5)	340 (7.7)	526 (7.4)	
Missing	188 (7.0)	279 (6.9)	550 (7.8)		113 (8.0)	304 (6.4)	597 (7.8)	

Pathological N-stage				0.231				0.961
N0	1,592 (63.7)	2,407 (63.4)	4,168 (63.7)		825 (63.5)	2,818 (63.5)	4,515 (63.7)	
N1	657 (26.3)	942 (24.8)	1,632 (25.0)		335 (25.8)	1,120 (25.3)	1,773 (25.0)	
N2	251 (10.0)	445 (11.7)	741 (11.3)		139 (10.7)	497 (11.2)	799 (11.3)	
Missing	201 (7.4)	272 (6.7)	550 (7.8)		115 (8.1)	312 (6.6)	593 (7.7)	
Pathological M-stage				0.151				0.002*
M0	2,344 (95.5)	3,612 (96.4)	6,041 (96.1)		1,198 (94.6)	4,160 (95.9)	6,628 (96.5)	
M1	111 (4.5)	133 (3.6)	242 (3.9)		69 (5.4)	179 (4.1)	237 (3.5)	
Missing	246 (9.1)	321 (7.9)	808 (11.4)		147 (10.4)	408 (8.6)	815 (10.6)	
Radiotherapy				0.013*				<0.001*
No radiotherapy	1,750 (64.8)	2,670 (65.7)	4,752 (67.0)		957 (67.7)	3,097 (65.2)	5,105 (66.5)	
Long Course	710 (26.3)	1,081 (26.6)	1,849 (26.1)		338 (23.9)	1,246 (26.2)	2,053 (26.7)	
Short Course	241 (8.9)	315 (7.7)	490 (6.9)		119 (8.4)	404 (8.5)	522 (6.8)	

Figure 1 – Flowchart for patients included in the study.

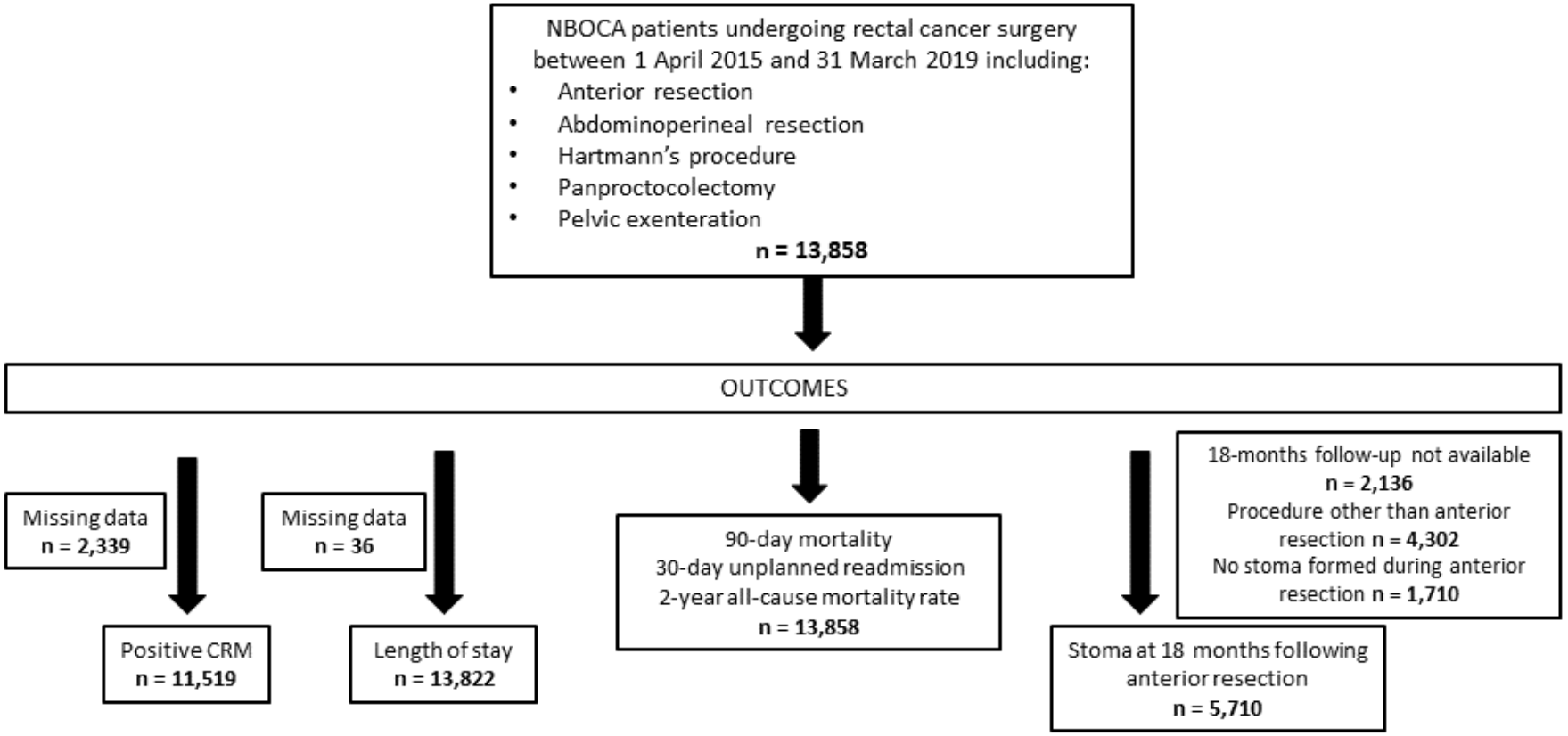
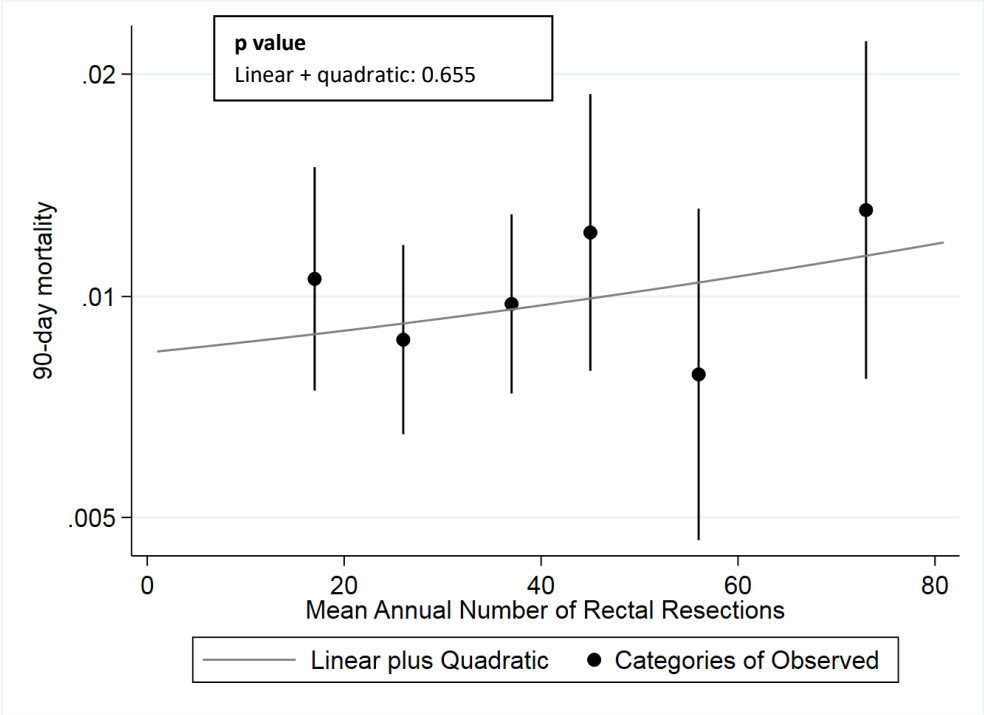
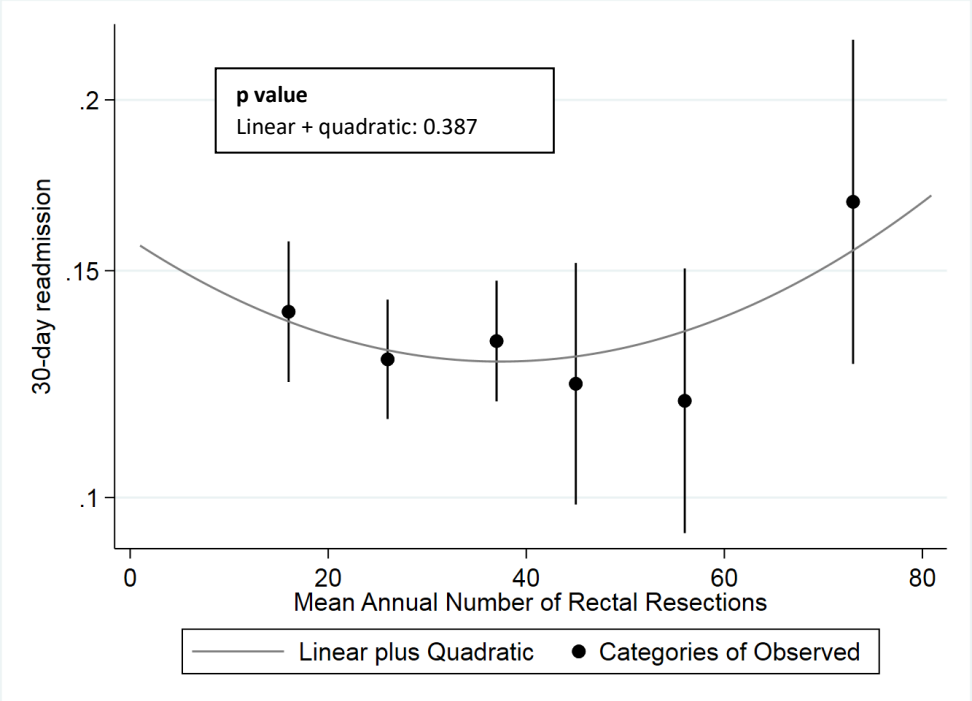


Figure 2 – Linear quadratic graphs showing the volume-outcome relationship at hospital level for: a) 90-day mortality, b) 30-day unplanned readmission, c) 30-day unplanned return to theatre, d) stoma at 18 months following anterior resection, e) positive CRM, f) prolonged length of stay (>14 days), and g) 2-year all-cause mortality rate. Y-axis is plotted on a risk scale for all graphs.

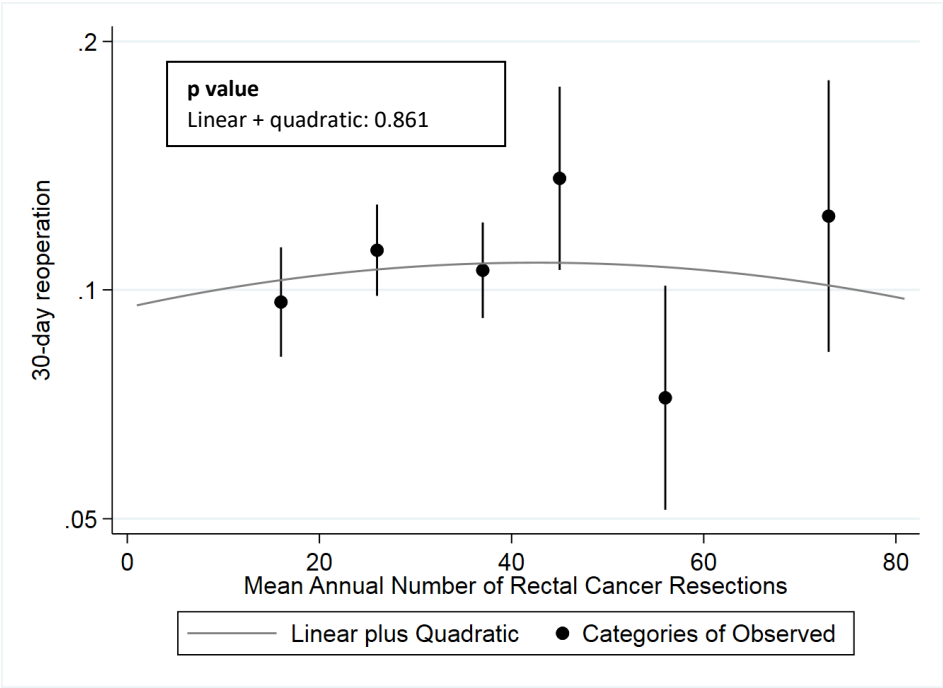
a)



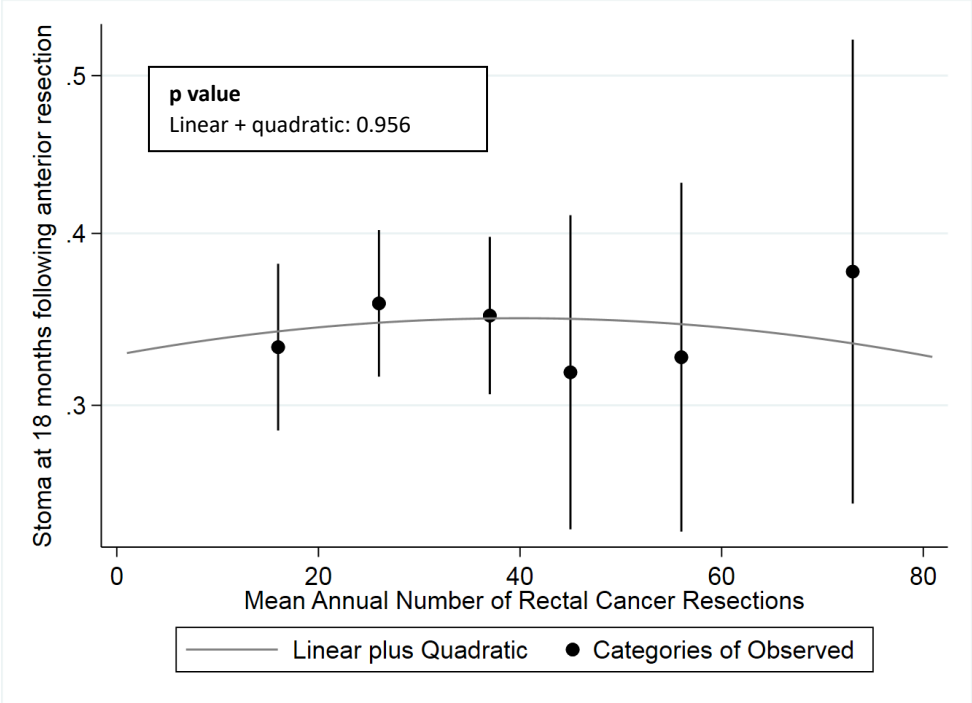
b)



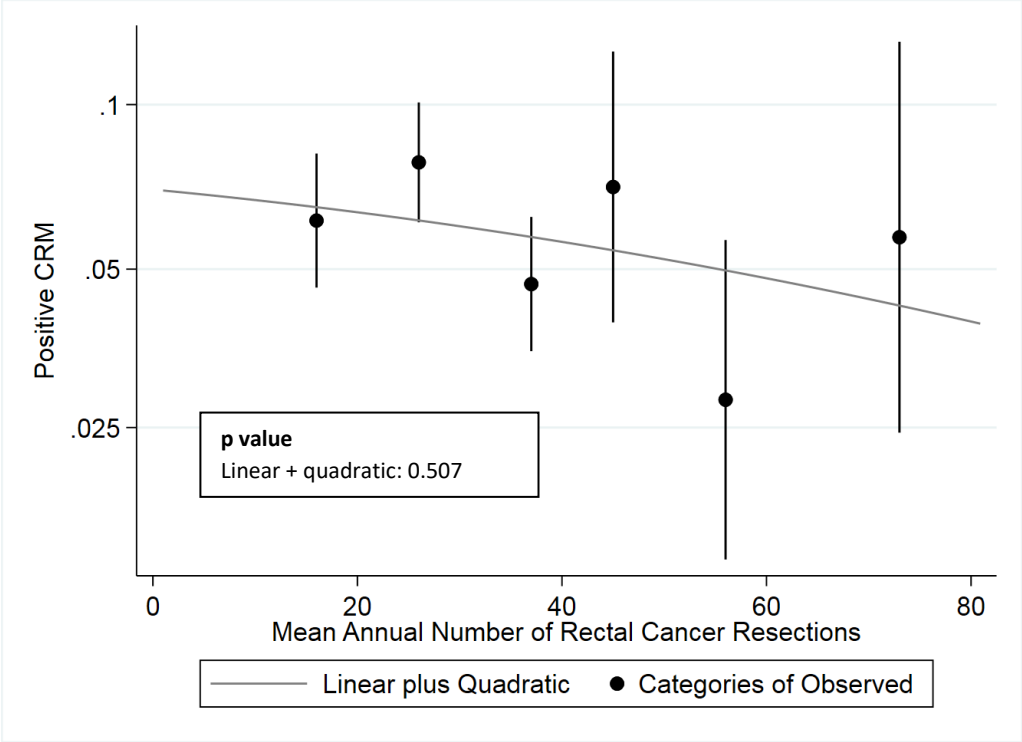
c)


p value
Linear + quadratic: 0.861
30-day reoperation
.2
.1
.05
0
20
40
60
80
Mean Annual Number of Rectal Cancer Resections
Linear plus Quadratic
Categories of Observed

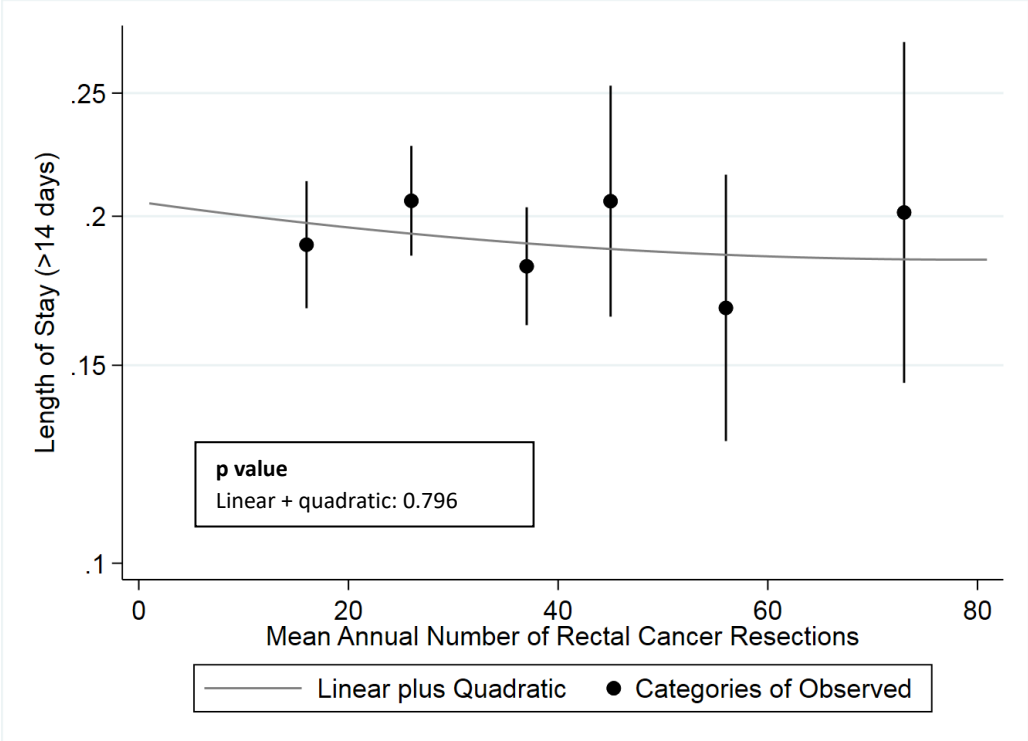
d)


p value
Linear + quadratic: 0.956
Stoma at 18 months following anterior resection
.5
.4
.3
0
20
40
60
80
Mean Annual Number of Rectal Cancer Resections
Linear plus Quadratic
Categories of Observed

e)


Positive CRM
.1
.05
.025
p value
Linear + quadratic: 0.507
0
20
40
60
80
Mean Annual Number of Rectal Cancer Resections
Linear plus Quadratic
Categories of Observed

f)


Length of Stay (>14 days)
.25
.2
.15
.1
p value
Linear + quadratic: 0.796
0
20
40
60
80
Mean Annual Number of Rectal Cancer Resections
Linear plus Quadratic
Categories of Observed

g)

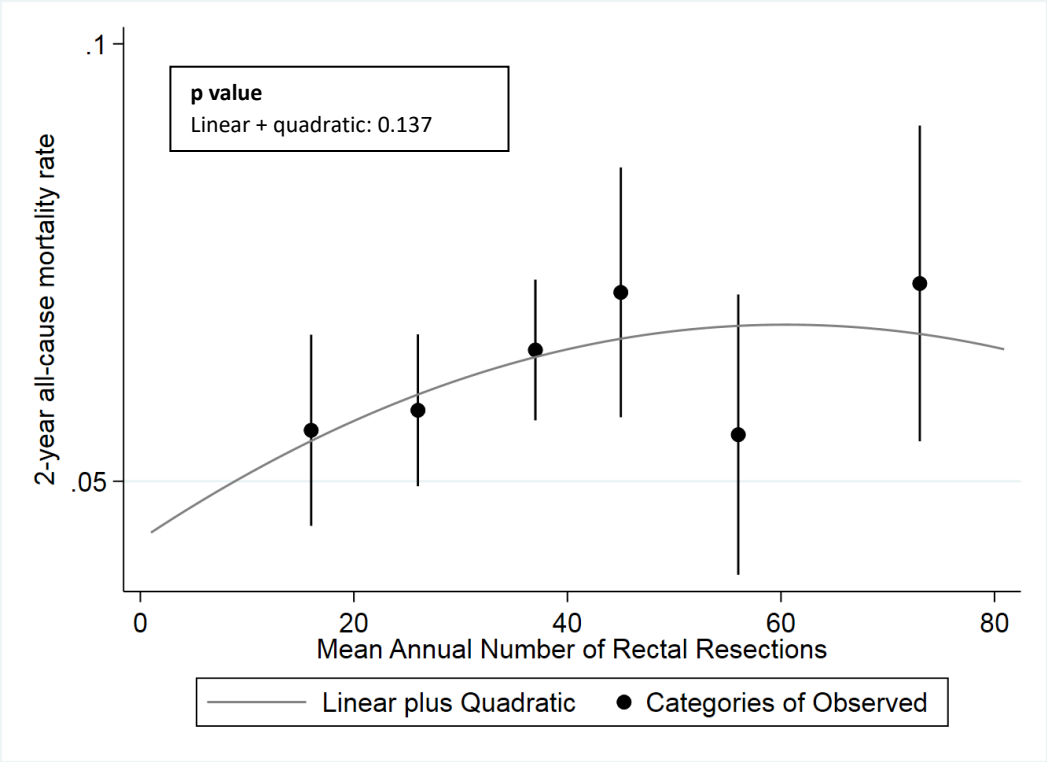
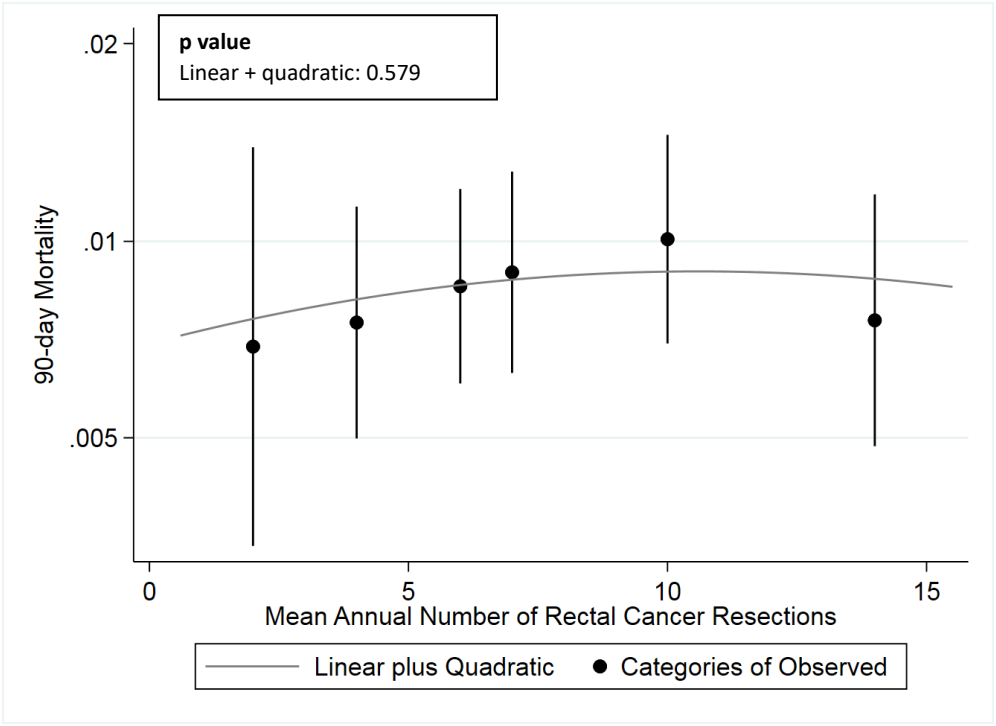
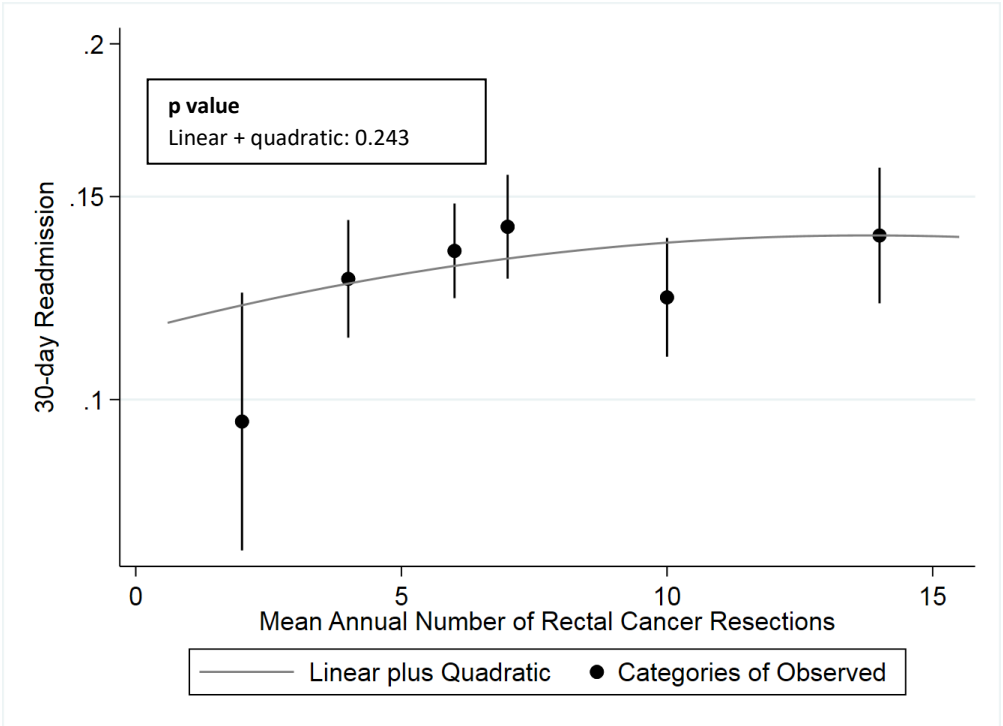

p value
Linear + quadratic: 0.137
2-year all-cause mortality rate
.1
.05
0
20
40
60
80
Mean Annual Number of Rectal Resections
Linear plus Quadratic
Categories of Observed

Figure 3 – Linear quadratic graphs showing the volume-outcome relationship at surgeon level for: a) 90-day mortality, b) 30-day unplanned readmission, c) 30-day unplanned return to theatre, d) stoma at 18 months following anterior resection, e) positive CRM, f) prolonged length of stay (>14 days), and g) 2-year all-cause mortality rate. Y-axis is plotted on a risk scale.

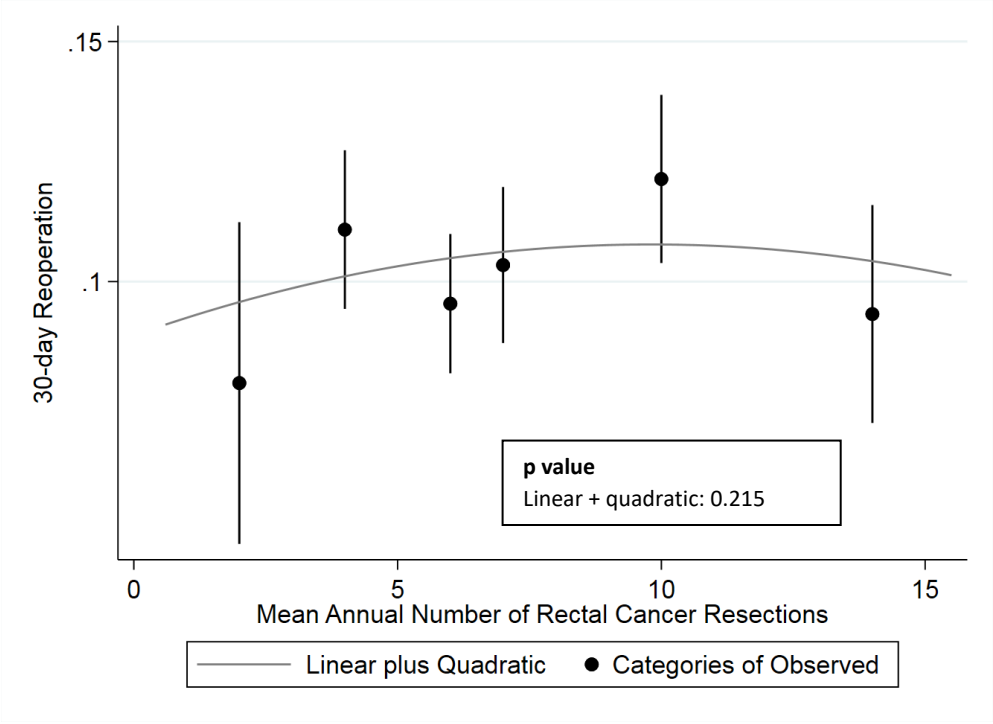
a)



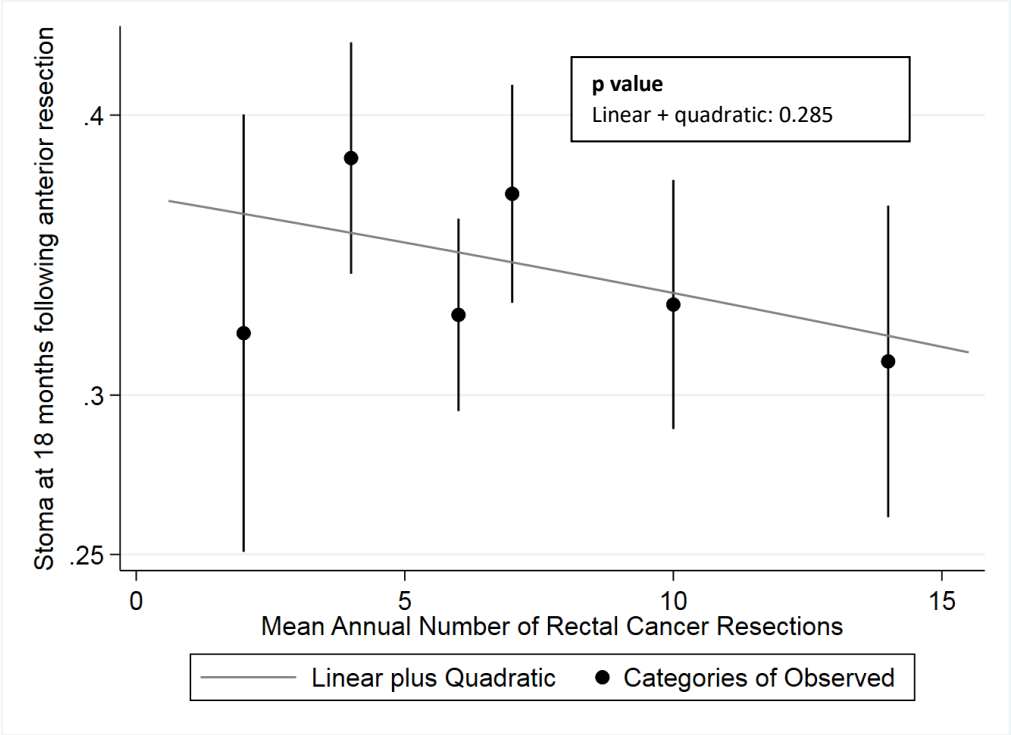
b)



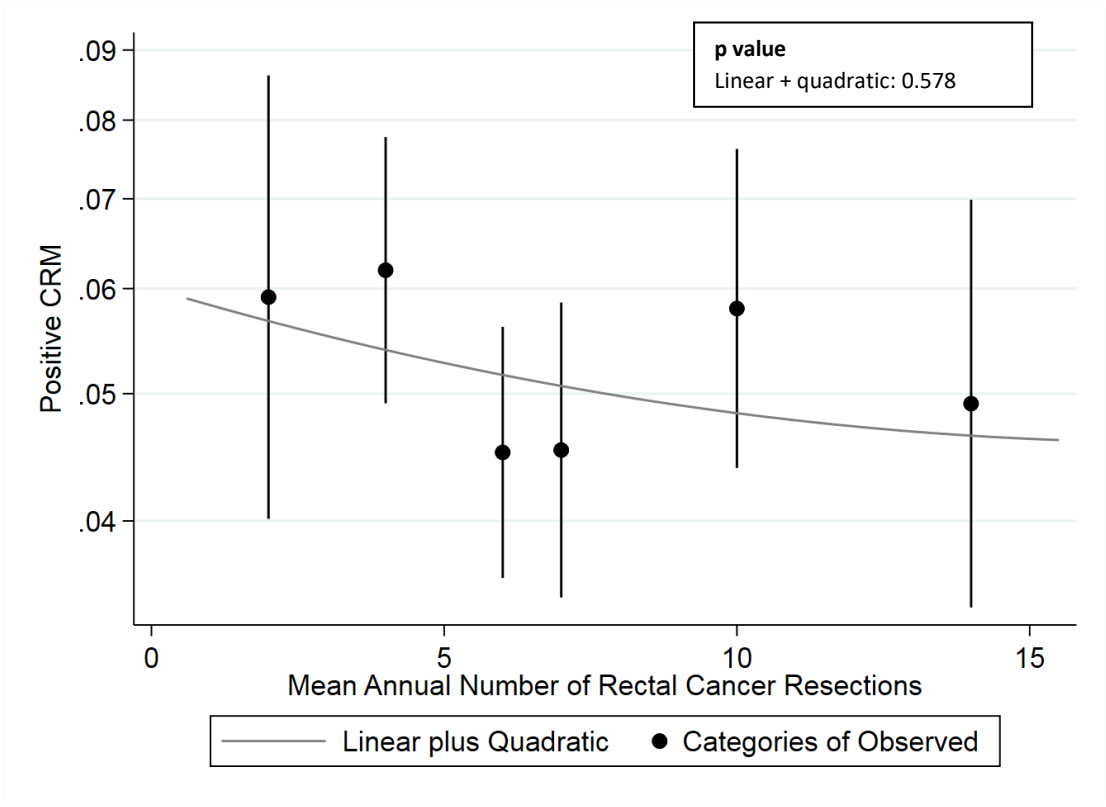
c)


.15
.1
30-day Reoperation
p value
Linear + quadratic: 0.215
0
5
10
15
Mean Annual Number of Rectal Cancer Resections
Linear plus Quadratic
Categories of Observed

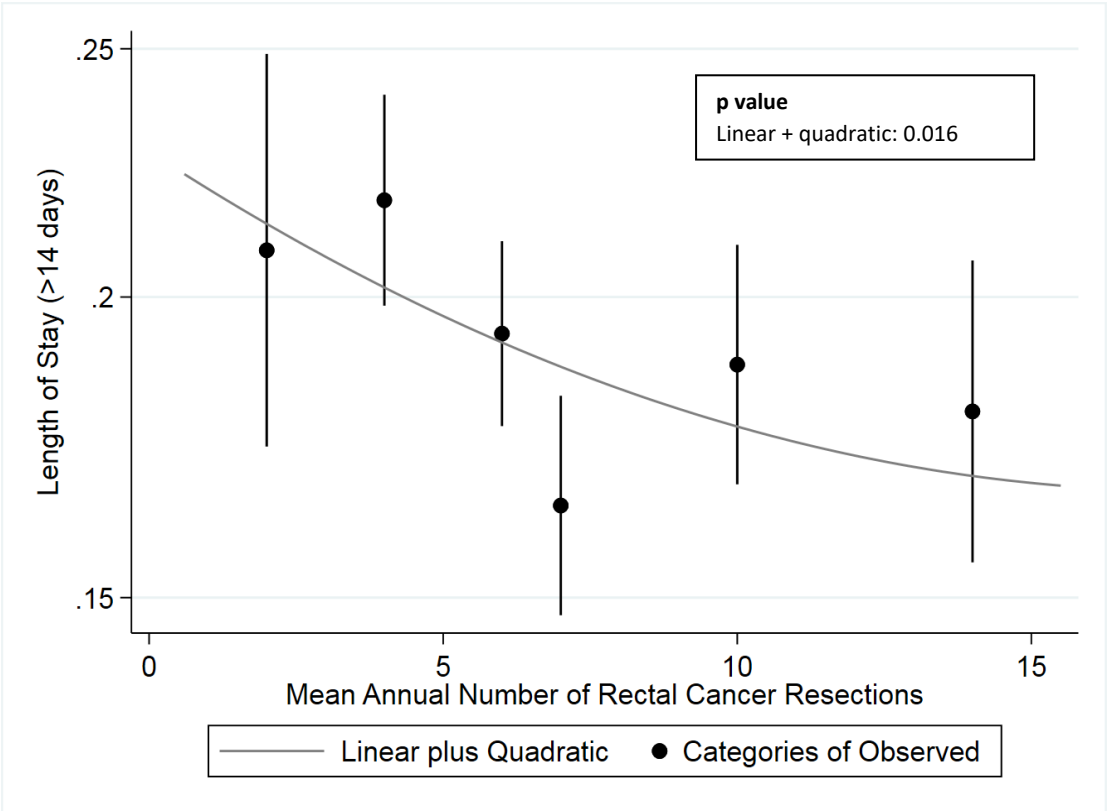
d)


.4
.3
.25
Stoma at 18 months following anterior resection
p value
Linear + quadratic: 0.285
0
5
10
15
Mean Annual Number of Rectal Cancer Resections
Linear plus Quadratic
Categories of Observed

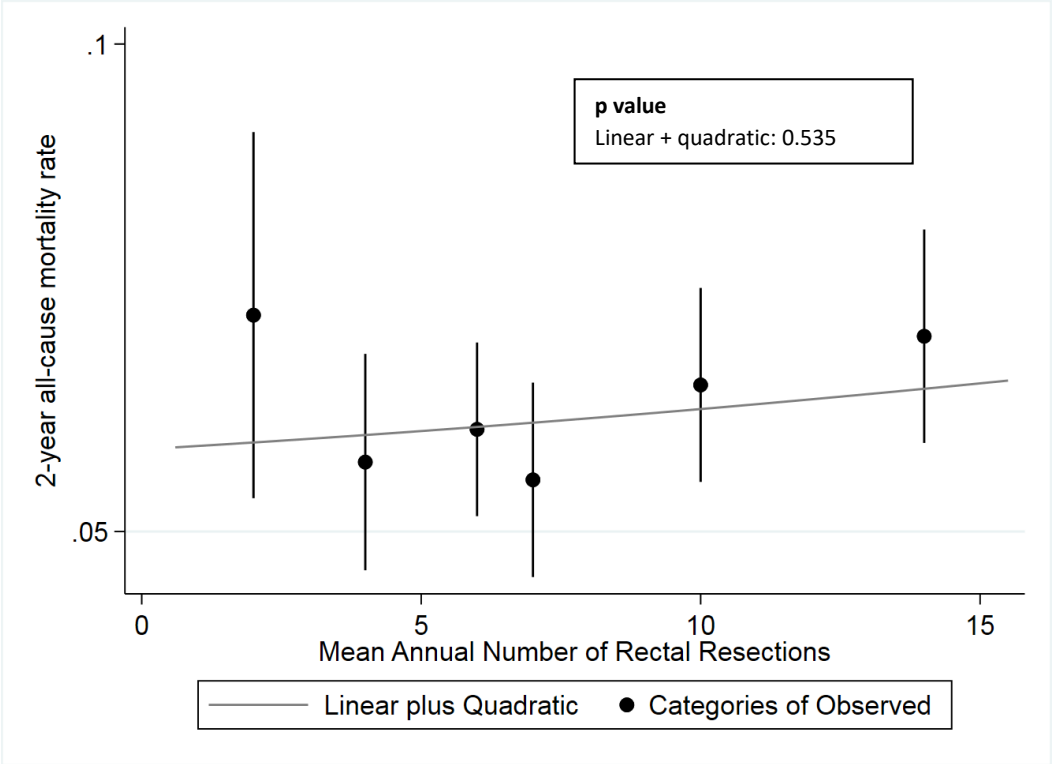
e)


p value
Linear + quadratic: 0.578
.09
.08
.07
.06
.05
.04
Positive CRM
0
5
10
15
Mean Annual Number of Rectal Cancer Resections
Linear plus Quadratic
Categories of Observed

f)


p value
Linear + quadratic: 0.016
.25
.2
.15
Length of Stay (>14 days)
0
5
10
15
Mean Annual Number of Rectal Cancer Resections
Linear plus Quadratic
Categories of Observed

g)


.1
.05
2-year all-cause mortality rate
p value
Linear + quadratic: 0.535
0
5
10
15
Mean Annual Number of Rectal Resections
Linear plus Quadratic
Categories of Observed

10. DISCUSSION

The research conducted within this thesis has aimed to improve the translation of the findings from routinely collected data for CRC patients into clinical practice and facilitate the high-quality reporting of care processes and outcomes. This has involved focussing on two important areas of the multimodal treatment of CRC: (i) the use and outcomes of SACT, and (ii) the volume-outcome relationship for rectal cancer surgery. This section will summarise the main findings from the thesis, discuss the overall strengths and limitations of the work, and finally explore the implications for clinical care, policy, and future research.

10.1 Summary of findings

10.1.1 Methodological

Overall, one of the key components of the research undertaken within this thesis has been the novel exploration and use of the SACT dataset, due to the scarcity of its application within the literature preceding the work undertaken here.

The first broad methodological aim was the validation of chemotherapy use and completion within SACT using hospital administrative data in HES-APC (Chapter 4). The findings demonstrated that 58% of patients had chemotherapy information in SACT and HES-APC, 27% in SACT alone, and 15% in HES-APC alone. This closely matched results from previous work conducted in lung cancer patients.[8] Overall, when chemotherapy information was available in both datasets, there was good accuracy in the capture of regimen and cycle number. The main discrepancy was the improved capture of oral chemotherapy in SACT alone.

Bias also existed when chemotherapy information was captured in only one dataset, with patients more likely to be old, comorbid, and less fit. The recommendation was that, where possible, both datasets should be used to capture chemotherapy information. This work was imperative to validate the SACT dataset and underpinned the remainder of work conducted within the thesis, ensuring that the identification of patients receiving chemotherapy was robust.

The next section of methodological work involved the development and validation of a broad and comprehensive coding framework using ICD-10 diagnostic codes in HES-APC to identify severe acute toxicity from SACT (Chapter 5). The coding framework performed well in each validation step and was able to differentiate a “signal” for severe acute toxicity from the “noise” of background diagnoses. Toxicity profiles (including those for biologic agents) were in keeping with RCTs, although generally showed higher rates. For example, toxicity rates for CAPOX compared to an RCT were 11.7% versus 8.8% for diarrhoea, 1.9% versus 0.6% for neutropenic sepsis, and 4.4% versus 1.3% for vomiting.

10.1.2 Variation in the multimodal treatment and outcomes of CRC patients

Use and outcomes of SACT

The next part of the thesis used the methodological work conducted in Chapter 4 to address two important clinical research questions exploring the use and outcomes of adjuvant chemotherapy in stage III colon cancer.

First, work was carried out to explore determinants of between-hospital variation in adjuvant chemotherapy use (Chapter 6). This was the first national study to explore this, demonstrating that approximately 60% of patients received adjuvant chemotherapy. This proportion is similar to that seen across international observational studies. Age was the strongest determinant of adjuvant chemotherapy use, but socioeconomic status was also identified as a determinant and persisted despite risk-adjustment.

There was considerably more between-hospital variation in practice for elderly patients (aged 70 or over). This variation also persisted despite comprehensive risk-adjustment, with funnel plot analyses showing 26 outlying hospitals in the elderly group compared to 10 in the younger group. There was overlap between the outlying hospitals with 7 of the 10 hospitals identified as outliers for the young cohort identified as outliers for the elderly cohort. For these 7 hospitals, there was also agreement as to whether they were high or low outliers. Overall, this work highlighted unwarranted variation and inequalities in adjuvant chemotherapy use within the English NHS, particularly for elderly and more deprived patients.

Second, work was carried out to evaluate the impact of actual completion rates of oxaliplatin-based adjuvant chemotherapy on cancer-specific mortality for patients with stage III colon cancer in "real-world" practice (Chapter 7). This was the largest cohort study to date and the first, to my knowledge, to evaluate the impact of treatment modifications (dose reduction or early discontinuation of oxaliplatin) on survival.

This work showed that patients who completed all of their treatment had significantly better survival outcomes compared to those who completed less than 50%, who do considerably worse. However, only half of patients completed their treatment, with particularly high early discontinuation rates (15-20%) in elderly patients. For patients that completed all of their chemotherapy there were no survival differences if they had treatment modifications. Finally, this study highlighted the significant disconnect between "real-world" practice and RCTs (Chapter 1.2) demonstrating that patients in the "real-world" are considerably less fit with significantly more advanced disease.

The next part of the thesis built on the methodological work conducted on capturing severe acute toxicity in Chapter 5. The validated coding framework was developed into a performance indicator to monitor the quality of SACT delivery across hospitals separately in stage III and IV cohorts (Chapter 8). Adequate statistical power was demonstrated for hospital-level reporting when results were pooled over 3 years. The "fairness" of the performance indicator was shown through reasonable discrimination and calibration of the risk-adjustment model used to account for case-mix differences. Despite risk-adjustment, severe acute toxicity rates varied

between 11% and 49% with 10 potential outlying hospitals for stage III patients, and between 25% and 67% with 13 potential outlying hospitals for stage IV patients.

Volume-outcome relationship for rectal cancer surgery

The final part of the thesis aimed to address the volume-outcome relationship for rectal cancer surgery at hospital- and surgeon-level (Chapter 9). This involved prior methodological work to improve the accuracy of hospital and surgeon volumes by increasing case ascertainment with unlinked HES-APC and validating surgeon-level information with the help of GMC information, as well as identifying and developing a set of rectal cancer surgery performance indicators (Appendix 7).

The methodological work showed that using unlinked HES-APC increased the number of included procedures by approximately 15%. Approximately 85% of patients had surgeon-level information in both NBOCA and HES-APC and, of these, 92% had records with matching GMC numbers. This suggested that the recording of the responsible consultant in HES-APC was very accurate.[153]

Only a small number of hospitals fell short of the minimum annual volume recommendation. However, a significant proportion of surgeons (45%) did not meet the threshold. Some differences in patient and clinical characteristics were identified according to volume. For example, high volume hospitals and surgeons were less likely to treat ethnic minority groups and deprived patients.

At surgeon-level, length of stay was significantly associated with high volumes. However, no other volume-outcome relationships were demonstrated at hospital- or surgeon-level for 90-day mortality, 30-day readmission, stoma at 18 months following anterior resection, positive CRM, 30-day unplanned return to theatre, or 2-year all-cause mortality rate.

10.2 Strengths and weaknesses

The strengths and limitations of each observational study are discussed in detail within the relevant chapter. This section aims to summarise the overarching themes occurring throughout the thesis.

10.2.1 Data sources

The main strength of the work conducted within this thesis is the use of multiple large national datasets linked at patient-level, meaning many of the included studies are the largest to date. This provides a wealth of information which many other researchers do not have access to, and allowed the validation of key information between datasets to increase the robustness of findings and reduce any potential bias from misclassification. The availability of multiple datasets also helped to reduce the amount of missing data.

The data used within this thesis includes more than 95% of all patients diagnosed with CRC in the English NHS and across all hospitals providing CRC care. The NHS is an excellent setting in which to conduct observational studies because it is a single payer tax-based healthcare system where care is free at the point of access. This makes the populations included within the studies more representative, particularly as CRC is a disease of the elderly who are under-represented in RCTs, and makes the findings more generalisable to "real-world" practice.

The NBOCA dataset is a well-established audit and so has excellent data completeness for most longstanding items (e.g., for patients having a major resection approximately 1% have missing information for surgical access, less than 1% for surgical urgency, and approximately 5% for ASA grade). In contrast to the NCRAS data used in other national audits, the NBOCA data also has excellent completion of staging information which is essential for both establishing patient populations and performing comprehensive risk-adjustment (e.g., pathological TNM staging is missing in around 5% of patients undergoing major resection).

SACT

To my knowledge, the SACT dataset is the world's first bespoke routinely collected chemotherapy database. It provides a rich and granular data source which has allowed detailed exploration of chemotherapy use. Linkage of the SACT dataset to other national datasets provided the unique opportunity to add context to the clinical interpretation of the SACT data.

A limitation of the SACT dataset was that because it is relatively new the follow-up period was restricted to 2 or 3 years for survival analyses. However, despite the short follow-up, the observed effects were often already large. In addition, accurate data is not currently captured for local recurrence which would be an important outcome for both the SACT and rectal volume work. There were also some deficiencies in the SACT dataset in determining the SACT provider. This is because generally only 3-digit provider codes were available for analysis at hospital trust level rather than individual hospital site. It is plausible that there might be even more variation

in SACT use and outcomes at hospital site level. Finally, there is no publicly available information about which facilities (e.g., acute oncology services) are available at each SACT provider. A better understanding of the hospital-level characteristics would have been helpful in further exploring variation in care and outcomes, and can be addressed via a future NBOCA organisational survey.

HES-APC

The use of the HES-APC database supported the classification of patients according to treatment and outcome. It has been shown to be accurate in comparison to medical notes, and its use within clinical research is well-supported.[17] The use of administrative data, whose primary purpose is for financial reimbursement, means that outcomes are not subject to observer bias or data manipulation. In addition, the use of ICD-10 and OPCS-4 codes in much of the methodological work means that findings are internationally applicable, and transferable across cancer types, increasing the importance of the work.

A limitation of the secondary use of the HES-APC data is that it is subject to coding errors and variation in coding practices between hospitals. However, it should be expected that any misclassification due to coding errors would result in minimal bias given that it should not be associated with any particular treatment or outcome.

10.2.2 Study design and statistical analysis

There are many strengths of the observational studies conducted within this thesis. The inclusivity of the studies allows the identification of potential inequalities in care (e.g., age and socioeconomic status being a barrier to adjuvant chemotherapy use) and, as discussed in the previous section, makes findings more generalisable to "real-world" practice. The national coverage of care also informs national evaluations.

The large sample sizes mean that there is sufficient statistical power to capture more rare events (e.g., patterns of toxicity not necessarily shown in RCTs may become apparent), and allows between-hospital comparisons to be made. These studies also tended to address research gaps which could not be explored by RCTs. For example, hospital and surgeon volumes could not practically nor ethically be randomised, and natural variation in treatment strategies (e.g., completion of treatment and treatment modifications) cannot be analysed with randomisation.

The main limitations with observational studies are that they are unlikely to fully account for selection bias or confounding. Selection bias occurs when patient or clinician preference is not taken into account. For example, in the rectal cancer volume-outcome work in Chapter 9, it could be argued that the high volume surgeons were operating on the most complex cases.

Confounding is the distortion of the association between independent and dependent variables because a third variable is independently associated with both. For example, in Chapter 7 it was not necessarily the case

that all of the association between completion of chemotherapy and reduced mortality was causal because the factors which make patients less likely to complete (e.g., advanced age and comorbidity) are also factors which make the patient more likely to die.

Throughout this thesis, selection bias and confounding have been addressed through comprehensive risk-adjustment, often with multi-level multivariable modelling, using rich case-mix data from multiple datasets. Residual confounding is the inability to account for all factors that might influence an outcome and is an issue with observational studies due to the lack of randomisation meaning it is never possible to fully eliminate the bias. Factors which may have contributed to selection bias and residual confounding include those that are not captured in routinely collected data, for example, psychosocial support, health behaviours, and patient choice. However, in most of the studies, the size of the observed effects was too large to be fully explained by selection bias or residual confounding.

Another limitation of routinely collected data is the reliance on the data collection processes at each individual hospital. This is particularly the case for the NBOCA and SACT datasets where the responsibility lies with individuals within each hospital to ensure that data is uploaded in both a timely and accurate manner. For Chapters 6 and 8, it is important to note that some of the unwarranted variation in hospital-level outcomes might be explained by differences in data completeness and quality. The use of both SACT and HES-APC datasets for the capture of chemotherapy information helps to minimise this. Additionally, when hospitals are identified as potential "outliers" within the public reporting programme for these outcome measures, the first step is to ask them to corroborate their data completeness and quality.[202]

Finally, with observational data, missing data is a limitation and the studies were adapted to reduce the impacts of this. For example, in Chapter 9, it would have been useful to have tumour height from anal verge and body mass index information to better account for operative complexity, but these were missing in up to 50% of patients. However, for all other data items included within the analyses (except performance status) the proportion of missing data was below 10%, and more often than not below 5%. Multiple imputation was used to further increase statistical power and reduce any bias from excluding patients with missing risk factors.

10.3 Implications

The implications of this work and areas highlighted for potential future work are summarised in Table 10.1.

10.3.1 Methodological implications

This section describes the methodological and research implications of this work. The majority of the methodological work has been undertaken for the SACT component of the thesis, including the ability to capture chemotherapy information (including assigning regimens) using diagnostic and procedural codes within HES-APC. This methodology is transferable to other cancer types and settings following appropriate validation.

In addition, because the diagnostic and procedural codes are internationally applicable, these findings can facilitate the examination of chemotherapy use and outcomes by data analysts and clinical researchers in other countries where there is currently no access to a bespoke chemotherapy dataset. For example, it has already been possible to apply this coding methodology to the Welsh equivalent of HES-APC, Patient Episode Database for Wales (PEDW) to allow the reporting of the adjuvant chemotherapy performance indicator. This was not previously possible because the SACT dataset only covers England.[30]

The clinical algorithms which were developed and applied to the HES-APC and SACT datasets can be used by data analysts and clinical researchers evaluating chemotherapy use in CRC patients. It also provides a structure for how one might approach this process which, again, can be adapted for different cancer types.

This work has validated chemotherapy use, regimens, and cycle number within SACT, and shown that this information is largely accurate. In addition, it has demonstrated that combining the capture of chemotherapy information with HES-APC helps to reduce under-reporting and bias. Given the limited use of this dataset within the wider literature, this provides important insight and guidance for clinical researchers and data analysts in the UK using the SACT dataset across different cancers.

The validated coding framework for the identification of severe acute toxicities enabled the development of a performance indicator to measure the quality of chemotherapy delivery. This performance indicator will facilitate the ongoing monitoring and benchmarking of chemotherapy delivery in CRC patients within a national audit setting, identifying variation in outcomes and supporting quality improvement initiatives. This work is important because there is a notable deficit in the meaningful ongoing reporting of the quality of SACT care in “real-world” clinical practice, with just one publicly reported outcome measure.

Table 10.1 – Summary of implications, application, and considerations for future work

Methodological
• The methodology developed allows international and UK-based data analysts and researchers to accurately capture chemotherapy information in SACT and/or hospital administrative data, both in CRC research and across different cancer types, following appropriate validation. In countries without bespoke chemotherapy datasets it is possible to obtain chemotherapy information from hospital administrative datasets, and I have demonstrated this by capturing chemotherapy information in Wales. • The work exploring severe acute toxicity rates between hospitals highlights the need to improve the capture of more specific provider information within SACT in order to better understand variation in SACT delivery. • The validation work demonstrates to an international audience that similar bespoke chemotherapy datasets using electronic prescribing systems are an efficient and valid approach to collecting rich and granular SACT information. The work conducted within this thesis showcases the scope for service evaluation and novel analysis to address clinical research gaps. • The validity and accuracy of capturing surgeon-level information for CRC patients within routinely collected data provides scope for including surgeon-level demographics in future CRC research. • The developed methodology, including novel linkage to GMC data, can be used by UK-based data analysts and researchers to validate consultant-level information across different specialities. • The validation work on responsible consultant led to NBOCA amending its data item for operating surgeon to enable the capture of multiple consultant surgeons. • International and UK-based data analysts and researchers can apply the methodology developed within this thesis to identify and validate severe acute toxicity from SACT within routinely collected data. This can be applied for different SACT drugs and across different cancer types.
Clinical
• The work surrounding SACT use and outcomes has highlighted important differences between RCTs and "real-world" populations. It demonstrates the importance of supplementing RCT findings with "real-world" findings and attempting to design RCTs to include under-represented groups e.g., elderly. • Based on the work exploring the impact of adjuvant chemotherapy completion and treatment modification, clinicians should consider the use of treatment modification strategies to improve completion. • The work on severe acute toxicity has the potential to provide clinicians, patients, and policy-makers, both in CRC and across different cancers, with a better understanding of toxicities in a "real-world" setting to aid decision-making and target preventative measures. • The wide variation in adjuvant chemotherapy use in the elderly has highlighted the need for targeted strategies (e.g., comprehensive geriatric assessments) to improve equity of access in this group. • Unwarranted variation identified within this work in multiple aspects of SACT use and outcomes supports the need for a detailed evaluation of SACT care pathways in order to improve the national standardisation of SACT delivery and care. • The significant rates and wide variation in severe acute toxicity might be improved through better patient education regarding the identification and management of toxicities. • Almost half of colorectal surgeons in England are not meeting the NICE standard for rectal cancer surgery volume. However, our results suggest that centralising rectal cancer surgery with the main focus of increasing operative volume will have a limited impact on surgical outcomes. Therefore, quality improvement initiatives should address a wider range of evidence-based process measures, across the whole multidisciplinary care pathway, to enhance rectal cancer surgery outcomes.
Policy
• On the basis of the wide variation in adjuvant chemotherapy rates identified, NHS England are undertaking an "Examination of Issues" investigation into the use of adjuvant chemotherapy. • The severe acute toxicity work can be used to better understand the economic implications of specific SACT drugs. • The development of performance indicators to report adjuvant chemotherapy use, severe acute toxicity rates, and rectal cancer surgery volumes, will facilitate benchmarking, reporting, monitoring, and feedback of results to individual hospitals to target quality improvement. • As a result of the work in this thesis, several of these performance indicators have also been incorporated into the NBOCA national quality improvement programme. This will provide additional focus on optimising adjuvant chemotherapy use and rectal cancer surgery volumes. • This work has identified the need to better establish and measure what constitutes good quality care for CRC patients across the entire MDT pathway to inform the debate on specialisation of services.

The results from Chapters 5 and 8 can be further validated during the process of rolling out the performance indicator with feedback requested from individual hospitals on how well this metric is capturing toxicities. This can allow the coding framework to be amended and adapted as necessary. In addition, the latest SACT dataset includes two new data items which collect information about whether a toxicity led to either non-completion or treatment modification. This could be used to help validate this measure, however, the SACT data items are binary and do not provide any information about severity or type of toxicity. There is also the opportunity to validate the performance indicator across different cancers (e.g., breast, prostate, oesophago-gastric) given the shared working which takes place in the Clinical Effectiveness Unit. Finally, it was evident that the comparator group used in Chapter 5 was sub-optimal, and the use of propensity score matching techniques may facilitate more robust comparisons.

This performance indicator can also be used to explore a wide scope of research gaps in "real-world" clinical practice. As highlighted earlier, this information is important to supplement RCT findings given the explicit differences in populations, with findings from Chapter 5 demonstrating that toxicity rates appear higher than those reported in RCTs. It is particularly important given the ongoing approval of novel SACT drugs for which there is limited "real-world" information. Again, this work is transferable across different cancer types and could be used in other national audit settings, as well as being internationally applicable due to the use of ICD-10 codes. Linkage of the SACT dataset to HES outpatient and HES A&E datasets may help to further explore the burden of toxicity.

This research has highlighted that improvements in coding within SACT data for the exact hospital site in which a patient received their chemotherapy would improve the understanding of SACT delivery. Given that it is still a relatively novel dataset, data completeness and quality are likely to further improve as there have already been several iterations of the dataset, as well as improvements made to the monitoring processes to ensure compliance with data submission.

More broadly, this work has showcased the potential scope for service evaluation and addressing research gaps with a bespoke chemotherapy dataset such as the SACT dataset. It has shown the richness and granularity of the SACT dataset, as well as showcasing the ability to link SACT data to other data sources. This supports the SACT dataset being an invaluable resource which should prompt an international audience to consider implementing a similar initiative using electronic prescribing systems in secondary care.

For the rectal cancer volume-outcome work, the novel use of GMC data in order to validate surgeon-level information is transferable to any clinical research and provides important methodological information for data analysts and clinical researchers in the UK. The GMC data is publicly available and provides additional information about surgeon demographics which have recently been increasingly in the spotlight.[203]
The agreement of surgeon-level data between NBOCA and HES-APC was very good and suggested that HES-APC accurately captures the consultant responsible for a patient's care. This validation has significant

implications across a broad spectrum of clinical research within the UK. Future work would be required to assess how well HES-APC captures consultant information in other multidisciplinary settings, including when the episode does not involve a surgical procedure. Finally, this work highlighted the importance of capturing dual consultant operating, particularly in light of the COVID-19 pandemic. As a result, the NBOCA dataset will now permit more than one consultant surgeon to be entered for each patient.

10.3.2 Clinical implications

SACT is an essential component of the multimodal care pathway for CRC patients meaning that translating the findings from this thesis into clinical practice has the potential for a considerable impact on a significant volume of patients. In addition, the studies presented within this thesis have highlighted important differences in results between RCTs and observational studies. For example, in Chapter 7, patients were shown to be less fit and have more advanced disease compared to RCTs. This demonstrates the importance of conducting such observational studies to better inform "real-world" clinical practice and complement RCT findings.

The SACT care pathway is complex and constantly evolving, involving a myriad of MDT members with a subsequently huge potential for variation in care processes and outcomes. The studies presented within this thesis have begun to identify aspects of SACT delivery within CRC patients that demonstrate unwarranted variation at a national level and these will now be discussed in more detail.

Unwarranted variation in adjuvant chemotherapy use

Wide variation in the use of adjuvant chemotherapy for stage III colon cancer was shown in Chapter 6, particularly in elderly patients for whom a significantly greater proportion of variation was identified between hospitals. This is coupled with findings from Chapter 7 which highlighted that completion rates for adjuvant chemotherapy were particularly poor in the elderly. Furthermore, the results from Chapter 5 did not suggest that chronological age was a determinant of severe acute toxicity.

The "under treatment" of the elderly has been described as one of the reasons for UK cancer survival rates lagging behind other countries.[204] The results within Chapter 6 suggest that barriers to adjuvant chemotherapy receipt in the elderly are evident. In the wider literature, older patients are less likely than their younger counterparts to receive cancer treatments and, if they do, they are often less intensive. It has been suggested that a reason for this is professional attitudes and biases towards the elderly.[205] In addition, elderly patients may be more willing to follow clinician's recommendations without question, perhaps influenced by the way in which treatment options are communicated.[204] [206]

There are multiple strategies that might improve the appropriate use of SACT in the elderly. It is essential that clinicians appreciate the importance of not allowing chronological age alone to be the determining factor in whether or not a patient receives SACT. Instead, a comprehensive assessment of their overall fitness should be undertaken, taking into account the likelihood of them tolerating treatment, as well as their personal

preferences.[204] Additionally, psychosocial issues should not be the only barrier to elderly patients receiving SACT. Generalised support for the elderly might include transport to appointments, help caring for a spouse or other dependent, and overall support with day-to-day activities if living alone with no adequate support network.

In addition, more widespread adoption of comprehensive geriatric assessments (CGAs) and direct involvement of geriatric specialists within the CRC MDT setting would help to provide a more holistic approach for treatment selection. A CGA is defined as a multidimensional, interdisciplinary diagnostic process for determining an older person's medical, psychosocial, and functional capabilities to develop a coordinated and integrated plan for treatment and long-term follow-up.[207] The CGA has been shown to accurately predict SACT toxicity, morbidity, and survival in older cancer patients.[208] The CGA can be time-consuming, but screening tools are available to identify high-risk patients who might benefit from a full CGA.[173]

There are examples outside of CRC of oncogeriatric services being developed and implemented within the English NHS with promising results.[209] For example, one study in elderly patients demonstrated better completion, fewer treatment modifications, and reduced toxicity rates with the use of a CGA in elderly patients compared to those receiving standard oncology care.[172] This has also been demonstrated in the GERICO trial, a single-centre RCT conducted in CRC patients in Denmark, which showed reduced toxicity, increased completion, and improved physical functioning in patients undergoing CGA prior to receipt of adjuvant or first-line palliative chemotherapy.[210]

Geriatric guidance in the ongoing management of pre-existing comorbidities, polypharmacy, and cognitive impairment, as well as support in the choice and modification of treatments, may help to improve completion rates for SACT. Data from 11 RCTs included in the ACCENT and IDEA databases was analysed to evaluate non-completion of adjuvant chemotherapy and early discontinuation of oxaliplatin in relation to survival outcomes for patients receiving adjuvant CAPOX or FOLFOX. Patients with non-completion of treatment had significantly reduced survival outcomes, and patients with early discontinuation of oxaliplatin had no difference in survival outcomes regardless of risk stratification and regimen.[211] This is in line with findings from Chapter 7 and suggests that treatment modifications and adequate support to complete treatment once started confers survival advantages over early discontinuation. This is particularly important in the elderly where fluoropyrimidine monotherapy may be a more appropriate treatment choice.

Up to date elderly-specific guidelines should be available with translation into local protocols. Currently, the International Society of Geriatric Oncology has guidelines available but these have not been updated since 2015.[212] Neither ESMO nor NICE guidelines give any specific recommendations for the treatment of elderly patients.

Finally, more RCTs need to be designed with the inclusion of elderly and frail patients to better inform their management.[213] [214] The FOCUS2 trial showed that this is possible by evaluating elderly patients with metastatic CRC who were deemed unfit for full-dose SACT, and demonstrated that use of a CGA is associated with treatment benefit.[213] In the UK, FOxTROT 2 has recently opened for recruitment with the aim of evaluating the use of neo-adjuvant chemotherapy in patients aged 70 and over.[215]

Unwarranted variation in severe acute toxicity rates

The work from Chapter 5 demonstrates the ability to describe in detail the "real-world" patterns of toxicity for specific SACT regimens. This includes rare side effects, for example the incidence of laryngeal spasm from oxaliplatin, which might not be well captured within the RCT setting. These results can be used to better inform and support patient choice in decision making processes. This is especially important for newly approved drugs (such as those funded by the Cancer Drugs Fund) where there is little information from observational studies regarding toxicities. These findings will complement RCT results and, more broadly, access to routinely collected data could allow longer term follow-up of trial patients and sequelae from SACT use.

It was also shown that the group of CRC patients who did not receive chemotherapy had a 12.5% rate of severe acute toxicity. Further work is required, but it is plausible that this figure represents the background rate of hospitalisations for other reasons in this particular group of CRC patients and therefore subtraction of this "noise" from the "signal" may generate more accurate estimations of toxicity rates for counselling patients.

The work from Chapter 5 can also help to target possible preventative measures, both generally and more specifically for certain demographic groups. For example, there has been some evidence that females are more prone to toxicities from 5-FU.[216] This work might help to identify other such associations which can prompt clinicians to consider regimen choices and preventative measures in particular patients. Finally, this work provides a potential means for examining the economic implications of using particular SACT drugs.

The work from Chapter 5 was then used to identify significant variation in severe acute toxicity rates which are demonstrated in Chapter 8. There are a number of points along the SACT care pathway which could be targeted in order to improve outcomes and these will now be discussed in more detail.

From the beginning of a patient's SACT journey, it is imperative to ensure that patients are being appropriately selected for treatments, linking back to the discussion in the previous section for elderly patients. In addition to this, it is important that once patients have been selected for SACT they are adequately counselled and consented, and involved in decision-making processes. Consent should include detailed information about the short- and long-term toxicities of different treatment options.

Once SACT has been commenced, the routine monitoring of patients has the potential to vary considerably. Sources of variation in practice might include differences in: the frequency of monitoring, who reviews the patient (i.e., consultant oncologist, junior doctor or nurse specialist), the extent of assessment undertaken at each appointment, the protocols for treatment modifications, and whether the consultations are virtual or face-to-face.

The processes involved in the recognition and management of toxicities are also likely to vary significantly between hospitals including differences in: access to Acute Oncology services, the delivery of Acute Oncology services (doctor- or nurse-led), facilities for out-of-hours care (e.g., emergency department access, direct referral to a specified ward, agreement with another hospital to take patients), availability of medical and clinical oncology specialists within the admitting hospital, access to out-of-hours advice (i.e., telephone hotline), and the processes for efficiently identifying toxicities.

Finally, there may be variation in wider aspects of SACT delivery. For example, the availability and expertise of allied healthcare professionals (e.g., specialist oncology pharmacists and nursing staff), the availability and training of junior doctors, data and information technology (e.g., access and safety of electronic prescribing systems), clinical governance processes (e.g., local engagement with audit and quality improvement), and human factors (e.g., communication and leadership).

The work in this thesis provides compelling evidence of the need for national standardisation of SACT delivery. It can also help to inform the production of national protocols, particularly for CRC patients. For example, it can highlight the most common toxicities associated with hospitalisation for each regimen.

There is currently no national standardisation of any of the previously highlighted aspects of care and, as a result, the availability and content of protocols to guide SACT delivery vary widely between hospitals. A protocol is intended to provide evidence-based guidance on the optimal prescribing and administration of SACT treatments for healthcare professionals. In January 2022, the UK Chemotherapy Board published a document to showcase a potential solution for the provision of national SACT protocols within the UK called the “National SACT Protocol Programme”.[217]

It has been estimated that the duplication of producing SACT protocols is costing £1.1 to £1.8 million each year in staff time. In addition, within England over a 12 month period, there were 38 new NICE indications for SACT drugs. Other countries, including the US, Australia, and Ireland, already have central repositories for national SACT protocols. The implementation of national protocols would improve the efficiency, safety, and clarity of SACT delivery processes, as well as reducing delays in access to new treatments. These protocols will be readily available on a central hosting website with a dedicated team to manage them. The standardisation of protocols nationally has the potential to help reduce a large proportion of unwarranted between-hospital variation.

Another area which might be targeted for reducing severe acute toxicity rates is the education of patients. The literature suggests that there can be both delays in reporting and underestimation of toxicities from patients and carers.[128] The concept of empowerment of patients has been described in the literature and includes the knowledge, skills, and confidence a person has to take ownership of their own healthcare. It has been suggested within the literature that proactive monitoring, for example, regular telephone calls from nurses, may result in earlier symptom management.[218]

Novel ways of picking up toxicities during chemotherapy use are also being explored. For example, patients may be encouraged to self-report toxicity symptoms using various tools including electronic technology (e.g., smartphone applications on personal mobile devices which have had positive feedback).[219] [220] Trials are also underway which use fitness trackers (e.g., smart watches) to monitor patients' vital signs.[221]

Unwarranted variation in rectal cancer surgery volumes

As detailed throughout this thesis, the multimodal management of rectal cancer surgery is also becoming increasingly complex with a multitude of individualised care pathways available dependent on patient and clinical factors. The input of the MDT throughout these care pathways is critical in selecting the right treatments, ensuring that patients are aware of the short- and long-term implications, and engaging patients in the shared decision-making processes.

There was considerable variation identified in both hospital and surgeon volumes, with just under half of surgeons falling short of the recommended threshold of 5 rectal cancer resections per year.[41] However, the work conducted within this thesis was unable to demonstrate any evidence of a volume-outcome relationship at either hospital or surgeon level (besides reduced length of stay for high volume surgeons) to support these guidelines.

10.3.3 Policy implications

Public reporting and quality improvement for adjuvant chemotherapy use

Although the variation in adjuvant chemotherapy use was most marked in the elderly, considerable variation existed generally. In order to address this, the methodological work conducted within this thesis has facilitated the development of a national performance indicator for more accurate and robust monitoring of adjuvant chemotherapy use. The proportion of patients receiving adjuvant chemotherapy is now publicly reported within NBOCA for England and Wales with feedback to individual hospitals.[30]

In addition, this performance indicator is now a focus of a national quality improvement initiative launched by NBOCA in 2021.[222] This novel and extensive programme of work includes both local and national quality improvement targets and will be supported by nationally run workshops. The quality improvement target is that at least 50% of patients at each hospital are expected to receive adjuvant chemotherapy.

Finally, the variation in adjuvant chemotherapy use identified in this work has been selected by NHS England for an "Examination of Issues" investigation. This means that the national commissioners of chemotherapy are carrying out additional work to understand the potential barriers to patients accessing adjuvant chemotherapy on the basis of the findings in this thesis with a view to improving equity in access.

Public reporting and quality improvement for severe acute toxicity

The performance indicator developed for measuring severe acute toxicity will be used within NBOCA for national reporting and comparative monitoring purposes. This measure will be provisionally publicly reported in the 2022 annual report and hospitals given the opportunity to provide feedback on their results. Following this, the indicator will be outlier reported on an annual basis and will be a trigger for ongoing quality improvement work.

The work in this thesis and the subsequent quality improvement initiatives that will be driven by reporting of the toxicity performance indicator will facilitate the identification and benchmarking of best practice, helping to target areas to help explore and reduce variation in care and outcomes.

Economic implications for severe acute toxicity

This work has demonstrated that, on average, a quarter of patients receiving adjuvant chemotherapy and half of patients receiving chemotherapy for metastatic disease, require hospitalisation for severe acute toxicity. The economic implications of this are significant and can be grouped into direct costs attributable to the management of the severe acute toxicity including resources and workforce considerations, and indirect costs such as lost work time, decreased productivity at work, and loss of caregiver time.[223]

Previous work in ovarian cancer patients in the US have shown stark figures for the cost implications of particular toxicities.[224] A recent study in breast cancer patients in the UK has ascribed total costs of £248 million to chemotherapy use.[225] The work in this thesis can be used to improve the understanding of the economic implications of severe acute toxicity for CRC patients and across different cancers. For example, it might be used to help inform the choice of chemotherapy regimen, and to evaluate the cost-effectiveness of novel drugs or specific interventions for the prevention of certain toxicities.

Public reporting and quality improvement for rectal cancer surgery volumes

The NBOCA is now publicly reporting hospital volumes for rectal cancer resections as a performance indicator using methodology undertaken within this thesis. In addition, the rectal cancer surgery volumes are a key target in the NBOCA quality improvement programme.[222]

Rectal cancer volume-outcome relationship

This work has helped to shed further light on the rectal cancer volume-outcome debate using more methodologically robust analyses through the use of high-quality national data, validation of critical information, modelling of volume as a continuous variable, comprehensive risk-adjustment, and multivariable modelling accounting for clustering.

A volume-outcome relationship was demonstrated at surgeon-level for length of stay. However, a volume-outcome relationship was not demonstrable for any of the other outcomes at hospital- or surgeon-level. The overarching conclusion of the work was that volume alone does not seem to infer better outcomes. This phenomenon has been seen with the specialisation of oesophago-gastric cancer whereby mortality rates were shown to improve, but this could not be explained by volume increases alone.[139]

Volume is often used as a proxy for good quality care based on the assumption that higher volumes generate more experience and therefore better outcomes – the "practice makes perfect" hypothesis.[226] However, it is clear that the factors influencing good outcomes are more complex than this and need to be better established. In addition to the likely residual confounding in accounting for case-mix differences in the complexities of individual patients, the performance indicators derived from routinely collected data also do not fully capture the nuances in the quality of shared decision-making and care along the rectal cancer pathway.

A prior Dutch study evaluating the validity of nine performance indicators within CRC found that in isolation each performance indicator was associated with better patient outcomes, but there was no internal consistency. [227] In line with this, it is difficult to develop a performance indicator to capture the complexities of the MDT discussion. However, broadening the development of performance indicators to target each aspect of MDT care may help by providing complementary information about different aspects of care, rather than an overall surrogate marker. For example, performance indicators related to radiotherapy use and toxicities, referral of appropriate patients to specialist liver and lung MDTs, and the proportion of patients undergoing watch-and-wait surveillance.

The advantages and disadvantages of specialisation of rectal cancer services have already been outlined in Chapter 9. An alternative solution to specialisation between hospitals might be specialisation within hospitals i.e., higher volume surgeons are allocated rectal cancer resections from lower volume surgeons within the same hospital.

This work suggests that, prior to any specialisation that might occur, it would be critical to ascertain more clearly which care providers specialisation should be occurring to. This should involve an assimilation of exactly which factors are contributing to good quality rectal cancer care across the entire pathway and how these factors can be measured and monitored. It should also take into account a number of other factors, for

example, the availability of established infrastructure, facilities and workforce, current hospital- and surgeon-level volumes, and the potential capacity to increase volumes based on redistribution of healthcare resources.

10.3.4 Future research areas

Potential areas for future research have already been discussed in the preceding sections. Some additional areas for consideration are highlighted here.

Evaluation of combinations of outcome measures

A combination of the different outcome measures identified for SACT could be explored in further work. In particular, it would be interesting to evaluate the relationship between adjuvant chemotherapy use from Chapter 6 and severe acute toxicity from Chapter 8. This might also be replicated in the metastatic patients. A further example would be to explore severe acute toxicity according to completion and treatment modifications as per Chapter 7.

Specialisation of SACT services

Several tertiary centres exist for SACT delivery within the English NHS, but there are also currently around 130 different hospital sites delivering SACT and this does not take into account satellite clinics or mobile chemotherapy units.[217] As demonstrated in Chapter 8, there appears to be huge variation in the volumes of patients receiving SACT at each hospital.

There has been some exploration in the literature regarding the volume-outcome relationship for SACT delivery.[228 229] However, similar to the rectal cancer surgery volume-outcome debate, there are significant methodological limitations to pre-existing studies including a lack of adequate case-mix information (e.g., performance status and comorbidities), analysis of volume as a categorical variable, and use of single level regression. Despite this, almost all of the studies evaluated have shown improved survival with higher volume hospitals.[228]

Future research might be directed towards further exploring the volume-outcome relationship in SACT delivery using the SACT dataset. This would be supported by the development of a more extensive panel of performance indicators for measuring the quality of SACT delivery to expand upon those developed within this work. These performance indicators might then be used together to form a public reporting programme for SACT outcomes in a similar manner to the established national reporting of radiation oncology outcomes in the National Prostate Cancer Audit.[124] It would also be interesting to adjust the analyses in Chapter 6 for chemotherapy volumes to ascertain whether this is associated with adjuvant chemotherapy use.

Measuring the quality of rectal cancer care

The rectal volume work highlighted some potential deficiencies in how best to capture the quality of rectal cancer care, including a lack of patient-reported outcome measures (PROMs). A one-off PROMs study was

conducted in CRC patients in 2013, and linkage to NBOCA data was undertaken in order to carry out a feasibility study. The results were promising in terms of accuracy and validity of survey responses, but there were issues with differential response rates for certain patient groups and hospitals which would need addressing.[230]

Currently, a quality of life survey is being conducted by NHS England which includes CRC patients who are 18 months after their diagnosis and may provide an opportunity for addressing this research gap in the future.[231] However, it is unclear how effectively this might capture the particular nuances of CRC treatments, and whether the timeframe of choice is adequate. For CRC patients, it would be particularly important to appreciate the impact of major pelvic surgery on bowel, bladder, and sexual function, as well as understanding the implications of having permanent or temporary stomas. In addition, a better understanding is required for the long-term impacts of radiotherapy and SACT treatments on quality of life and function.

This is a really important area for CRC survivorship that NBOCA will be working towards in conjunction with the Patient and Carer panel. Again, the National Prostate Cancer Audit provides an existing example of this with the public reporting of measures for urinary, bowel, and sexual function.[182]

11. CONCLUSIONS

Overall, this research has demonstrated that multiple national routinely collected datasets can be effectively linked and subjected to novel analysis with clinically important findings. Underlying methodological work has involved the interpretation and validation of critical information from multiple data sources, as well as the development of appropriate performance indicators for measuring quality of care. This methodological work has then been used to evaluate variation in the multimodal treatment of CRC, specifically focussing on the use and outcomes for SACT, and the volume-outcome relationship for rectal cancer surgery.

This research has shown that the SACT dataset provides a unique and rich source of data, especially when linked to other national datasets, with a huge scope for addressing clinical research gaps. In addition, it has developed methods for deriving chemotherapy information from hospital administrative data using diagnostic and procedural codes. The work provides a rationale and basis to use the same methodology across different tumour types.

The studies in this thesis have already highlighted unwarranted variation in the use and completion of adjuvant chemotherapy, and rates of severe acute toxicity. Similarly, the rectal cancer work showed variation in the volumes of major resections performed at hospital- and surgeon-level, with a significant proportion of surgeons not meeting national recommendations. A volume-outcome relationship was shown for length of stay at surgeon-level, but otherwise there were no demonstrable volume-outcome relationships at hospital- or surgeon-level for any of the other outcomes.

Overall, this work has demonstrated the translation of findings from routinely collected data into clinical practice through the development of performance indicators which facilitate the ongoing reporting and monitoring of important aspects of the multimodal treatment of CRC patients. As described above, these can be used to identify unwarranted variation and trigger ongoing targeted quality improvement initiatives at both national and local levels, in order to improve the quality of CRC care on a large scale.

With increasingly complex multidisciplinary decisions and management in CRC care, routinely collected data is paramount for the exploration of use and outcomes in “real-world” clinical practice to complement RCT findings. It is also essential for the development of performance indicators for timely monitoring across the whole CRC pathway, and should strive to include patient-reported outcomes and quality of life measures which can provide further evidence to inform the debate for the need and appropriateness of specialisation of CRC services.

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13. APPENDICES

Appendix 1 – NBOCA relevant data items.[3]

Data Item	Additional Explanation
Tumour ID	Unique patient identifier assigned prior to receipt of data in place of patient-identifiable information.
Gender	
Organisation first seen	Hospital where patient was diagnosed.
Date of diagnosis	
Source of referral	Mode of initial presentation i.e., Accident and Emergency, General Practice.
ICD-10 major site	ICD-10 code which represents the anatomical location of the tumour.
Tumour height above anal verge	Pathological descriptor for rectal cancer tumours only.
Performance status	Recorded according to the Eastern Co-operative Oncology Group score.
Care plan intent	Whether treatment is expected to be curative or not at diagnosis.
Planned cancer treatment type	
No cancer treatment reason	
T-stage	Tumour stage prior to treatment.
N-stage	Node stage prior to treatment.
M-stage	Metastasis stage prior to treatment.
Provider organisation	Hospital where patient underwent surgery.
ASA grade	Recorded according to ASA grading.
Cancer treatment curability	Whether the surgical procedure was deemed curative or palliative.
Date of surgery	
Surgical urgency	Whether the surgical procedure was elective/planned versus urgent/emergency.
Primary procedure	Procedure which best describes resection of the primary tumour.
Surgical access	Whether an open, laparoscopic, or robotic approach was used.
Status of circumferential excision margin	Completeness of the surgeon's resection margin.
Number of nodes examined	Number of lymph nodes found within the pathological specimen.
Number of nodes positive	
Pathological T-stage	Tumour stage following surgery.
Pathological N-stage	Node stage following surgery.
Pathological M-stage	Metastasis stage following surgery.
Lesion size	Size of the tumour.
Differentiation by worst area	Tumour grade.
Vascular or lymphatic invasion	Pathological inspection for lymphovascular invasion.
Pre-operative initial cancer treatment modality	Whether the patient received any pre-operative treatments e.g., chemotherapy or radiotherapy.
Post-operative treatment modality	Whether the patient received any post-operative treatments e.g., chemotherapy or radiotherapy.

Appendix 2 – SACT relevant data items.[147]

Data Item	Additional Explanation
Tumour ID	Allows linkage to NBOCA dataset.
Ethnicity	
Organisation code	Hospital where SACT was administered.
Primary diagnosis (on SACT initiation)	ICD-10 code for tumour relating to episode of SACT.
Pre-treatment (final) TNM stage	
Decision to treat date	
Start date (drug regimen)	
Drug treatment intent	Whether SACT is being given with curative or palliative intent.
Performance status (adult)	
Chemo-radiation indicator	Whether the patient received chemo-radiotherapy.
SACT programme number	Numbered according to the chronological order of commencement in the patient's management.
Anti-cancer regimen number	Regimen number.
Regimen analysis grouping	Planned SACT regimen.
Person height (metres)	
Person weight (kilograms)	
Co-morbidity adjustment indicator	Whether the patient's comorbidities influenced any aspect of chemotherapy treatment i.e., regimen chosen, dosage.
Clinical trial indicator	
Number of planned SACT cycles	
Cycle identifier	Numbered according to the chronological order of commencement in the patient's management.
Start date (cycle)	
Performance status adult (start cycle)	
Person weight (start cycle)	
Drug analysis grouping	Name of the SACT drug administered.
Actual dose	Dose of SACT drug administered.
SACT drug route of administration	
SACT administration date	
Start date (Final therapy)	Date of the final cycle of SACT.
Regimen modification indicator (dose reduction)	
Regimen modification indicator (time delay)	
Regimen modification indicator (days reduced)	
Planned treatment change reason	Reason why SACT was not completed as planned.
Date of death	

Appendix 3 - Summary of key developments in adjuvant chemotherapy for colon cancer.

Development	Year	Evidence	Comments
12 months intravenous 5-FU with levamisole	1989-1990	Laurie *et al.* [232] Moertel *et al.* [233]	Formed the basis of the 1990 NIH consensus statement.[234]
Six months intravenous 5-FU with leucovorin	1995-2001	O'Connell *et al.* [235] NSABP C-04 trial [236] adjCCA-01 trial [237] FOGT-1 trial [238] QUASAR trial [239] IMPACT pooled analysis [240] INT-0089 trial [241]	Combinations of leucovorin and 5-FU improved outcomes compared to levamisole. No survival advantage with 12 months of adjuvant therapy versus six months.
5-FU therapy in patients aged ≥70 years	2001	Sargent *et al.* [242]	Pooled analysis of seven randomised trials demonstrating comparable survival outcomes in patients 70 years and over. Minimal differences in toxicity.
Bolus 5-FU versus continuous infusion 5-FU	2005	GERCOR C96.1 trial [98] Chau *et al.* [99] Intergroup 0153 trial [100]	No significant difference in survival outcomes. Continuous infusion has more favourable toxicity profile but increased incidence of hand-foot syndrome.
Oral fluoropyrimidines e.g. capecitabine introduced	2005	X-ACT trial *[46 243]*	Designed to overcome complications and inconvenience of intravenous administration. Mimics infusional 5-FU with comparable toxicity. At least equivalent survival outcomes, including in patients 70 years and over.
Combination intravenous 5-FU therapy with oxaliplatin	2004-2007	MOSAIC trial [61 103] NSABP C-07 trial [244 245]	Improved survival outcomes with addition of oxaliplatin.
Combination intravenous 5-FU therapy with irinotecan	2007-2009	PETACC-3 trial [246] CALGB 89803 trial [247] Accord02 trial [248]	No improvement in survival outcomes with the addition of irinotecan. Increased significant acute toxicity.
Addition of bevacizumab to combination therapy (5-FU and oxaliplatin)	2011	NSABP C-08 trial [249 250] AVANT trial [251]	No improvement in survival outcomes with the addition of bevacizumab.
Combination oral capecitabine with oxaliplatin	2011	XELOXA trial [252 253]	Improved survival outcomes with the addition of oxaliplatin.
Addition of cetuximab to combination therapy (5-FU and irinotecan)	2011	NCCTG Intergroup N0147 trial [254 255]	Following the results of the irinotecan trials above, this trial was discontinued. Trends towards improved survival reported with cetuximab but limited by small numbers and discontinuation.
Oxaliplatin-based therapy in patients ≥70 years	2013-2015	ACCENT database [256] Haller *et al. [257]*	Benefit of oxaliplatin in patients 70 years and over is uncertain – conflicting evidence.
Three months oxaliplatin-based adjuvant therapy versus six months	2018	SCOT trial [258] IDEA collaboration [62]	IDEA consisted of pooled results from six randomised trials. Confirmed non-inferiority of three versus six months for CAPOX. Reduced burden from neurotoxicity.
Neo-adjuvant chemotherapy	2019	FOxTROT trial [44]	Improved 2-year failure rate but not statistically significant.

			Deemed safe but longer follow-up needed.

Appendix 4 - Summary of SACT drugs identified during timeframe of data used.

SACT drug	Mechanism of action	Indication	Common Toxicities	NICE approved
5-fluorouracil	Antimetabolite drug – inhibits thymidylate synthase causing DNA damage.	Adjuvant setting. Palliative setting - 1st line +	Gastrointestinal disturbances, cardiac issues, myelosuppression (impaired bone marrow function which can lead to anaemia, predisposition to infections, and bleeding), and skin disorders (hand-foot syndrome).[97]	Yes
Capecitabine	Oral pro-drug of 5-FU.	Adjuvant setting. Palliative setting – 1st line +	Gastrointestinal disturbances, cardiac issues, myelosuppression (impaired bone marrow function which can lead to anaemia, predisposition to infections, and bleeding), and skin disorders (hand-foot syndrome).[97]	Yes
Oxaliplatin	Platinum-based drug - binds to DNA, interferes with transcription and replication, and causes cell death.	Adjuvant setting. Palliative setting – 1st line +	Cumulative neurotoxicity, most commonly presenting as loss of sensation in the hands and feet, which can be permanent.[103] Hearing loss, cardiac issues, renal impairment, and gastrointestinal disturbances.	Yes
Irinotecan	Topoisomerase I inhibitor.	Palliative setting - 1st line +	Neutropenia, diarrhoea, alopecia, and cholinergic syndrome.[105 106]	Yes
Panitumumab	Recombinant humanised monoclonal antibody (IgG2 backbone) – epidermal growth factor receptor blocker.	Palliative setting - 1st line RAS wild-type With FOLFOX or FOLFIRI	Skin reactions and electrolyte disorders.[108]	Yes
Cetuximab	Recombinant humanised monoclonal antibody (IgG1 backbone) – epidermal growth factor receptor blocker.	Palliative setting - 1st line RAS wild-type. With FOLFOX or FOLFIRI.	Skin reactions, infusion-related reactions, and electrolyte disorders.[109]	Yes
Trifluridine tipiracil	Antimetabolite drug – inhibits cell proliferation.	Palliative setting - 3rd line	Myelosuppression.[259]	Yes
Bevacizumab	Recombinant humanised monoclonal antibody – binds to Vascular Endothelial Growth Factor A. Inhibits tumour angiogenesis (formation of blood vessels).	Palliative setting - 1st line + With FOLFOX or CAPOX.	Hypertension, fatigue, asthenia, diarrhoea, abdominal pain, renal dysfunction, gastrointestinal perforation, gastrointestinal fistulation, haemorrhage, venous or arterial thromboembolism.[107]	No
Aflibercept	Recombinant fusion protein – binds Vascular Endothelial Growth Factor and placental growth factors. Inhibits tumour angiogenesis.	Palliative setting - 2nd line With FOLFIRI. Prior oxaliplatin-based therapy.	Hypertension, fatigue, diarrhoea, renal dysfunction, gastrointestinal perforation, gastrointestinal fistulation, haemorrhage, venous or arterial thromboembolism.[260]	No
Raltitrexed	Antimetabolite drug – inhibits thymidylate synthase and interferes with RNA and DNA formation.	Palliative setting - 1st line + Alternative for patients who cannot have fluoropyrimidines.	Gastrointestinal disturbance, myelosuppression, and liver dysfunction.[261]	Yes

Appendix 5 – Summary of evidence for the relationship between hospital rectal cancer surgery volumes and outcomes.[143]

Outcome	Volume threshold (cases per year)	Summary of evidence for volume threshold
Positive CRM rate	1 to 9	Moderate-quality evidence Two population-based studies (N=113,694) No evidence of difference
	10 to 19	Moderate-quality evidence One population-based study (N=113,113) No evidence of difference
	20 to 29	Moderate-quality evidence One population-based study (N=113,113) No evidence of difference
	Per additional case	Very low-quality evidence One population-based study (N=581) No evidence of difference
Overall survival	1 to 9	Moderate-quality evidence Three population-based studies (N=4,903) No evidence of difference
	10 to 19	Moderate-quality evidence Four population-based studies (N=7,894) *One study showed evidence in favour of high volume centres*
	20 to 29	Moderate-quality evidence Four population-based studies (N=10,405) No evidence of difference
	30 to 39	Moderate-quality evidence Four population-based studies (N=16,021) *Two studies showed evidence in favour of high volume centres*
	40 to 49	Moderate-quality evidence 1 population-based study (N=7,441) No evidence of difference
	50 to 59	Moderate-quality evidence One population-based study (N=2,095) No evidence of difference
	Per additional case	High-quality evidence One population-based study (N=1,469) No evidence of difference
Perioperative complications (Grade 3/4)	1 to 9	Very low-quality evidence One population-based study (N=581) No evidence of difference
	10 to 19	Moderate-quality evidence Two population-based studies (N=6,852) *1 study showed evidence in favour of high volume centres*
	20 to 29	Low-quality evidence One population-based study (N=1,511) No evidence of difference
	30 to 39	Moderate-quality evidence Three population-based studies (N=14,293) No evidence of difference
	40 to 49	Moderate-quality evidence One population-based study (N=7,441) No evidence of difference
	50 to 59	Low-quality evidence One population-based study (N=1,511) No evidence of difference
	Per additional case	Very low-quality evidence One population-based study (N=581) No evidence of difference

Unplanned return to theatre	N/a	No evidence available
Local recurrence	1 to 9	Moderate-quality evidence Two population-based studies (N=2,799) No evidence of difference
	10 to 19	Moderate-quality evidence Two population-based studies (N=4,718) *One study showed evidence in favour of high volume centres*
	20 to 29	Moderate-quality evidence Three population-based studies (N=7,855) *One study showed evidence in favour of high volume centres*
	30 to 39	Moderate-quality evidence Two population-based studies (N=6,298) *One study showed evidence in favour of high volume centres*
	Per additional case	Moderate-quality evidence One population-based study (N=1,469) No evidence of difference
Overall quality of life	N/a	No evidence available
Permanent stoma rate	1 to 9	Moderate-quality evidence Four population-based studies (N=19,922) No evidence of difference
	10 to 19	Moderate-quality evidence Four population-based studies (N=20,795) *Three studies showed evidence in favour of high volume centres*
	20 to 29	Moderate-quality evidence Two population-based studies (N=15,055) No evidence of difference
	30 to 39	Moderate-quality evidence One population-based study (N=5,021) No evidence of difference
	Per additional case	High-quality evidence One population-based study (N=4,622) No evidence of difference
Perioperative mortality	1 to 9	Moderate-quality evidence Three population-based studies (N=14,584) *One study showed evidence in favour of high volume centres*
	10 to 19	Moderate-quality evidence 10 population-based studies (N=79,714) *Two studies showed evidence in favour of high volume centres*
	20 to 29	Moderate-quality evidence Three population-based studies (N=14,293) No evidence of difference
	30 to 39	Moderate-quality evidence Four population-based studies (N=41,519) No evidence of difference
	40 to 49	Moderate-quality evidence Two population-based studies (N=53,010) *One study showed evidence in favour of high volume centres*
	50 to 59	Moderate-quality evidence One population-based studies (N=16,039) No evidence of difference

Appendix 6 – Summary of evidence for the relationship between surgeon rectal cancer surgery volumes and outcomes.[143]

Outcome	Volume threshold (cases per year)	Summary of evidence for volume threshold
Positive CRM rate	1 to 4	Low-quality evidence Two population-based studies (N=1,609) No evidence of difference
	5 to 9	Low-quality evidence One population-based study (N=1,028) *Evidence in favour of high volume surgeon*
Overall survival	5 to 9	Low-quality evidence Two population-based studies (N=807) No evidence of difference
	10 to 14	Moderate-quality evidence One population-based study (N=7,441) *Evidence in favour of high volume surgeon*
	20 to 24	Moderate-quality evidence One population-based study (N=7,441) No evidence of difference
Perioperative complications (Grade 3/4)	1 to 4	Moderate-quality evidence Two population-based studies (N=1,609) No evidence of difference
	5 to 9	Moderate-quality evidence Two population-based studies (N=15,861) *One study showed evidence in favour of high volume surgeons*
	10 to 14	Moderate-quality evidence One population-based study (N=7,441) No evidence of difference
	20 to 24	Moderate-quality evidence One population-based study (N=7,441) *Evidence in favour of high volume surgeon*
	Per additional case	Very low-quality evidence One population-based study (N=581) No evidence of difference
Unplanned return to theatre	5 to 9	Moderate-quality evidence One population-based study (N=14,833) No evidence of difference
Local recurrence	5 to 9	Moderate-quality evidence One population-based study (N=521) *Evidence in favour of high volume surgeon*
Overall quality of life	N/a	No evidence available
Permanent stoma rate	5 to 9	Low-quality evidence One population-based study (N=521) *Evidence in favour of high volume surgeon*
	10 to 14	Moderate-quality evidence One population-based study (N=7,798) No evidence of difference
Perioperative mortality	1 to 4	Low-quality evidence One population-based study (N=1,028) No evidence of difference
	5 to 9	Low-quality evidence One population-based study (N=1,028) No evidence of difference
	10 to 14	Moderate-quality evidence Two population-based studies (N=15,239) *One study showed evidence in favour of high volume surgeons*
	20 to 24	Moderate-quality evidence One population-based study (N=7,441) No evidence of difference

Appendix 7 – Rectal cancer surgery performance indicators available from routinely collected data and rationale for their use.

Indicator	Data source	Relevant methodology	Rationale for use
90-day mortality	ONS	Death recorded within 90 days of NBOCA date of surgery.	Vast majority of deaths occur within 90 days of surgery.[262]
30-day readmission	HES	Any unplanned admission for any cause within 30 days of the discharge date.	Readmission rates used previously as indicator of surgical quality.[263]
30-day unplanned return to theatre	HES	Pre-existing, validated algorithm using OPCS-4 codes.[191]	Shown to be an important quality indicator which impacts morbidity, short- and long-term mortality, and also oncological and functional outcomes.[195]
Stoma at 18 months following anterior resection	HES	Proportion of patients with a stoma at 18 months following anterior resection.	Evidence suggests retaining a stoma has a long-term detrimental impact on renal function and survival.[74]
Positive CRM	NBOCA	Not applicable.	A positive CRM is one of the main predictors of local and distant recurrence.[264]
Length of stay	HES	Length of stay from date of rectal cancer surgery.	Routinely used as a marker of the quality of care.[30]
2-year all-cause mortality rate	ONS	Any cause of death recorded within two years of the NBOCA date of surgery.	This measure aims to capture patients who develop recurrent disease as it has been shown that most will do so within this timeframe, or else die from other causes.[30]

Appendix 8 – Establishing chemotherapy information for stage IV patients

For stage IV CRC patients, it was not possible to assign specific regimens within HES-APC. This was because, due to the breadth of SACT drugs used within this setting, there was too much overlap in the same combinations of procedural codes being used for different regimens. However, validation of adjuvant chemotherapy information within SACT using HES-APC, has shown the accuracy and reliability of regimen and cycle number captured within SACT.

For stage IV patients with information in HES-APC alone, this precluded regimen-specific analyses. However, this affected only a small proportion of patients with 67% of patients having records in both datasets, 21% in SACT alone, and just 11% in HES-APC alone (table below).

A clinical algorithm was developed for stage IV CRC patients which was applied to both SACT and HES-APC. Patients needed to receive chemotherapy within four months of diagnosis of stage IV disease. Chemotherapy cycles were then included in an attempt to capture first-line therapy. This meant any cycles of the same regimen administered continuously with gaps of no more than 8 weeks between cycles, with a maximum of 12 months of chemotherapy in total. Although specific regimens could not be assigned in HES-APC, changes in regimen could still be inferred by a change in the procedural codes.

Numbers of patients identified as commencing chemotherapy as first treatment within four months of diagnosis of stage IV colorectal cancer, according to either SACT or HES datasets

	Chemotherapy according to SACT		
Chemotherapy according to HES-APC	**Yes**	**No**	**Total**
Yes	5,192	882	6,074
No	1,630	8,399	10,029
Total	6,822	9,281	16,103

Appendix 9 – Example of the presence of diagnostic codes per patient, by organ system, according to receipt of SACT and stage of rectal cancer

	Stage III (n=2,754)	**Stage IV (n=2,758)**
Overall	26.5%	43.2%
Gastrointestinal	12.3%	19.9%
Infection	11.2%	20.7%
Cardiovascular	5.6%	12.6%
Metabolic & Endocrine	4.3%	8.0%
Constitutional	5.2%	7.9%
Renal	6.3%	8.0%
Haematology	4.7%	10.5%
Pain	3.6%	5.7%
Respiratory	0.7%	1.3%
Neurological	2.4%	3.2%
Line Complications	1.6%	3.1%
Psychological	1.2%	4.1%
Bleeding	1.7%	3.5%
Dermatology & Rheumatology	0.7%	2.1%
Ophthalmic	0.4%	0.9%
Drug Reaction	0.2%	0.2%
Death	0.9%	9.7%

Appendix 10 – Summary of missing data for NBOCA/HES-APC datasets used within this thesis

Variable	Overall % missing data	Time trend
All patients*		
Age group	Complete	N/a
Sex	<1%	Nil
RCS Charlson score	7%	Nil
Performance status	17%	Improving
Socioeconomic status	<1%	Nil
Tumour site	Complete	N/a
Pre-treatment T-stage	18%	Improving
Pre-treatment N-stage	16%	Improving
Pre-treatment M-stage	11%	Improving
Surgical patients**		
RCS Charlson score	4%	Nil
Performance status	14%	Improving
Pathological T-stage	6%	Nil
Pathological N-stage	6%	Nil
Pathological M-stage	10%	Improving
Surgical procedure	Complete	N/a
Surgical urgency	<1%	Nil
Surgical access	<1%	Nil
ASA grade	5%	Nil
Unplanned 30-day readmission	Complete	N/a
Other variables		
Chemotherapy on-site	Complete	N/a
University Teaching Hospital	Complete	N/a
High-volume centre	Complete	N/a
Time to surgery	Complete	N/a
Radiotherapy use	Complete	N/a

**All patients – all patients within the dataset regardless of treatment*

***Only patients who are recorded as having a major surgical resection*

Appendix 11 – Summary of proportion of patients with missing data items for NBOCA/HES-APC

	Overall %	Cumulative %
All patients*		
0 missing data items	68%	68%
1 missing data item	16%	84%
2 missing data items	7%	91%
3 missing data items	7%	98%
4 missing data items	3%	100%
Surgical patients**		
0 missing data items	66%	66%
1 missing data item	7%	73%
2 missing data items	13%	86%
3 missing data items	7%	93%
4 missing data items	4%	97%
≥5 missing data items	3%	100%

**All patients – 7 variables which are incomplete (sex, RCS Charlson score, performance status, socioeconomic status, pre-treatment T-stage, pre-treatment N-stage, and pre-treatment M-stage)*

***Surgical patients – 7 variables (sex, RCS Charlson score, performance status, socioeconomic status, pre-treatment T-stage, pre-treatment N-stage, and pre-treatment M-stage) plus the 6 variables specific to surgery which are incomplete (pathological T-stage, pathological N-stage, pathological M-stage, surgical urgency, surgical access, and ASA grade)*

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Observational / Interventions Research Ethics Committee

Dr Jemma Boyle
LSHTM

4 September 2019

Dear Jemma

Study Title: Using National Routine Data to Explore the Utilisation and Outcomes of Multimodal Treatment in the Mangement of Locally Advanced Colorectal Cancer

LSHTM Ethics Ref: 15712

Thank you for responding to the Observational Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Investigator CV	CV_Kate_Walker	07/05/2019	1
Investigator CV	CV_Tom_Cowling	07/05/2019	1
Investigator CV	CV_Ajay	10/05/2019	1
Investigator CV	Curriculum_Vitae 110619	11/06/2019	1
Protocol / Proposal	J Boyle Study Protocol	05/07/2019	1
Covering Letter	Cover Letter Clarifications	30/08/2019	1
Protocol / Proposal	J Boyle Study Protocol Amended 300819	30/08/2019	2

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,

Professor Jimmy Whitworth

Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Appendix 13 – Supplementary material for Research Paper 1

Supplementary Table 1 – First potentially curative colonic chemotherapy regimen given within first 4 months after surgery (only available for patients identified in SACT database).

Chemotherapy regimen	% (n = 6 660)
Bevacizumab	0.06
Bevacizumab + Capecitabine + Irinotecan	0.02
Bevacizumab + Capecitabine + Oxaliplatin	0.20
Bevacizumab + Capecitabine	0.08
Bevacizumab + Fluorouracil	0.05
Bevacizumab + Irinotecan + Fluorouracil	0.03
Bevacizumab + Oxaliplatin + Fluorouracil	0.06
Capecitabine	22.61
Capecitabine + Cetuximab + Irinotecan	0.05
Capecitabine + Irinotecan	0.24
Capecitabine + Oxaliplatin	38.90
Cetuximab	0.15
Cetuximab + Irinotecan + Fluorouracil	0.47
Cetuximab + Fluorouracil	0.02
Cetuximab + Oxaliplatin + Fluorouracil	0.23
Fluorouracil	6.17
Fluorouracil + Irinotecan + Oxaliplatin	0.17
Irinotecan	0.02
Irinotecan + Fluorouracil	1.89
Irinotecan + Fluorouracil + Panitumumab	0.05
Oxaliplatin	0.08
Oxaliplatin + Fluorouracil	27.87
Oxaliplatin + Fluorouracil + Panitumumab	0.15
Oxaliplatin + Raltitrexed	0.33
Raltitrexed	0.15

Supplementary Table 2 – OPCS-4 and ICD-10 codes for chemotherapy use in HES-APC

OPCS-4 code	Classification
X701	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 1
X702	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 2
X703	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 3
X704	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 4
X705	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 5
X708	Other specified procurement of drugs for chemotherapy for neoplasm in Bands 1-5
X709	Unspecified procurement of drugs for chemotherapy for neoplasm in Bands 1-5
X711	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 6
X712	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 7
X713	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 8
X714	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 9
X715	Procurement of drugs for chemotherapy for neoplasm for regimens in Band 10
X718	Other specified procurement of drugs for chemotherapy for neoplasm in Bands 6-10
X719	Unspecified procurement of drugs for chemotherapy for neoplasm in Bands 6-10
X721	Delivery of complex chemotherapy for neoplasm including prolonged infusional treatment at first attendance
X722	Delivery of complex parenteral chemotherapy for neoplasm at first attendance
X723	Delivery of simple parenteral chemotherapy for neoplasm at first attendance
X724	Delivery of subsequent element of cycle of chemotherapy for neoplasm
X728	Other specified delivery of chemotherapy for neoplasm
X729	Unspecified delivery of chemotherapy for neoplasm
X731	Delivery of exclusively oral chemotherapy for neoplasm
X738	Other specified delivery of oral chemotherapy for neoplasm
X739	Unspecified delivery of oral chemotherapy for neoplasm
X748	Other specified other chemotherapy drugs
X749	Unspecified other chemotherapy drugs
X352	Intravenous chemotherapy
X373	Intramuscular chemotherapy
X384	Subcutaneous chemotherapy
ICD-10 code	**Classification**
Z082	Follow-up exam after chemotherapy for malignant neoplasm
Z292	Other prophylactic chemotherapy
Z511	Chemotherapy session for neoplasm
Z512	Other chemotherapy
Z542	Convalescence following chemotherapy

Supplementary Table 3(a) – Distribution of patient and hospital characteristics and their effect on ACT use in patients aged less than 70.

	Total (%) n=5,345	Received ACT (%) n=4,339	p-value (X^2)	Adjusted odds ratios (95% CI)	p-value
Sex			0.003		0.06
Male	2,892 (54.1)	2,306 (79.7)		1.0	
Female	2,453 (45.9)	2,033 (82.9)		1.15 (1.00-1.34)	
Socioeconomic status (IMDQ)			<0.001		0.05
1 (most deprived)	933 (17.5)	708 (75.9)		1.0	
2	950 (17.8)	774 (81.5)		1.24 (1.00-1.55)	
3	1,162 (21.8)	948 (81.6)		1.21 (0.97-1.52)	
4	1,158 (21.7)	942 (81.4)		1.17 (0.93-1.46)	
5 (least deprived)	1,131 (21.2)	962 (85.1)		1.40 (1.12-1.75)	
Missing	11	5			
RCS Charlson score			<0.001		<0.001
0	3,337 (65.8)	2,831 (84.8)		1.0	
1	1,307 (25.8)	1,034 (79.1)		0.85 (0.70-1.03)	
≥2	425 (8.4)	268 (63.1)		0.52 (0.42-0.64)	
Missing	276	206			
Performance status			<0.001		<0.001
0	2,983 (64.6)	2,537 (85.1)		1.0	
1	1,235 (26.8)	975 (79.0)		0.82 (0.68-1.00)	
2	314 (6.8)	224 (71.3)		0.58 (0.43-0.79)	
≥3	83 (1.8)	34 (41.0)		0.22 (0.13-0.35)	
Missing	730	569			
ASA fitness grade			<0.001		<0.001
I	1,080 (21.4)	938 (86.9)		1.0	
II	2,984 (59.2)	2,512 (84.2)		0.98 (0.79-1.21)	
III	898 (17.8)	615 (68.5)		0.56 (0.43-0.72)	
IV or V	77 (1.5)	33 (42.9)		0.26 (0.16-0.42)	
Missing	306	241			
Urgency of resection			<0.001		0.011
Elective/scheduled	4,042 (75.7)	3,332 (82.4)		1.0	
Emergency/urgent	1,299 (24.3)	1,003 (77.2)		0.78 (0.65-0.95)	
Missing	4	4			
Surgical access			<0.001		0.027
Open	2,052 (38.6)	1,595 (77.7)		1.0	
Laparoscopic-converted	462 (8.7)	365 (79.0)		1.04 (0.81-1.33)	
Laparoscopic	2,808 (52.8)	2,361 (84.1)		1.26 (1.06-1.50)	
Missing	23	23			
Pathological T-stage			0.244		0.109
T1	138 (2.6)	103 (74.6)		1.0	
T2	371 (6.9)	305 (82.2)		1.60 (1.01-2.53)	
T3	2,658 (49.8)	2,162 (81.3)		1.62 (1.08-2.42)	
T4	2,175 (40.7)	1,766 (81.2)		1.69 (1.11-2.56)	
Missing	3	3			
Pathological N-stage			0.007		0.002
N1	3,314 (62.0)	2,653 (80.1)		1.0	
N2	2,031 (38.0)	1,686 (83.0)		1.27 (1.09-1.47)	
30-day readmission			0.002		0.005
No	4,832 (90.4)	3,949 (81.7)		1.0	
Yes	513 (9.6)	390 (76.0)		0.74 (0.60-0.91)	
University teaching hospital			0.246		0.283

No	3,914 (73.2)	3,192 (81.6)		1.0	
Yes	1,431 (26.8)	1,147 (80.2)		0.90 (0.74-1.09)	
On-site chemotherapy facilities			0.355		0.405
No	614 (11.5)	490 (79.8)		1.0	
Yes	4,731 (88.5)	3,849 (81.4)		1.10 (0.88-1.36)	
High volume centre			0.403		0.952
No	1,125 (21.1)	923 (82.0)		1.0	
Yes	4,220 (79.0)	3,416 (81.0)		0.99 (0.80-1.23)	

Supplementary Table 3(b) – Distribution of patient and hospital characteristics and their effect on ACT use in patients aged 70 and over.

	Total (%) n=6,587	Received ACT (%) n=2,900	p-value (X^2)	Adjusted odds ratios (95% CI)	p-value
Sex			<0.001		0.006
Male	3,335 (50.6)	1,541 (46.2)		1.0	
Female	3,252 (49.4)	1,359 (41.8)		0.86 (0.77-0.96)	
Socioeconomic status (IMDQ)			0.002		0.020
1 (most deprived)	882 (13.4)	353 (40.0)		1.0	
2	1,040 (15.8)	419 (40.3)		1.02 (0.80-1.30)	
3	1,441 (21.9)	654 (45.4)		1.34 (1.09-1.65)	
4	1,584 (24.1)	724 (45.7)		1.23 (0.99-1.53)	
5 (least deprived)	1,628 (24.8)	746 (45.8)		1.33 (1.07-1.66)	
Missing	12	4			
RCS Charlson score			<0.001		<0.001
0	3,091 (49.6)	1,594 (51.6)		1.0	
1	2,037 (32.7)	879 (43.2)		0.76 (0.66-0.88)	
≥2	1,099 (17.7)	302 (27.5)		0.49 (0.41-0.58)	
Missing	360	125			
Performance status			<0.001		<0.001
0	2,006 (36.1)	1,187 (59.2)		1.0	
1	2,189 (39.4)	999 (45.6)		0.83 (0.70-0.97)	
2	1,005 (18.1)	297 (29.6)		0.51 (0.42-0.63)	
≥3	358 (6.4)	33 (9.2)		0.15 (0.10-0.23)	
Missing	1,029	384			
ASA fitness grade			<0.001		<0.001
I	389 (6.3)	244 (62.7)		1.0	
II	3,107 (50.5)	1,714 (55.2)		0.91 (0.72-1.16)	
III	2,374 (38.6)	724 (30.5)		0.52 (0.40-0.67)	
IV or V	288 (4.7)	39 (13.5)		0.21 (0.13-0.33)	
Missing	429	179			
Urgency of resection			<0.001		0.007
Elective/scheduled	4,963 (75.5)	2,336 (47.1)		1.0	
Emergency/urgent	1,609 (24.5)	557 (34.6)		0.79 (0.67-0.94)	
Missing	15	7			
Surgical access			<0.001		0.004
Open	2,833 (43.1)	1,094 (38.6)		1.0	
Laparoscopic-converted	509 (7.8)	215 (42.2)		0.95 (0.72-1.26)	
Laparoscopic	3,227 (49.1)	1,586 (49.2)		1.27 (1.08-1.50)	
Missing	18	5			
Pathological T-stage			0.036		0.040
T1	103 (1.6)	52 (50.5)		1.0	
T2	335 (5.1)	166 (49.6)		1.09 (0.65-1.83)	
T3	3,318 (50.4)	1,477 (44.5)		1.31 (0.86-2.00)	
T4	2,829 (43.0)	1,205 (42.6)		1.49 (0.97-2.30)	
Missing	2	0			

Pathological N-stage			<0.001		<0.001
N1	4,306 (65.4)	1,811 (42.1)		1.0	
N2	2,281 (34.6)	1,089 (47.7)		1.34 (1.17-1.53)	
30-day readmission			<0.001		<0.001
No	6,089 (92.4)	2,726 (44.8)		1.0	
Yes	498 (7.6)	174 (34.9)		0.59 (0.48-0.74)	
University teaching hospital			0.848		0.792
No	4,966 (75.4)	2,183 (44.0)		1.0	
Yes	1,621 (24.6)	717 (44.2)		0.96 (0.73-1.27)	
On-site chemotherapy facilities			0.928		0.571
No	722 (11.0)	319 (44.2)		1.0	
Yes	5,865 (89.0)	2,581 (44.0)		0.94 (0.74-1.18)	
High volume centre			0.399		0.805
No	1,518 (23.1)	654 (43.1)		1.0	
Yes	5,069 (77.0)	2,246 (44.3)		1.04 (0.78-1.38)	

Supplementary Table 4 – Proportion of patients aged ≥70 years receiving adjuvant chemotherapy (ACT) according to comorbidities, performance status, and ASA grade.

	70-74 years n=1,996		**75-79 years n=1,976**		**≥80 years n=2,615**	
	ACT n=1,423	**No ACT n=573**	**ACT n=992**	**No ACT n=984**	**ACT n=485**	**No ACT n=2,130**
RCS Charlson score						
0/1	1,233 (74.9)	413 (25.1)	836 (54.6)	695 (45.4)	404 (20.7)	1,547 (79.3)
≥2	138 (51.9)	128 (48.1)	107 (32.0)	227 (68.0)	57 (11.4)	442 (88.6)
Missing	52	32	49	62	24	141
Performance status						
0/1	1,085 (74.7)	367 (25.3)	747 (56.9)	565 (43.1)	354 (24.7)	1,077 (75.3)
≥2	141 (55.1)	115 (44.9)	115 (31.6)	249 (68.4)	74 (10.0)	669 (90.0)
Missing	197	91	130	170	57	384
ASA fitness grade						
I/II	1,042 (78.8)	280 (21.2)	612 (59.5)	417 (40.5)	304 (26.6)	841 (73.5)
III-V	307 (53.9)	263 (46.1)	310 (39.0)	485 (61.0)	146 (11.3)	1 151 (88.7)
Missing	74	30	70	82	35	138

Appendix 14 – Supplementary material for Research Paper 2

Supplementary Table 1 – Multivariable analysis of factors associated with 3-year colon cancer-specific death following receipt of FOLFOX.

	Adjusted sHR[a]	95% Confidence Interval	*P* value
Recorded cycles			**<0.001**
12	1		
6-11	1.40	1.09 to 1.78	
<6	2.18	1.56 to 3.03	
Sex			0.269
Male	1		
Female	0.89	0.72 to 1.10	
Age, years			0.083
<60	1		
60-69	0.95	0.72 to 1.25	
70-79	1.20	0.88 to 1.62	
≥80	2.11	1.07 to 4.18	
IMDQ			0.919
1 (most deprived)	1		
2	0.87	0.57 to 1.32	
3	0.85	0.56 to 1.28	
4	0.81	0.52 to 1.27	
5 (least deprived)	0.83	0.53 to 1.30	
RCS Charlson Score			0.313
0	1		
1	1.04	0.76 to 1.43	
≥2	1.44	0.89 to 2.36	
Performance Status			0.228
0	1		
1	1.01	0.75 to 1.35	
≥2	1.45	0.94 to 2.24	
Pathological T-stage			**<0.001**
T4	1		
T3	0.42	0.33 to 0.53	
T1/T2	0.22	0.01 to 0.49	
Pathological N-stage			**<0.001**
N1	1		
N2	2.52	1.97 to 3.22	
Liver Disease			0.465
No	1		
Yes	1.24	0.70 to 2.21	
Renal Disease			0.980
No	1		
Yes	0.99	0.52 to 1.90	
Cardiac History			0.840
No	1		
Yes	1.06	0.60 to 1.87	
Surgical Urgency			**0.001**

Elective/Scheduled	1.0		
Emergency/Urgent	1.70	1.25 to 2.30	
Emergency Readmission			0.691
No	1.0		
Yes	0.90	0.53 to 1.52	
Surgical Access			0.177
Open operation	1.0		
Laparoscopic converted	0.90	0.61 to 1.34	
Laparoscopic	0.78	0.59 to 1.01	
Time from Surgery			0.761
<8 weeks	1.0		
≥8 weeks	0.96	0.73 to 1.26	
Chemo on-site			0.422
No	1.0		
Yes	1.25	0.72 to 2.18	
University Teaching Hospital			0.178
No	1.0		
Yes	0.79	0.57 to 1.11	

[a]sHR: subdistribution hazard ratios

Supplementary Table 2 – Multivariable analysis of factors associated with 3-year colon cancer-specific death following receipt of CAPOX.

	Adjusted sHR[a]	95% Confidence Interval	*P* value
Recorded cycles			**<0.001**
8	1		
4-7	1.63	1.27 to 2.10	
<4	2.02	1.53 to 2.67	
Sex			0.180
Male	1		
Female	1.16	0.93 to 1.45	
Age, years			**<0.001**
<60	1		
60-69	1.16	0.88 to 1.54	
70-79	1.84	1.42 to 2.38	
≥80	2.78	1.35 to 5.71	
IMDQ			0.119
1 (most deprived)	1		
2	0.71	0.51 to 0.99	
3	0.79	0.58 to 1.07	
4	0.67	0.47 to 0.94	
5 (least deprived)	0.82	0.57 to 1.19	
RCS Charlson Score			0.070
0	1		
1	0.90	0.66 to 1.23	
≥2	1.44	0.98 to 2.13	
Performance Status			0.355
0	1		
1	1.18	0.93 to 1.49	
≥2	1.15	0.75 to 1.77	
Pathological T-stage			**<0.001**
T4	1		
T3	0.43	0.34 to 0.56	
T1/T2	0.28	0.15 to 0.54	
Pathological N-stage			**<0.001**
N1	1		
N2	2.72	2.20 to 3.35	
Liver Disease			0.295
No	1		
Yes	1.33	0.78 to 2.27	
Renal Disease			0.378
No	1		
Yes	0.73	0.37 to 1.46	
Cardiac History			0.199
No	1		
Yes	0.63	0.31 to 1.28	
Surgical Urgency			**<0.001**
Elective/Scheduled	1.0		
Emergency/Urgent	1.64	1.24 to 2.17	

Emergency Readmission			0.731
No	1.0		
Yes	0.94	0.64 to 1.36	
Surgical Access			0.631
Open operation	1.0		
Laparoscopic converted	1.15	0.79 to 1.66	
Laparoscopic	0.98	0.78 to 1.22	
Time from Surgery			**0.037**
<8 weeks	1.0		
≥8 weeks	0.79	0.64 to 0.99	
Chemo on-site			0.575
No	1.0		
Yes	1.12	0.76 to 1.66	
University Teaching Hospital			0.665
No	1.0		
Yes	0.95	0.77 to 1.18	

[a]sHR: subdistribution hazard ratios

Supplementary Table 3 – Dose reduction and early discontinuation of oxaliplatin according to level of completion of FOLFOX or CAPOX for patients with SACT records (*n*=3,375)

	Dose Reduction			Stopped Oxaliplatin	
% completion	**No**	**Yes**	**Missing**	**No**	**Yes**
FOLFOX					
<50%	134 (79%)	36 (21%)	5	160 (91%)	15 (9%)
50-99%	340 (61%)	218 (39%)	5	380 (68%)	183 (33%)
100%	396 (53%)	351 (47%)	11	303 (40%)	455 (60%)
CAPOX					
<50%	179 (77%)	55 (24%)	17	217 (87%)	34 (14%)
50-99%	364 (56%)	286 (44%)	6	411 (63%)	245 (37%)
100%	489 (52%)	452 (48%)	31	608 (63%)	364 (37%)

Appendix 15 – Supplementary material for Research Paper 3

Supplementary Table 1 – ICD-10 coding framework used to identify severe acute toxicity

Haematology
D701 D702 D703 D708 D709 D70X D695 D696 D699 M311 R233 D65X D65 D611 D618 D619 D648 D509* D630 D649*
Constitutional
R530 R531 R538 R53X R64 R64X R630 R634 R638 E877 E860 E86X E861 E869 R600 R601 R609 R60X
Cardiovascular*
I200* I201* I208* I209* I210 I211 I212 I213 I214 I219 I220 I221 I228 I229 I230 I231 I232 I233 I234 I235 I236 I238 I500* I501* I509* I440* I441* I442* I443* I444* I445* I446* I447* I471* I472* I480* I483* I484* I489* I48X* I450* I451* I452* I453* I454* I455* I456* I458* I459* I490* I491* I492* I493* I494* I495* I498* I499* R000 R001 R002 R008 I10* I10X* I110* I119* I120* I129* I130* I131* I132* I139* I150* I151* I152* I158* I159* I630* I631* I632* I633* I634* I635* I636* I638* I639* I600* I601* I602* I603* I604* I605* I606* I607* I608* I609* I64* I64X* I610* I611* I612* I613* I614* I615* I616* I618* I619* I620* I621* I629* I690* I691* I692* I693* I694* I698* G450* G451* G452* G453* G454* G458* G459* G460* G461* G462* G463* G464* G465* G466* G467* G468* I950 I951 I952 I958 I959 I260 I269 I313 I319 I427 I429 I740 I741 I742 I743 I744 I745 I748 I749 I822 I823 I828 I829 I800 I801 I802 I803 I808 I809
Respiratory
R05X R05 J80X J80 J81 J81X R060
Infection
R502 R508 R509 R680 R650 R651 R659 A410 A411 A412 A413 A414 A415 A418 A419 A020 A021 A022 A028 A029 A040 A041 A042 A043 A044 A045 A046 A047 A048 A049 A050 A051 A052 A053 A054 A058 A059 A070 A071 A072 A073 A078 A079 A080 A081 A082 A083 A084 A085 A150 A151 A152 A153 A154 A155 A156 A157 A158 A159 A170 A171 A178 A179 A180 A181 A182 A183 A184 A185 A186 A187 A188 A190 A191 A192 A198 A199 A38 A38X A390 A391 A392 A394 A395 A398 A399 A400 A401 A402 A403 A408 A409 A420 A421 A422 A427 A428 A429 A46 A46X A480 A481 A482 A483 A484 A488 A490 A491 A492 A493 A498 A499 A810 A811 A812 A818 A819 A850 A852 A858 A86X A86 A870 A871 A872 A878 A879 A880 A881 A888 A89 A89X B001 B002 B003 B004 B005 B007 B008 B009 B010 B011 B012 B018 B019 B020 B021 B022 B023 B027 B028 B029 B07X B07 B080 B081 B082 B083 B084 B085 B088 B09X B150 B159 B160 B161 B162 B169 B170 B171 B172 B178 B179 B190 B199 B250 B251 B252 B258 B259 B270 B271 B278 B279 B300 B301 B302 B303 B308 B309 B330 B331 B332 B333 B334 B338 B340 B341 B342 B343 B344 B348 B349 B371 B372 B373 B374 B375 B376 B377 B378 B379 B440 B441 B442 B447 B448 B449 B450 B451 B452 B453 B457 B458 B459 B49X B59X B950 B951 B952 B953 B954 B955 B956 B957 B958 B960 B961 B962 B963 B964 B965 B966 B967 B968 B970 B971 B972 B973 B974 B975 B976 B977 B978 B99 B99X J200 J201 J202 J203 J204 J205 J206 J207 J208 J209 J120 J121 J122 J123 J128 J129 J13 J14 J13X J14X J150 J151 J152 J153 J154 J155 J156 J157 J158 J159 J160 J168 J170 J171 J172 J173 J178 J180 J181 J182 J188 J189 J09 J100 J101 J22X J108 J110 J111 J118 J850 J851 J852 J853 J860 J869 N10X N390 N300 N308 N309 N340 N151 N450 N459 N410 N412 N413 L00X L010 L011 L020 L021 L022 L023 L024 L028 L029 L030 L031 L032 L033 L038 L039 L040 L041 L042 L043 L048 L049 L050 L059 L080 L081 L088 L089 N700 N709 N710 N72X N730 N732 N733 N735 N760 N762 N764 N61X T814 G000 G001 G002 G003 G008 G009 G01X G020 G021 G028 G030 G038 G039 G040 G041 G042 G048 G049 G050 G051 G052 G058 G060 G061 G062 G07X G08X A851 M600 I330 I339 I300 I301 I308 I309 I400 I401 I408 I409 I514 I518 H700 K052 K113 J040 J041 J042 H600 H601 H603 H660 J010 J011 J012 J013 J014 J018 J019 J020 J028 J029 J030 J038 J039 M871 K102 M860 M861 M869 M000 M001 M002 M008 M009 K750 K610 K611 K612 K613 K614 K800 K803 K804 K810 K830 K630 K65 K65X
Renal
N170 N171 N172 N178 N179 N19X N19 N10 N10X N12X N12 N130 N131 N132 N133 N134 N135 N136 N137 N138 N139 N141 N142 N144 N158 N159 N280
Line Complications

T825 T827 T828 T829 Z452 T800 T801 T802 T808 T809
Gastrointestinal
K521 K528 K529 A090 A099 R110 R111 R112 R11X R13X K590 K564 K121 K123 B370 K710 K711 K712 K716 K719 K720 K729 R17 R17X K221 K223 K251 K253 K255 K261 K262 K263 K265 K271 K273 K275 K281 K283 K285 K291 K293 K295 K914 K631 N321 N820 N822 N823 N824 K316 K603 K605 K604
Bleeding
R040 R310 R31X N938 N939 R042 J942 K625 I850 K920 K921 K922 K250 K252 K254 K256 K260 K262 K264 K266 K270 K272 K274 K276 K280 K282 K284 K286 K290 K292 K294 K296
Metabolic & Endocrine
E870 E871 E872 E873 E874 E875 E876 E878 E833 E835 E838 E839 E883 E834 R730 R739 E15 E15X E160 E161 E162 E032 E058 E064 E273 E231
Pain
R100 R101 R102 R103 R104 M255 M540 M541 M542 M543 M544 M545 M546 M548 M549 R07 R07X R070 R071 R072 R073 R074 R520 R529 H920 K146 H571 M796
Neurological*
R55X R55 R42 R42X G400* G401* G402* G403* G404* G405* G406* G407* G408* G409* G410* G411* G412* G418* G419* R56* R560* R568* G620 G628 G629 R200 R201 R202 R203 R208 R209 H910 H931 J385 G250 G251 G252 G253 G258 G259 G240 G254 G256 G711 G720 R270 R260 G430 G431 G432 G433 G438 G439 G440 G441 G442 G443 G444 G448 R51 R51X
Dermatology & Rheumatology*
R21X R21 L270 L271 L298 L299 L51 L510 L511 L512 L518 L519 L539 R238 R239 M100* M102* M104* M109*
Drug Reaction
L500 T782 T783 T784 T886 T887 T451
Ophthalmic*
H320 H191 H192 H10 H100 H101 H102 H103 H105 H108 H109 H11 H111 H112 H113 B300 B301 B302 B303 B308 B309 H150 H151 H158 H159 H160 H161 H162 H163 H164 H168 H169 M350 H170 H171 H178 H179 H180 H181 H182 H183 H184 H186 H187 H188 H189 H200 H202 H208 H209 H210 H211 H212 H213 H214 H215 H218 H219 H263 H278 H279 H406 H531 H532 H533 H534 H535 H536 H538 H539 H540* H541* H542* H543* H544* H545* H546* H549* H000 H001 H010 H018 H019 H041 H042 H043 H020 H021 H050 H052 H058 H059 H578 H579 H490* H491* H492* H493* H494* H498* H499* H500* H501* H502* H503* H504* H505* H506* H508* H509* H510* H511* H512* H518* H519* H46X* H46* H470* H471* H472* H473* H474* H475* H476* H477* H300* H301* H302* H308* H309* H310* H311* H313* H314* H318* H319* H330* H332* H335* H340* H341* H342* H348* H349* H350* H352* H353* H356* H357* H358* H359* H431 H432 H433 H438 H439 H440 H441 H448 H449
Psychological*
F320 F321 F322 F323 F328 F329* F410 F411 F412 F413 F418 F419*

*Codes excluded if present in the 12 months preceding chemotherapy administration

Supplementary Table 2 – Severe acute toxicity following SACT administration, the number of colorectal cancer patients receiving SACT annually, and the statistical power according to different reporting periods

			Statistical power according to different reporting periods		
Cohort	**National severe acute toxicity rate (%)**	**Median annual number per hospital**	**1-year**	**3-year**	**5-year**
Stage III	25%	24	33%	70%	88%
Stage IV	47%	22	63%	98%	100%

5% significance level. Poor performance defined as 50% increase in the national overall severe acute toxicity rate.

Appendix 16 – Supplementary material for Research Paper 4

Supplementary Table 1 – Distribution of surgeon volumes (n=846), according to associated hospital volume

Hospital Volume	**Surgeon volume**			
	Low (1-3) Column %	**Middle (4-6) Column %**	**High (>6) Column %**	**P value (χ^2)**
Low (<22)	105 (39.2)	86 (26.7)	33 (12.9)	<0.001
Row %	*(46.9)*	*(38.4)*	*(14.7)*	
Middle (22-31)	72 (26.9)	113 (35.1)	66 (25.8)	
Row %	*(28.7)*	*(45.0)*	*(26.3)*	
High (32-74)	91 (34.0)	123 (38.2)	157 (61.3)	
Row %	*(24.5)*	*(33.2)*	*(42.3)*	