Outcomes of colorectal cancer resection in patients with inflammatory bowel disease: a national population-based analysis in England and Wales

Authors:

*Angela J Kuryba	MSc	Quantitative Analyst [1,2]
*Abigail E Vallance	MD	Academic Clinical Lecturer in Colorectal Surgery [3]
Jemma M Boyle	MB ChB	Clinical Research Fellow [1,2]
Michael S Braun	PhD	Consultant in Medical Oncology, Senior Lecturer in Cancer Sciences [5,6]
Helen A Blake	PhD	Research Fellow [2,1]
Jan van der Meulen	PhD	Professor of Clinical Epidemiology [2,1]
Nicola S Fearnhead	DM	Consultant Colorectal Surgeon [4]
Kate Walker	PhD	Associate Professor of Medical Statistics [2,1]

* Joint first authors

[1] Clinical Effectiveness Unit, Royal College of Surgeons of England, London, UK

[2] Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, London, UK

[3] Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK

[4] Department of Colorectal Surgery, Cambridge University Hospitals, Cambridge, UK

[5] Department of Oncology, The Christie NHS Foundation Trust, Manchester, UK

[6] School of Medical Sciences, University of Manchester, Manchester, UK

Corresponding Author:

Angela Kuryba *e-mail:* akuryba@rcseng.ac.uk
Orcid ID: 0000-0002-6607-2205

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Abstract

Aim: To compare early postoperative outcomes and 2-year cancer-specific survival following colorectal cancer (CRC) resection in patients with and without inflammatory bowel disease (IBD) in England and Wales.

Method: Records for patients in the National Bowel Cancer Audit who had major CRC resection between April 2014 and December 2017 were linked to routinely collected hospital level administrative datasets and chemotherapy and radiotherapy datasets.

Multivariable regression models were used to compare outcomes with adjustment for patient and tumour characteristics.

Results: 63,365 patients were included. 1,285 (2.0%) had an IBD diagnosis: 839 (65.3%) ulcerative colitis, 435 (33.9%) Crohn's disease, and 11 (0.9%) were indeterminate. IBD patients were younger, had more advanced cancer staging and a higher proportion of right sided tumours. They also had a higher proportion of emergency resection, total/subtotal colectomy, open surgery, and stoma formation at resection, with longer hospital admissions and higher rates of unplanned readmission and reoperation. Fewer rectal cancer patients with IBD received neoadjuvant radiotherapy (24.8% v 36.0%, p=0.005) whilst similar proportions of stage III colon cancer patients received adjuvant chemotherapy. 90-day postoperative mortality was similar, but unadjusted 2-year cancer-specific mortality was significantly higher in patients with IBD (SHR 1.35, 95% CI 1.18-1.55). Risk adjustment for patient and tumour factors reduced this association (adjSHR 1.22, 95% CI 1.05-1.43).

Conclusion: Patients with IBD and CRC are a distinct patient group who develop CRC at a younger age and undergo more radical surgery. They have worse cancer survival, with the difference in prognosis appearing after the early postoperative period.

What does this paper add to the literature?

We demonstrate that patients with inflammatory bowel disease who develop colorectal cancer differ from other patients with colorectal cancer. They develop more advanced cancers at a younger age, tend to need more radical surgery and have a poorer long-term cancer prognosis even though their early postoperative mortality rates are similar.

Introduction

Globally, in 2020 colorectal cancer (CRC) was estimated to be the third most common cancer (10% of cases) and the second most common cause of cancer death (9.4%) [1]. In the United Kingdom (UK) alone, over 40,000 patients are diagnosed with the disease each year [2] and just under 150,000 patients were diagnosed in the USA in the past year [3]. Inflammatory bowel disease (IBD) is a well-accepted risk factor for the development of CRC [4-8]. An estimated 2.5–3 million people in Europe are affected by IBD and epidemiological data suggests that the incidence and prevalence of both ulcerative colitis (UC) and Crohn's disease are increasing [9]. CRC accounts for one in six deaths in patients with UC [4], with patients being diagnosed at a younger age than in sporadic CRC [10]. A recent population-based study has demonstrated that the incidence of CRC in patients with UC is 1.7 times higher than in patients without [11]. Another population-based study demonstrated an increased incidence of CRC in patients with Crohn's disease [12].

As well as being more likely to develop CRC, there is evidence to suggest that despite being diagnosed with less advanced disease than patients with sporadic CRC, IBD patients are at a higher risk of dying from CRC [12, 13]. Some outcomes have also been found to be poorer for IBD patients in the short-term after major CRC resection [14]. The reasons behind this are not clear and could relate to differences in the pathogenesis of CRC, variation in receipt of neoadjuvant and adjuvant treatment, or poorer surgical outcomes due to morbidities associated with IBD such as malnutrition and immune suppression [15].

The aim of our national population-based study was to compare the patient and disease characteristics, operative and oncological management, and outcomes up to 2 years after a major resection for colorectal cancer in patients with and without IBD.

Methods

Patients in the National Bowel Cancer Audit (NBOCA) database were eligible for inclusion if they were recorded as having undergone a major colorectal cancer resection (segmental colectomy, anterior resection, abdominoperineal excision of rectum, Hartmann's procedure, or total excision of colon and rectum) between 1 June 2014 and 31 December 2017 [16]. Patients were included if they could be linked to the English Hospital Episode Statistics (HES) or the Patient Episode Data for Wales (PEDW), administrative hospital datasets that include records of all inpatient hospital admissions covered by the National Health Service (NHS) in that nation [17, 18], and if the date of surgery was between 6 months before and 15 months after their date of diagnosis. Patients were also excluded if

there was a CRC diagnosis in the linked HES or PEDW data more than 6 months before their NBOCA date of diagnosis in order to include only major resections for the primary CRC diagnosis. Full exclusion details are given in Figure 1.

The NBOCA database is a prospective mandatory database for all patients aged 18 years or older when newly diagnosed with CRC in the English or Welsh National Health Service, collecting health care information under Section 251 approval (CAG ECC 1-3(d)/2012)[19]. The NBOCA database provided data on age, gender, Eastern Cooperative Oncology Group (ECOG) performance status [20], referral source, surgical urgency (elective/emergency), American Society of Anaesthesiologists (ASA) score [21], pathological staging (TNM), cancer site, and the Index of Multiple Deprivation (IMD), an area-based measure of socioeconomic deprivation across seven domains in England and eight in Wales [22, 23]. IMD is based on an area of residence typically including about 1500 people and 650 households. Patients were grouped into five categories based on quintiles of the national ranking of the IMD.

Further patient and treatment information was obtained through linkage to the HES and PEDW databases, mortality data from the Office for National Statistics (ONS) [24], and, for patients diagnosed in England only, to the Systemic Anti-Cancer Therapy (SACT) Database and the National Radiotherapy Dataset (RTDS) [25, 26]. HES and PEDW data were used to provide information about IBD, the use of a stoma, and the presence of comorbid conditions, length of hospital stay, unplanned readmission, and unplanned re-operation after CRC resection. Date and underlying cause of death was obtained from ONS data.

The presence of IBD was identified using ICD-10 codes for Crohn's disease (K50) and ulcerative colitis (K51). Patients were considered to have IBD at the time of the major CRC resection, if they had an IBD ICD-10 code in a HES or PEDW record of a hospital episode before or in the 6 months after the date of the CRC diagnosis. Patients with ICD-10 codes for both Crohn's disease and ulcerative colitis were classified as having indeterminate IBD. The Royal College of Surgeons Charlson co-morbidity score was used to identify the number of co-morbid conditions in the HES or PEDW records in the preceding year [27]. Length of stay was defined as the number of days between the date of surgery and the date of discharge. Unplanned readmission was defined as an emergency admission to any hospital within 30 days of the date of surgery. Unplanned re-operation was defined as the presence of a previously described OPCS code for an operation related to post-operative complications within 30 days of surgery [28].

Stage III colon cancer patients were considered to have received adjuvant chemotherapy if a linked record of any potentially curative chemotherapy regimen within 4 months after surgery was

identified in the SACT or HES databases (for patients in England), or in the PEDW database (for patients in Wales) [29]. Rectal cancer patients in England were considered to have received neoadjuvant radiotherapy if linked RTDS records contained a radiotherapy record prior to surgery [28]. Patients in Wales were excluded from the analysis of neoadjuvant radiotherapy.

Statistical analysis

The statistical significance of differences in patient characteristics between IBD and non-IBD patients was assessed using the $\chi 2$ test. Logistic regression was used to estimate relative differences in the odds of short-term post-operative outcomes (30-day unplanned readmission, 30-day unplanned reoperation, 90-day mortality and length of hospital stay >14 days) according to IBD diagnosis. Fine and Gray competing risks proportional hazards models were used to evaluate the impact of IBD on cancer-specific mortality with death from other causes considered a competing event and with follow-up considered to be censored at two years or 31st December 2019, whichever was earliest [30]. Cancer-specific mortality was defined as death from any cause within 90 days of surgery or death with bowel cancer or cancer of an unspecified site as the underlying cause in the 91 days to two years after surgery (Appendix). Robust standard errors were used in all models to account for clustering of outcomes within the NHS organisation reporting surgery.

The following risk factors were included in the logistic regression and competing risk models: gender, age (in years, modelled as age and age^2), IMD quintile, Charlson co-morbidity score (0, 1, ≥2), ECOG performance status, tumour site, admission type, ASA score, TNM stage and the interaction between age and distant metastases (also modelled in years as age and age^2).

Missing values for the risk factors were imputed with multiple imputation using chained equations, creating ten imputed data sets and Rubin's rules were used to combine the model estimates across the data sets [31]. The imputation model included all risk factors and outcomes used in the analyses, including time to death/ censoring. STATA® version 15.1 (StataCorp, College Station, Texas, USA) was used for all analyses.

Results

Study population

63,365 patients diagnosed with primary CRC who underwent major resection between 1 June 2014 and 31 December 2017 were linked to HES or PEDW data. Of these, 1,285 (2.0%) had a diagnosis of

IBD. Of these 1,285 patients, 839 (65.3%) had ulcerative colitis, 435 (33.9%) Crohn's disease, and 11 (0.9%) indeterminate IBD).

Patient characteristics and surgical factors according to IBD status are outlined in Table 1. Patients with IBD tended to be much younger than non-IBD patients, with a third of IBD patients aged under 60 years. IBD patients more commonly had right-sided tumours (caecum/ ascending colon/ hepatic flexure/ transverse colon) compared to non-IBD patients. The proportion of patients with rectal cancer was similar across cohorts.

IBD patients were less commonly diagnosed via primary care referral or the NHS Bowel Cancer Screening (BCSP) programme [32], and were more likely to be diagnosed through an emergency admission or an "other source", which includes endoscopic surveillance. IBD patients were more likely to have a more advanced cancer stage and more likely to require an emergency resection for colorectal cancer. IBD patients more commonly underwent total/subtotal colectomy, had open surgery and had a stoma formed at resection. Despite tending to be much younger, IBD patients had similar comorbidities, performance status and ASA grade.

Neoadjuvant and adjuvant treatment details, for patients with rectal cancer (England only) and stage III colon cancer (England and Wales) respectively, are presented in Table 2. Fewer rectal cancer patients with IBD underwent neoadjuvant radiotherapy (24.8% vs 36.0 %, $p<0.001$). Similar proportions of stage III colon cancer patients with and without IBD received adjuvant chemotherapy (57.7% vs 57.3% respectively, p=0.878).

Postoperative outcomes

Observed postoperative outcomes are shown in Table 3 and Table 4. IBD patients were more likely to undergo unplanned re-operation within 30-days of CRC resection (OR 1.31, 95% CI 1.12-1.54), have an unplanned hospital readmission within 30-days of surgery (OR 1.31, 95% CI 1.10-1.55), and have a postoperative stay greater than 14 days (OR 1.43, 95% CI 1.25-1.63). 90-day mortality for patients with IBD was similar to patients without IBD, although confidence intervals were wide because of low numbers of events in patients with IBD (OR 1.18, 95% CI 0.91-1.54).

The adjusted results in Table 4 show that some of the associations between IBD and unplanned re-operation and between IBD and unplanned hospital readmission were attenuated by patient and tumour characteristics (adjOR 1.22, 95% CI 1.04-1.44 and 1.17, 95% CI 0.98-1.39 respectively).

Two-year survival

Observed two-year cancer-specific mortality was substantially higher in IBD patients (SHR 1.35, 95% CI 1.18-1.55) (Table 4). CRC mortality was similar in the early postoperative period but increased in IBD patients later in follow-up (Figure 2). Adjustment for patient and tumour characteristics reduced the size of this association but it remained statistically significant (adjSHR 1.22, 95% CI 1.05-1.43).

Discussion

This national population-based study demonstrates that patients with IBD developing CRC are a distinct patient group, presenting at a younger age with more right-sided disease. The presence of IBD results in different surgical management, with more extensive resections, more open surgery, and a higher stoma rate. These differences in patient, tumour and particularly surgical management, are reflected in poorer outcomes for patients with IBD. Neoadjuvant radiotherapy for rectal cancer is less used in patients with IBD, whereas there are no differences in the use of adjuvant chemotherapy for colon cancer.

The characteristics of the IBD CRC patients compared to non-IBD CRC patients in this cohort are in line with previous studies. The average age of CRC diagnosis in IBD CRC patients has previously been shown to be 10 to 15 years younger than in patients without IBD [5]. There were also stark differences in the surgical management of patients in this cohort. Nearly a third of IBD patients with CRC underwent a subtotal or total colectomy, as opposed to a segmental resection, and a greater proportion had emergency surgery. These may be contributing factors in the observed differences in the rates of laparoscopic and open surgery across patient groups, which in turn may contribute to the longer length of stay demonstrated in the IBD cohort. Indeed, with adjustment for surgical factors, differences in length of stay disappeared. Ramsey *et al.* (2017) similarly demonstrated higher rates of total colectomy and open surgery amongst IBD CRC patients in a US population-based study [14]. Patients with IBD may undergo more extended resections for symptomatic relief of colitic symptoms, to reduce the risk of metachronous CRC, and to avoid the requirement for regular endoluminal evaluation of the remaining lower gastro-intestinal tract [33]. Some tumours are also found as incidental findings following planned colorectal resection for IBD symptoms.

IBD CRC patients with rectal cancer were less likely to undergo neoadjuvant radiotherapy. Possible explanations include an unexpected finding of a rectal cancer in the specimen of IBD patients having a panproctocolectomy, or reservations among radiation oncologists about administering radiotherapy to IBD patients with rectal cancer and active inflammation. A systematic review by

Tromp *et al.* (2015) demonstrated IBD to be associated with a moderate increase in both acute and late toxicity in rectal cancer patients undergoing external beam radiotherapy, but concluded that this risk must be balanced against potential gains in long-term survival [34]. Neoadjuvant radiotherapy is therefore likely to be avoided in IBD patients with rectal cancer if a straight to surgery approach is possible, with long course chemoradiotherapy offered if margins are threatened, to minimise risk of acute toxicity. Further research is required in a dedicated cohort of rectal cancer patients with IBD to further explore best practice in these patients.

The distinct presentation and management of CRC in patients with IBD is reflected in poorer postoperative outcomes, despite their much younger age at diagnosis. IBD CRC patients had increased risks of 30-day re-operation, 30-day unplanned readmission and long hospital stay. Unplanned re-operation after CRC surgery is most commonly undertaken for postoperative bleeding or anastomotic leak and is associated with increased local recurrence and poorer overall survival [35, 36]. Higher re-operation rates in the IBD cohort may relate to immunosuppression, malnutrition, active inflammation or infection at the time of surgery or the impact of biological therapies used to treat IBD [37]. As here, a US population-based study demonstrated IBD patients to have an increased likelihood of postoperative complications including wound infection and deep vein thrombosis, but not of postoperative mortality, and rates of re-operation were not analysed [14]. Postoperative deep vein thrombosis is a particular risk for patients with IBD and has led to recommendations for extended thromboprophylaxis after surgery including for non-malignant resections [38]. Risk of postoperative deep vein thrombosis in patients with IBD is associated with stoma formation (itself a marker of more severe disease or a more compromised patient), preoperative steroid therapy, ileoanal pouch formation and increased length of stay [39].

This highlights the importance of focused optimisation of patients with IBD pre-operatively, close monitoring of patients postoperatively, and enhanced informed consent to appropriately counsel patients regarding increased operative risks.

Cancer survival was found to be poorer in IBD patients, with the difference appearing later in follow-up rather than in the early postoperative period. The rates of receipt of adjuvant chemotherapy for stage III colon cancer did not differ between groups. However, we have not assessed the tolerability and completion of chemotherapy between patient groups to know whether early cessation of chemotherapy may have affected longer term outcomes. Treatment of patients on relapse, including the proportion of patients receiving palliative chemotherapy and its tolerance also has not been assessed. The high rate of stoma formation in the IBD CRC cohort, particularly ileostomies, may

result in increased risk of high stoma output, dehydration, acute kidney injury, and worse tolerance of adjuvant chemotherapy regimens.

The mechanism behind poorer CRC outcomes for IBD patients is unknown, although it has been postulated that it may be related to the nature of IBD-CRC, which is thought to develop through a dysplasia-carcinoma sequence secondary to chronic inflammation of colorectal mucosa, as opposed to the adenoma-carcinoma sequence commonly associated with sporadic CRC [40-42]. In colorectal cancer, right colon primary tumour location (PTL), which is more common in IBD patients, has been associated with poorer prognosis than left colon or rectal PTL [43]. The incidence of RAS and BRAF mutations associated with a poor prognosis and/ or lack of response to targeted agents appears to be greater in right PTL tumours [44, 45]. However, there is little data regarding the incidence of these mutations in IBD related colorectal cancers.

Previous studies of long-term cancer survival in IBD patients have had conflicting findings [13, 46-48]. Gearhart *et al.* (2012) in a US population-based study showed poorer cancer-specific survival for IBD-associated CRC compared to sporadic CRC (mean 32.9 months vs 42.4 months), whereas Wantanabe *et al.* (2010) found no difference between the groups [46, 48]. In a UK population-based analysis of CRC patients diagnosed between 2000 and 2010 (with or without surgical resection), IBD patients had significantly worse all-cause survival than sporadic CRC patients, with differences varying by cancer stage [13]. This up-to-date UK analysis of CRC patients undergoing major resection indicates that even when measuring only deaths from CRC, IBD CRC patients have a poorer prognosis than non-IBD CRC patients.

A limitation of this study is that patients with ulcerative colitis and Crohn's disease were grouped together in an IBD group for analysis to allow an adequate group size for adjustment for multiple risk factors in multivariable analysis. Postoperative outcomes were therefore not examined separately to understand if the poorer short- and long-term postoperative outcomes varied by disease entity. A further limitation of using routinely collected national data is the impact of missing data. Although generally data completeness was good, there were around 16% of patients with no recorded performance status and 15% with missing data regarding pre-treatment staging. The proportion of patients with missing pre-treatment staging was higher in the IBD group (20.8 vs 14.6%). A multiple imputation model including all risk factors and outcomes, was used to maximise the analysis cohort and reduce bias.

IBD patients were identified from ICD-10 codes in the HES/PEDW databases, however the duration, severity and extent of IBD was not known, nor the degree of active inflammation or the endoscopic surveillance that the patient had undergone. In addition, no medication data is included within the

HES/PEDW databases, therefore the pre-operative use of immunosuppressant and biological medications, and its impact upon postoperative outcomes, could not be determined.

This large cohort study demonstrates that the presentation and management of IBD patients with CRC is very different to patients with sporadic CRC. These differences are reflected in poorer cancer-specific survival compared to CRC patients without IBD, with the difference appearing after the early postoperative period.

Table 1: Baseline demographics and clinico-pathological characteristics of the 63,365 patients according to IBD status

			No IBD		IBD		
			N	%	N	%	
			62,080		1,285		p-value
Patient characteristics	Gender	Male	35,039	56.4	750	58.4	0.169
		Female	27,041	43.6	535	41.6	
	Age group (years)	<60	11,492	18.5	431	33.5	<0.001
		60-69	17,077	27.5	339	26.4	
		70-79	20,814	33.5	362	28.2	
		>=80	12,697	20.5	153	11.9	
	Index of Multiple Deprivation (IMD) Quintile	1	9,464	15.3	190	14.8	0.073
		2	11,306	18.2	249	19.5	
		3	12,993	21.0	302	23.6	
		4	14,035	22.6	266	20.8	
		5	14,186	22.9	273	21.3	
		Missing	96 (0.2)		5 (0.4)		
	Charlson Co-morbidity Score	0	33,540	54.0	679	52.8	0.433
		1	18,566	29.9	397	30.9	
		2+	9,974	16.1	209	16.3	
	ECOG Performance Status	Normal activity	27,742	53.0	582	54.5	0.084
		Walk & light work	16,790	32.1	320	30.0	
		Walk & all self care:up >50%	6,150	11.8	119	11.2	
		Ltd self care/ completely disabled	1,649	3.2	46	4.3	
		Missing	9,749 (15.7)		218 (17.0)		
	Referral Source	Emergency Admission	10,013	16.1	264	20.5	<0.001
		GP (Primary Care) Referral	35,065	56.5	456	35.5	
		Screening Referral	8,003	12.9	70	5.4	
		Other / Not Known	8,999	14.5	495	38.5	
Cancer characteristics	Tumour Site	Caecum/ Appendix/ Ascending Colon	17,805	28.7	393	30.6	<0.001
		Hepatic flexure	2,792	4.5	61	4.7	
		Transverse colon	4,213	6.8	137	10.7	
		Splenic flexure/ Descending colon	3,947	6.4	95	7.4	
		Sigmoid colon	14,661	23.6	226	17.6	
		Rectosigmoid	3,430	5.5	53	4.1	
		Rectum	15,232	24.5	320	24.9	
	Pre-treatment staging	1	10,835	20.5	249	25.0	0.001
		2	13,668	25.8	271	27.2	
		3	23,431	44.3	394	39.5	
		4	4,968	9.4	83	8.3	
		Missing	9,178 (14.8)		288 (22.4)		

	Pathological Staging	**1**	11,380	19.5	243	20.4	0.052
		2	21,798	37.4	401	33.6	
		3	20,427	35.1	443	37.1	
		4	4,615	7.9	106	8.9	
		Missing	3,860 (6.2)		92 (7.2)		
Surgical characteristics	**ASA grade**	**1**	7,569	12.9	140	11.6	0.339
		2	32,814	55.9	668	55.5	
		3	16,714	28.5	366	30.4	
		4+	1,573	2.7	29	2.4	
		Missing	3,410 (5.5)		82 (6.4)		
	Surgical Urgency	**Elective**	52,270	84.5	1040	81.1	0.001
		Emergency	9,612	15.5	243	18.9	
		Missing	198 (0.3)		2 (0.2)		
	Surgical procedure	**Right hemi/ Transverse colectomy**	25,483	41.1	444	34.6	<0.001
		Left hemicolectomy	2,678	4.3	38	3.0	
		Sigmoid colectomy	2,887	4.7	32	2.5	
		Total/subtotal colectomy	1,660	2.7	426	33.2	
		Anterior resection	20,332	32.8	168	13.1	
		Hartmann	4,704	7.6	64	5.0	
		APER/ PE	4,336	7.0	113	8.8	
	Surgical Access	**Open operation**	21,910	35.3	559	43.5	<0.001
		Laparoscopic converted	5,238	8.4	122	9.5	
		Laparoscopic completed	34,932	56.3	604	47.0	
	Stoma location	**None**	39,726	64.0	551	42.9	<0.001
		Ileostomy	11,533	18.6	548	42.6	
		Colostomy	10,821	17.4	186	14.5	

Table 2: Neoadjuvant and adjuvant treatment for patients with rectal cancer and stage III colon cancer

	No IBD		IBD		
	N	**%**	**N**	**%**	**p-value**
Rectal Cancer only	**14,170**		**303**		
Preoperative radiotherapy	5,100	36.0	75	24.8	<0.001
Stage III Colon Cancer only	**14,538**		**324**		
Adjuvant chemotherapy	8,329	57.3	187	57.7	0.878

Rectal Cancer: England only
Stage III Colon Cancer: England and Wales

Table 3: Observed postoperative outcomes

	No IBD		IBD		
	N	%	N	%	
	62,080		**1,285**		**p-value**
30 day unplanned reoperation	6,775	10.9	179	13.9	0.001
30 day unplanned readmission	6,125	9.9	152	11.8	0.020
90 day postoperative mortality	1,981	3.2	48	3.7	0.273
2 year mortality - all cause	10,103	16.3	282	21.9	<0.001
2 year cancer-specific mortality	8,305	13.4	228	17.7	<0.001
LOS*	**61,878**		**1,284**		
LOS >14 days	11,199	18.1	309	24.1	<0.001
Median LOS (IQR)	7	5, 12	9	6, 14	

*Only patients with an overnight stay included

Table 4: Unadjusted and adjusted postoperative outcomes

	Unadjusted				Adjusted*			
	OR	**95% CI**		**p-value**	**OR**	**95% CI**		**p-value**
30 day unplanned reoperation	1.31	1.12	1.54	0.001	1.22	1.04	1.44	0.017
30 day unplanned readmission	1.31	1.10	1.55	0.002	1.17	0.98	1.39	0.08
90 day postoperative mortality	1.18	0.91	1.54	0.21	1.17	0.88	1.56	0.29
Length of stay >14 days	1.43	1.25	1.63	<0.0001	1.53	1.32	1.77	<0.0001
	SHR	**95% CI**		**p-value**	**SHR**	**95% CI**		**p-value**
2 year cancer-specific mortality	1.35	1.18	1.55	<0.0001	1.22	1.05	1.43	0.011

*Adjusted for gender, age (in years, modelled as age and age2), IMD quintile, Charlson co-morbidity score, ECOG performance status, tumour site, admission type, ASA score, TNM stage and the interaction between age and distant metastases

OR: Odds Ratio
SHR: Subdistribution Hazard Ratio

Figure 1: Flow Chart showing full inclusion criteria

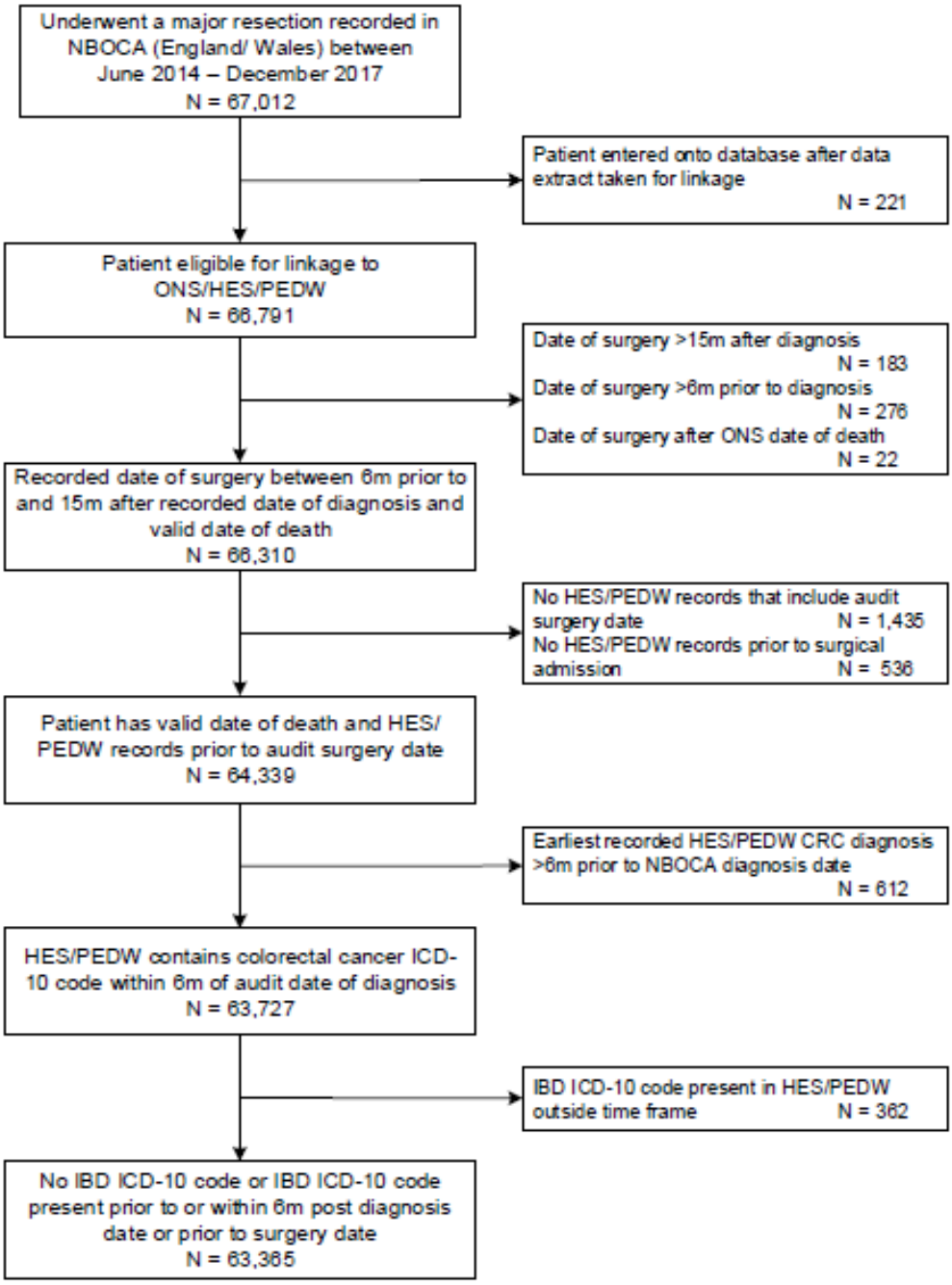
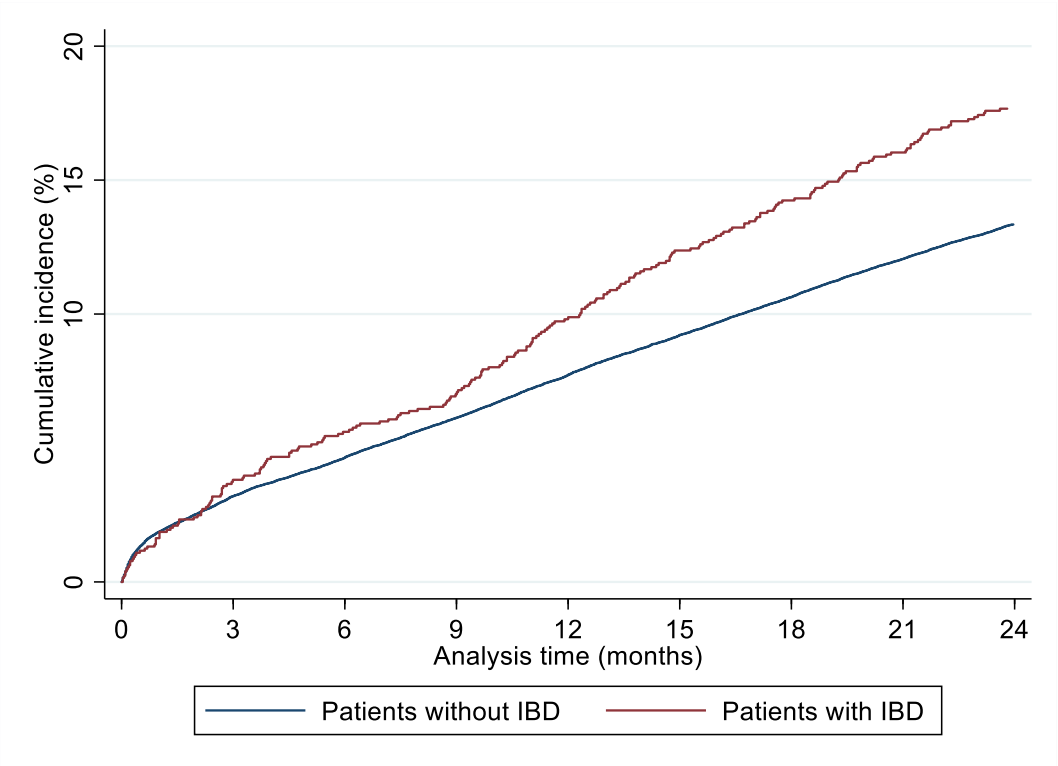


Figure 2: 2-year cumulative incidence of cancer-specific mortality by IBD status



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