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Functional outcomes and health-related quality of life following curative treatment for rectal cancer: A population-level study in England

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Summary

This large-scale population-level study investigated functional outcomes and health-related quality of life (HRQL) 12-36 months after curative rectal cancer treatment using linked survey and administrative data. We observed that patients who received pre-operative radiotherapy reported clinically and statistically significantly worse bowel and sexual function compared to patients who had surgery alone. Patients who received short-course radiotherapy reported worse bowel control than those who had long-course chemoradiotherapy. Patients with a stoma reported more sexual difficulties and worse HRQL outcomes.

Abstract

Background: There is a growing population of cancer survivors at risk of treatment-related morbidity. This study investigates how potentially curative rectal cancer treatment influences subsequent function and health-related quality of life (HRQL) using data from a large-scale survey of patient-reported outcomes.

Methods: All individuals 12-36 months post-diagnosis of colorectal cancer in England were sent a survey in January 2013. The survey responses were linked with cancer registration, hospital admissions and radiotherapy data through the National Cancer Registration and Analysis Service. Outcome measures were cancer-specific (FACT and Social Difficulties Inventory items related to faecal incontinence, urinary incontinence and sexual difficulties) and generic (EQ-5D).

Results: Surveys were returned by 6,713 (64.2%) of 10,452 rectal cancer patients. 3,998 were in remission after a major resection and formed the final analysis sample. Compared to those who had surgery alone, patients who received pre-operative radiotherapy had higher odds of reporting poor bowel control (43.6% vs. 33.0%; OR=1.55, 95%CI 1.26-1.91), severe urinary leakage (7.2% vs. 3.5%; OR=1.69, 95%CI 1.18-2.43) and severe sexual difficulties (34.4% vs. 18.3%; OR=1.73, 95%CI 1.43-2.11). Patients who received long-course chemoradiotherapy reported significantly better bowel control than those who had short-course radiotherapy, with no difference for other outcomes. Respondents with a stoma present reported significantly higher levels of severe sexual difficulties and worse HRQL compared to those who had never had a stoma or had undergone reversal.

Conclusions: This study demonstrates the feasibility of a large-scale assessment of patient-reported outcomes and provides 'real world' data regarding the impact of rectal cancer treatment. The results show that patients who receive pre-operative radiotherapy report poorer outcomes, particularly for bowel and sexual function, and highlight the negative impact of a stoma. We hope that our experience will encourage researchers to perform similar studies in other healthcare systems.

Introduction

Survival rates for patients with colorectal cancer have improved over recent decades. In the United Kingdom (UK) 59% of cases survive for more than five years(1) and in the United States (US) five-year survival is 65%.(2) Consequently, there is a growing population of survivors at risk of morbidity secondary to the disease and its treatment. There are now more than one million survivors of colorectal cancer in the US).(3)

Around 25-30% of colorectal cancers are located in the rectum. Whilst surgery is the main stay of curative treatment for rectal cancer, the selective use of pre-operative radiotherapy is indicated to lower the risk of loco-regional failure. Both short-course radiotherapy (SCRT) and long-course chemoradiotherapy (LCCRT) are used in keeping with the recommendations from international guidelines.(4, 5) The rate of permanent colostomy after surgery varies. However, in the UK almost 50% of rectal cancer patients have a stoma at 18 months post-surgery.(6) There is conflicting evidence as to whether quality of life is significantly different between patients who receive a temporary or permanent stoma and those who do not.(7)

The risk of local recurrence has been significantly reduced by the use of pre-operative radiotherapy, but without any clear impact on survival.(8, 9) However, the addition of pre-operative radiotherapy leads to an increased risk of late toxicity, particularly for bowel, urinary and sexual function. Most information on toxicity and quality of life outcomes is from randomised clinical trials(10) and relatively little population-based data is available.(11-13)

We chose to explore outcomes for rectal cancer patients using population-based data from the 2013 patient-reported outcome measures (PROMs) survey of colorectal cancer survivors in England.(14) We linked the survey responses to existing datasets (cancer registration, hospital admissions and radiotherapy) to investigate how potentially curative rectal cancer treatment influences subsequent function (bowel, urinary and sexual) and health-related quality of life (HRQL) 12-36 months after diagnosis.

Methods

Individuals diagnosed with colorectal cancer (ICD10(15) C18-20) in 2010 and 2011 in England were identified via the National Cancer Registration & Analysis Service (NCRAS). Those still alive in January 2013 were sent a postal survey with two reminders. The survey covered a range of areas, including HRQL, functional outcomes and social difficulties (Supplementary File 1) and was designed and administered by NHS England. The methodology has been described in more detail previously.(14, 16) This study includes only the respondents diagnosed with rectal cancer (n=10,452). The survey responses were linked with cancer registration, hospital admission and radiotherapy data through NCRAS who hold this information for all cancer patients.(17)

This study focused on the impact of potentially curative treatments, therefore patients who self-reported that they had active or recurrent disease, or that their cancer had not been treated were excluded (n=1,671). Through linkage with Hospital Episodes Statistics (HES) data,(18) surgical procedure was derived. For each individual, all episodes of care were searched using standard algorithms to identify the type and date of the major surgical resection undertaken to manage their rectal cancer.(19) Cases where no major surgical resection could be identified were excluded (n=589). Patients undergoing abdominoperineal excision (APE), anterior resection (AR) or Hartmann's procedure (HP) were included, whilst those undergoing other, less common types of rectal resection were excluded as the numbers were too small for robust analysis (n=302). Figure 1 details the cases included and excluded.

Stoma status (never formed, present or reversed) was defined using a combination of the PROMs survey data (two questions asked about stoma presence) and HES data (stoma-forming operation or specific stoma open and/or close codes). Where there was a conflict between the data sources the records were excluded (n=163). Using the major resection and stoma status information, records were split into the following categories for analysis: APE

(necessitates a permanent stoma); AR – Stoma present; AR – Stoma reversed; AR – No Stoma; HP – Stoma present; HP – Stoma reversed.

Information on receipt of radiotherapy was added through linkage with the Radiotherapy Data Set (RTDS), which is retrieved from the linear accelerators in use across England.(20) Using pre-defined algorithms based on the number of fractions delivered(21), individuals were split into those who received pre-operative SCRT (5 fractions either with immediate surgery [within 35 days; SCRT-I] or delayed surgery [>35 days; SCRT-D]), pre-operative LCCRT (25, 28 or 30 fractions), post-operative radiotherapy (up to a year after surgery; PORT) and those who did not receive any radiotherapy (surgery alone). In this study, the SCRT-I, LCCRT and surgery alone groups were compared. SCRT-D is a treatment generally used in more frail patients and PORT is not standard care.

Information on receipt of chemotherapy was limited and available only from the survey responses, as a self-reported 'Yes/No'. It was not possible to identify whether chemotherapy was received pre- or post-surgery, except where RTDS records indicated pre-operative LCCRT. Routine data on chemotherapy use in England is available through the Systemic Anti-Cancer Therapy (SACT) dataset, however for the period of this study these data were not complete and were not considered reliable enough for use.

Age, sex and stage of disease at diagnosis (TNM I, II, III, or IV) was obtained from cancer registration data. Postcode of residence at time of completion of the survey was used to measure socioeconomic background using the 2010 Index of Multiple Deprivation.(22) Information on the presence of other long-term conditions (LTCs) was derived from the survey and categorised as: none, one, two, three or more LTCs.

The PROMs survey collected information on faecal and urinary incontinence using FACT(23, 24). Specific items "I have control of my bowels" and "I leak urine" were analysed. Analyses relating to bowel control were limited to those without a stoma as individuals with a stoma present could interpret the question in different ways. One item relating to sexual function was

taken from the Social Difficulties Inventory(25): “Have you had any difficulties concerning sexual matters”. The possible response options to this item included ‘does not apply’. The patients who responded with ‘does not apply’ were excluded as the response is ambiguous, and could suggest either that the respondent is not sexually active or did not wish to answer. Generic HRQL was assessed using EQ-5D-5L.(26) This records self-assessed problems on five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression).

Binary logistic regression models were developed to assess the effect of curative treatments on bowel control, urinary leakage, sexual difficulties and HRQL. For bowel control, the outcome was categorised as ‘some/a little/no control’ versus ‘quite a bit/very much control’. For urinary leakage, the outcome was categorised as ‘quite a bit/very much leakage’ versus ‘some/a little/no leakage’. For sexual difficulties, the outcome was categorised as ‘quite a bit/very much difficulty’ versus ‘a little/no difficulty’. For HRQL, the outcome was categorised as reporting ≥1 problem on any EQ-5D domain (regardless of severity) versus no problems. Each model was run separately to assess the effect of pre-operative radiotherapy (compared to surgery alone), type of pre-operative radiotherapy (SCRT-I compared to LCCRT in patients who received radiotherapy), and stoma status (never formed compared to reversed and still present. All models were adjusted for relevant confounders, informed by univariable analyses and directed acyclic graphs. Analyses were undertaken using STATA version 15 (StataCorp, Tx, USA).

Results

Study population

The survey response rate for the rectal cancer survivors was 64.2% (6,713 out of 10,452). After exclusions, 3,988 rectal cancer cases were available for analysis (Figure 1). The median time between cancer diagnosis and completing a questionnaire was 770 days (interquartile range [IQR]: 596-944). The characteristics of the population are shown in Table 1. The majority (66.4%) of survivors were aged 55-74 years with a median age of 66 (IQR: 60-74

years). Two thirds (66.6%) were male. A quarter (24.0%) of respondents were diagnosed with stage I disease and 3.3% with stage IV. Half (49.7%) of the respondents lived in the most affluent areas (IMD quintiles 1 and 2). Comorbidity was common with 69.3% of individuals reporting one or more other LTCs and 17.5% reporting three or more.

Treatment received

Radiotherapy

Just under half (47.6%) of individuals did not receive radiotherapy (Table 1). Pre-operative LCCRT was given in 29.7% of cases and SCRT-I in 13.2%. Smaller proportions received PORT (1.1%) and SCRT-D (0.9%). A further 4.6% could not be classified (the number of fractions received did not fit any standard pattern) and 2.9% could not be linked. Table 2 details the characteristics of the SCRT-I, LCCRT and surgery alone groups. There was significant variation across the groups by age, socioeconomic deprivation, stage of disease, number of other LTCs and stoma status.

Surgery

AR was the most common operation performed (67.1% of cases), followed by APE (26.2%) and HP (6.7%). At survey completion, 44.1% of survivors had a stoma present, 40.4% had undergone a reversal and 15.5% had never had a stoma. There was significant variation across the three stoma groups by age, sex, socioeconomic deprivation, stage of disease, number of other LTCs and receipt of pre-operative radiotherapy (Table 2).

Chemotherapy

Just over half (54.2%) of the respondents ticked 'Yes' to having some form of chemotherapy. Of those reporting having chemotherapy, 58.1% had this in combination with pre-operative radiotherapy (LCCRT) according to the routine data. Around a third of those in the surgery alone (32.8%) and SCRT-I (35.7%) groups reported having some form of chemotherapy.

Impact on subsequent function

Faecal incontinence

Of the respondents without a stoma at the time of completing the questionnaire, 12.8% reported having no control of their bowels, 24.3% stated they had a little or some control, whilst 62.9% reported having quite a bit/very much control (Table 2). Respondents who had undergone a stoma reversal were more likely to report poor bowel control (none/a little/some control) than those who never had a stoma (39.6% vs. 30.7%; adjusted OR 1.37, 95% CI 1.10-1.73) (Table 4). Respondents who had pre-operative radiotherapy reported worse bowel control: 43.6% reported poor control compared to 33.0% in the no radiotherapy group (adjusted OR 1.55, 95% CI 1.26-1.91) (Table 4 and Figure 2a). Patients who had LCCRT reported better bowel control than those who had SCRT-I (39.9% vs. 50.6%; adjusted OR 0.64, 95% CI (0.46-0.89) (Table 4).

Urinary incontinence

Overall, 31.6% of respondents reported problems (of any severity) with leaking urine, and 5.4% reported severe problems (quite a bit/very much leakage) (Table 2). Severe problems were more commonly reported by those who had pre-operative radiotherapy (7.2% compared to 3.5% in those who did not have radiotherapy; adjusted OR 1.69, 95% CI 1.18-2.43) (Figure 2b and Table 4). There was no evidence of a difference between the two radiotherapy subgroups (Table 4).

Severe problems were most common in those who underwent an APE (10.0%) and least common in those who had an AR with stoma reversal (2.8%). Respondents with a stoma present had higher odds of reporting severe problems than those who never had a stoma (8.4% compared to 3.1%; adjusted OR 2.05, 95% CI 1.16-3.61). There was no difference between the respondents who had undergone stoma reversal and those who never had a stoma.

Sexual difficulties

Excluding those who answered 'does not apply' (n=1,132), 55.2% reported difficulties (of any severity) with sexual matters, and 37.6% reported severe difficulties (quite a bit/very much) (Table 2). Receipt of pre-operative radiotherapy resulted in a higher level of difficulties (47.7% answered quite a bit/very much compared to 26.7% in those who did not receive radiotherapy; adjusted OR 1.73, 95% CI 1.43-2.11) (Figure 2c and Table 4). There was no evidence of a difference in outcomes between the two radiotherapy subgroups (Table 4).

Severe difficulties were most commonly reported by those who underwent APE (54.0%) or AR with stoma still present (50.8%). Respondents who underwent AR with no stoma reported fewer severe difficulties (18.2%). Respondents with a stoma present reported the highest level of severe sexual difficulties (51.9%), followed by the group whose stoma had been reversed (31.3%) and those who never had a stoma (18.3%). The adjusted ORs were 3.71 (95% CI 2.70-5.12) for the stoma present group and 1.71 (95% CI 1.25-2.32) for the stoma reversed group compared to those who never had a stoma.

Some 29.8% answered 'does not apply' (Table 2). The proportion of respondents answering in this way increased with age ($p<0.001$) and was higher in those with a stoma present ($p<0.001$). A smaller proportion of females reported severe sexual difficulties (23.5% compared to 42.8% in males, $p<0.001$), but females were more likely to answer 'does not apply' (41.8% compared to 23.9%, $p<0.001$). Supplementary Table 1 shows the level of sexual difficulties reported by males and females separately.

Impact on health-related quality of life

Overall, 32.9% reported no HRQL problems (on EQ-5D) whilst 67.1% reported ≥1 problem. A higher proportion of respondents who had pre-operative radiotherapy (either SCRT-I or LCCRT) reported ≥1 HRQL problem than those who did not have radiotherapy (70.0% compared to 62.6% respectively), but this was not statistically significant after adjustment

(OR=1.14, 95% CI 0.97-1.34) (Table 4). There was no difference in outcomes between the two radiotherapy subgroups.

Regarding operation type, HRQL problems were highest in those individuals who had an AR with a stoma still present (78.5%), followed by HP with stoma present (74.6%) and APE (72.8%) and lowest in those individuals who had an AR with no stoma (55.0%) (Supplementary Figure 1). Overall, 74.6% of those with a stoma still present reported ≥1 problem, followed by 62.9% of those who had their stoma reversed and 55.0% of those without a stoma. The adjusted ORs were 2.42 (95% CI 1.92-3.04) for the stoma present group and 1.14 (95% CI 1.13-1.74) for the stoma reversed group compared to those who never had a stoma.

Discussion

This study is the largest assessment of HRQL and functional outcomes in rectal cancer survivors after treatment with curative intent in a population-based setting. It demonstrates the feasibility of this process in the English NHS and the willingness of patients to complete a one-off survey. It also shows how linkage with routinely collected clinical datasets can enhance the level of information available. The results show that patients who received pre-operative radiotherapy reported clinically and statistically significantly worse bowel and sexual function. The presence of a stoma also impacted negatively on HRQL and sexual function outcomes. Despite the exclusions through non-response to the survey and the focus on patients treated curatively, these data are much more representative of 'real world' outcomes compared to trials. Only around 5% of colorectal cancer patients in England enter intervention trials(27) and these individuals tend to be younger and fitter than the patient population as a whole, thus skewing outcomes.

Patients who received pre-operative SCRT and LCCRT experienced greater impairment of bowel function compared with surgery alone, with worse outcomes for SCRT than LCCRT. The analysis presented here is based on the reporting of some, little or no control. If we look only at those reporting little or no control (i.e. severe dysfunction), the results show 25.9% of

the SCRT group and 21.4% of the LCCRT group reporting this level of impairment and the difference is no longer statistically significant (p=0.284). In the clinical trial setting, the MRC CR07(28) and Dutch TME(29) trials both reported a similar pattern. In addition, we observed that SCRT resulted in worse bowel function compared with LCCRT. This finding is different to the trial data. The Polish(30) and TROG(31) randomised phase III trials reported no significant difference in late toxicity between SCRT and LCCRT. The reported rates, however, are low and are clinician assessed which may underestimate toxicity.(10)

A possible confounding factor is that the target volumes used are likely to have been larger for the use of SCRT than for LCCRT. During the time of the survey, the SCRT target volume commonly reflected the Swedish approach, with a superior border of the sacral promontory and the anterior border 2-3 cm beyond this point. In contrast, LCCRT target volumes were CT planned and more conformally contoured. Intensity modulated radiotherapy (IMRT) was not used during this period. Unfortunately, we do not have access to field size or target volume data to test this hypothesis.

Rates of sexual difficulties were higher in patients who had received radiotherapy, with fewer difficulties reported by females. This pattern of reporting has been seen in other rectal cancer trials(32-34), however, high rates of missing data, particularly in women, are found. In the CR07 trial, only 11% of women completed items on sexual function and they were unable to report these data.(28) In this study, 4% of males and 6% of females did not respond to the item on sexual difficulties. Of those that responded, 24% of males and 42% of females answered 'does not apply'. Without additional information on the reasons for these responses, for example, whether the patients were sexually active or not, these data are difficult to interpret and so were excluded from the analysis of sexual difficulties.

Regarding urinary incontinence, the proportion of respondents reporting problems was low, as seen in several trials.(29, 35, 36) Whilst there was evidence of a difference between those

who did and did not have pre-operative radiotherapy, the observed difference is of limited clinical importance.

The results show a clear difference in the outcomes of those with and without a stoma. This is in contrast to the Cochrane review (last updated 2012) which compared quality of life in rectal cancer patients with or without permanent colostomy.(7) Whilst they found some differences in outcomes, these were not always in favour of non-stoma patients, and no firm conclusions could be made. In this study, respondents without a stoma (never formed or reversed) were less likely to report HRQL problems than those with a stoma present. Stoma status also had a clear impact on sexual function, with the level of difficulties being consistently greater in the stoma groups, as has been shown by other studies.(37, 38) This dysfunction may be physical, due to damage to the pelvic anatomy by surgery and radiotherapy, or psychological, with the presence of a stoma itself being the cause of the difficulties. Late reversal of stomas may be beneficial, in terms of function and overall HRQL, in appropriately selected patients; however, the resulting function will be dependent on the height of the tumour within the rectum. Data on tumour height is not routinely available and could not be included in this study.

The strengths of the study are the large number of respondents and the method of identifying eligible individuals using population-based cancer registration data. The survey achieved a good response rate of 64%, which is comparable to other similar studies,(39-41) with low levels of missing data. The routine datasets utilised in this study are comprehensive and cover all patients treated in the English NHS.

There are limitations and learning points from our study. It is a single retrospective cross-sectional snapshot. It therefore lacks a control group and baseline data. The study was not designed to measure outcomes over multiple time points, however, comparison of those 12-24 months and 24-36 months post-diagnosis showed no differences in HRQL or functional outcomes (data not shown). Individuals aged under 55 or over 85, those from non-white ethnic

groups and those living in the most socio-economically deprived areas were less likely to participate in the survey.(14) Generalisability is limited to patients with good oncologic outcomes (in remission) and those who have survived at least 12 months from diagnosis. The findings may reflect worse disease at the outset, hence the use of pre-operative radiotherapy or the creation of a stoma. Whilst we have data on stage, this was missing in 7% of cases and does not always reflect stage prior to any down-sizing with radiotherapy. The routine radiotherapy data contains limited data on dose and we were unable to look at the effect of this on outcomes. Analysis by the number of fractions received by the LCCRT patients (25, 28 or 30 fractions) showed no significant differences in HRQL or functional outcomes, although the numbers in each group were relatively small and not sufficiently statistically powered for this analysis (Supplementary table 2). Additionally, limited data was available on use of chemotherapy and this prevented detailed analysis of outcomes in relation to this treatment. Data on other important considerations, such as performance status and patient choice are not routinely available.

Studies of patient-reported toxicity report higher rates of symptoms than clinician-reported studies,(10) with patients reporting on a wider range and milder side effects, which are not systematically reported in trials publishing clinician-reported toxicity. The selection of appropriate, psychometrically validated scales to measure outcomes is crucial. The use of FACT-C limited our ability to assess differences in bowel control between stoma and non-stoma patients. Only one item on sexual function was included in the survey thereby limiting more detailed analysis. Instruments such as the Lower Anterior Resection Syndrome Score(42) or EORTC-CR29(43) may be better suited to assessing multiple toxicity items including bowel urgency and vaginal dysfunction.

Conclusion

This study demonstrates the feasibility of a large-scale assessment of patient-reported outcomes and provides ‘real world’ data regarding the impact of rectal cancer treatment. In

addition, it highlights the advantages of linking together different datasets to enhance the amount of information available. The results show that patients who receive pre-operative RT report poorer outcomes, particularly for bowel and sexual function, and highlight the negative impact of a stoma. These findings highlight key areas on which to focus to improve the on-going care and support of patients treated curatively for rectal cancer. We hope that our experience will encourage researchers to perform similar studies in other healthcare systems and that they can learn from our approach.

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Table 1: Characteristics of the study population

Characteristic		n	%
Age at diagnosis	<55	494	12.4
	55-64	1,176	29.5
	65-74	1,471	36.9
	75-84	759	19.0
	85+	88	2.2
Sex	Males	2,657	66.6
	Females	1,331	33.4
Index of Multiple Deprivation quintile	1 (Most affluent)	990	24.8
	2	994	24.9
	3	897	22.5
	4	661	16.6
	5 (Most deprived)	446	11.2
Stage at diagnosis	I	957	24.0
	II	1,034	25.9
	III	1,572	39.4
	IV	132	3.3
	Unknown	293	7.4
Number of long-term conditions	0	997	25.0
	1	1,278	32.1
	2	785	19.7
	≥3	699	17.5
	No response	229	5.7
Surgical procedure (with stoma status)	APE (with permanent stoma)	1,044	26.2
	AR - Stoma present	497	12.5
	AR - Stoma reversed	1,563	39.2
	AR - No stoma	616	15.5
	HP - Stoma present	218	5.5
	HP - Stoma reversed	50	1.3
Radiotherapy	No RT	1,900	47.6
	SCRT - immediate surgery	526	13.2
	SCRT - delayed surgery	34	0.9
	LCCRT	1,186	29.7
	Post-op RT	45	1.1
	Other RT	182	4.6
	No link	115	2.9
Chemotherapy	No	1,826	45.8
	Yes	2,162	54.2
Total		3,988	100

APE: Abdominoperineal excision; AR: Anterior resection; HP: Hartmann's procedure; RT: Radiotherapy; SCRT: Short-course radiotherapy; LCCRT: Long-course chemoradiotherapy

Table 2: Variation in characteristics by treatment type

Characteristic		Pre-operative radiotherapy None *n=1,900*	SCRT-I *n=526*	LCCRT *n=1,186*		Stoma status Present *n=1,759*	Reversed *n=1,613*	Never *n=616*	
Age at diagnosis	**<55**	9.5	12.0	17.4		11.2	14.8	9.6	
	55-64	28.9	30.0	30.9		26.2	32.9	30.0	
	65-74	36.5	39.0	36.1	p<0.01	36.3	37.1	38.0	p<0.01
	75-84	21.6	17.5	15.2		23.1	14.4	19.5	
	85+	3.5	1.5	0.4		3.2	0.9	2.9	
Sex	**Males**	65.5	68.1	68.4	p=0.21	68.3	67.1	60.4	p<0.01
	Females	34.5	31.9	31.6		31.7	32.9	39.6	
Index of Multiple Deprivation quintile	**1 (Most affluent)**	26.7	20.7	23.8		22.5	26.0	28.6	
	2	26.3	28.3	21.8		24.3	25.8	24.5	
	3	21.8	27.9	21.9	p<0.01	22.7	22.7	21.4	p=0.01
	4	15.8	16.3	17.5		18.2	14.9	16.4	
	5 (Most deprived)	9.4	6.7	15.0		12.4	10.7	9.1	
Stage at diagnosis	**I**	32.7	23.8	11.6		20.3	27.5	25.5	
	II	29.3	26.8	20.7		26.0	23.5	32.0	
	III	32.1	43.0	48.7	p<0.01	39.7	40.4	36.2	p<0.01
	IV	2.3	3.0	4.3		4.4	2.4	2.4	
	Unknown	3.6	3.4	14.7		9.6	6.3	3.9	
Number of long term conditions	**0**	24.2	23.2	28.2		22.5	28.7	22.6	
	1	31.2	31.9	33.3		32.0	32.1	32.0	
	2	20.9	19.6	17.9	p<0.01	20.4	18.4	20.9	p<0.01
	≥3	18.6	16.5	14.7		19.4	15.1	18.5	
	No response	5.1	8.7	5.9		5.7	5.6	6.0	
Stoma status	**Present**	27.5	51.3	63.9		0.0			
	Reversed	44.9	43.2	34.2	p<0.01	0.0			
	Never formed	27.6	5.5	1.9		0.0			
Pre-operative radiotherapy	**None**					33.7	57.4	91.1	
	SCRT-I					17.4	15.3	5.0	p<0.01
	LCCRT					48.9	27.3	3.8	
Total		**100**	**100**	**100**		**100**	**100**	**100**	

SCRT-I: Short-course radiotherapy – immediate surgery; LCCRT: Long-course chemoradiotherapy

Table 3: Functional outcomes by treatment type

		'I have control of my bowels' (in the past week)					
		Very much	**Quite a bit**	**Somewhat**	**A little**	**Not at all**	**Total**
All respondents (without a stoma)		**760 (35.4%)**	**590 (27.5%)**	**347 (16.1%)**	**176 (8.2%)**	**276 (12.8%)**	**2,149 (100%)**
Surgical procedure	AR/HP - Stoma reversed	467 (30.0%)	474 (30.4%)	282 (18.1%)	159 (10.2%)	177 (11.4%)	1,559 (100%)
	AR - No stoma	293 (49.7%)	116 (19.7%)	65 (11.0%)	17 (2.9%)	99 (16.8%)	590 (100%)
Pre-operative radiotherapy	No (surgery alone)	524 (41.7%)	319 (25.4%)	169 (13.4%)	77 (6.1%)	169 (13.4%)	1,258 (100%)
	Yes	156 (24.0%)	211 (32.4%)	134 (20.6%)	77 (11.8%)	73 (11.2%)	651 (100%)
Type of radiotherapy	SCRT-I	46 (19.2%)	72 (30.1%)	59 (24.7%)	30 (12.6%)	32 (13.4%)	239 (100%)
	LCCRT	110 (26.7%)	139 (33.7%)	75 (18.2%)	47 (11.4%)	41 (10.0%)	412 (100%)
Chemotherapy (any)	No	403 (36.6%)	283 (25.7%)	175 (15.9%)	87 (7.9%)	153 (13.9%)	1,101 (100%)
	Yes	357 (34.1%)	307 (29.3%)	172 (16.4%)	89 (8.5%)	123 (11.7%)	1,048 (100%)

		'I leak urine' (in the past week)					
		Not at all	**A little**	**Somewhat**	**Quite a bit**	**Very much**	**Total**
All respondents		**2,569 (68.4%)**	**831 (22.1%)**	**156 (4.2%)**	**115 (3.1%)**	**87 (2.3%)**	**3,758 (100%)**
Surgical procedure	APE (permanent stoma)	550 (55.7%)	276 (27.9%)	63 (6.4%)	53 (5.4%)	46 (4.7%)	988 (100%)
	AR - Stoma present	315 (68.3%)	103 (22.3%)	19 (4.1%)	13 (2.8%)	11 (2.4%)	461 (100%)
	HP - Stoma present	127 (64.8%)	46 (23.5%)	8 (4.1%)	8 (4.1%)	7 (3.6%)	196 (100%)
	AR/HP - Stoma reversed	1,149 (75.0%)	293 (19.1%)	43 (2.8%)	32 (2.1%)	14 (0.9%)	1,531 (100%)
	AR - No stoma	428 (73.5%)	113 (19.4%)	23 (400%)	9 (1.5%)	9 (1.5%)	582 (100%)
Pre-operative radiotherapy	No (surgery alone)	1,284 (72.1%)	367 (20.6%)	67 (3.8%)	38 (2.1%)	24 (1.3%)	1,780 (100%)
	Yes	1,051 (65.0%)	380 (23.5%)	70 (4.3%)	63 (3.9%)	53 (3.3%)	1,617 (100%)
Type of radiotherapy	SCRT-I	318 (64.1%)	121 (24.4%)	25 (5.0%)	20 (4.0%)	12 (2.4%)	496 (100%)
	LCCRT	733 (65.4%)	259 (23.1%)	45 (4.0%)	43 (3.8%)	41 (3.7%)	1,121 (100%)
Chemotherapy (any)	No	1,166 (68.7%)	378 (22.3%)	65 (3.8%)	55 (3.2%)	34 (2.0%)	1,698 (100%)
	Yes	1,403 (68.1%)	453 (22.0%)	91 (4.4%)	60 (2.9%)	53 (2.6%)	2,060 (100%)

		'Have you had any difficulties concerning sexual matters?' (in the past month)					
		None	**A little**	**Quite a bit**	**Very much**	**Total**	***Does not apply****
All respondents		**1,196 (44.8%)**	**471 (17.6%)**	**368 (13.8%)**	**635 (23.8%)**	**2,670 (100%)**	***1,132 (29.8%)***
Surgical procedure	APE (permanent stoma)	202 (30.5%)	103 (15.5%)	111 (16.7%)	247 (37.3%)	663 (100%)	*338 (33.8%)*
	AR - Stoma present	104 (34.1%)	46 (15.1%)	55 (18.0%)	100 (32.8%)	305 (100%)	*164 (35.0%)*
	HP - Stoma present	43 (38.7%)	21 (18.9%)	15 (13.5%)	32 (28.8%)	111 (100%)	*87 (43.9%)*
	AR/HP - Stoma reversed	554 (47.4%)	249 (21.3%)	152 (13.0%)	214 (18.3%)	1,169 (100%)	*379 (24.5%)*
	AR - No stoma	293 (69.4%)	52 (12.3%)	35 (8.3%)	42 (10.0%)	422 (100%)	*164 (28.0%)*
Pre-operative radiotherapy	No (surgery alone)	683 (55.1%)	226 (18.2%)	134 (10.8%)	197 (15.9%)	1240 (100%)	*566 (31.3%)*
	Yes	402 (34.2%)	213 (18.1%)	202 (17.2%)	359 (30.5%)	1176 (100%)	*453 (27.8%)*
Type of radiotherapy	SCRT-I	124 (24.6%)	67 (13.3%)	60 (11.9%)	106 (21.0%)	357 (100%)	*148 (29.3%)*
	LCCRT	278 (24.7%)	146 (13.0%)	142 (12.6%)	253 (22.5%)	819 (100%)	*305 (27.1%)*
Chemotherapy (any)	No	556 (49.1%)	193 (17%)	140 (12.4%)	243 (21.5%)	1132 (100%)	*603 (34.8%)*
	Yes	640 (41.6%)	278 (18.1%)	228 (14.8%)	392 (25.5%)	1538 (100%)	*529 (25.6%)*

APE: Abdominoperineal excision; AR: Anterior resection; HP: Hartmann's procedure; SCRT-I: Short-course radiotherapy – immediate surgery; LCCRT: Long-course chemoradiotherapy

Due to small numbers in the 'HP – Stoma reversed' group (some cells <5), this group has been merged with the 'AR – Stoma reversed' group

*The denominator for the percentages in this column is the total number of respondents plus the 'Does not apply' group

Table 4: Multivariable analysis of functional outcomes and health-related quality of life

		Severe faecal incontinence		Severe urinary incontinence		Severe sexual difficulties		≥1 EQ-5D problem	
		OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Pre-operative radiotherapy*	**No (surgery alone)**	1.00		1.00		1.00		1.00	
	Yes	1.55	1.26-1.91	1.69	1.18-2.43	1.73	1.43-2.11	1.14	0.97-1.34
Type of radiotherapy*	**SCRT-I**	1.00		1.00		1.00		1.00	
	LCCRT	0.64	0.46-0.89	0.98	0.63-1.52	0.93	0.70-1.21	1.04	0.82-1.33
Stoma status**	**Never formed**	1.00		1.00		1.00		1.00	
	Reversed	1.37	1.10-1.73	0.87	0.48-1.57	1.71	1.25-2.32	1.41	1.13-1.74
	Present	*Excluded*		2.05	1.16-3.61	3.71	2.70-5.12	2.42	1.92-3.04

SCRT-I: Short-course radiotherapy – immediate surgery; LCCRT: Long-course chemoradiotherapy

*Pre-operative radiotherapy and type of radiotherapy models adjusted for age, sex, other long term conditions, surgical procedure

**Stoma status models adjsuted for age, sex, other long term conditions and receipt of pre-operative radiotherapy

Figure 1: Selection of the study population

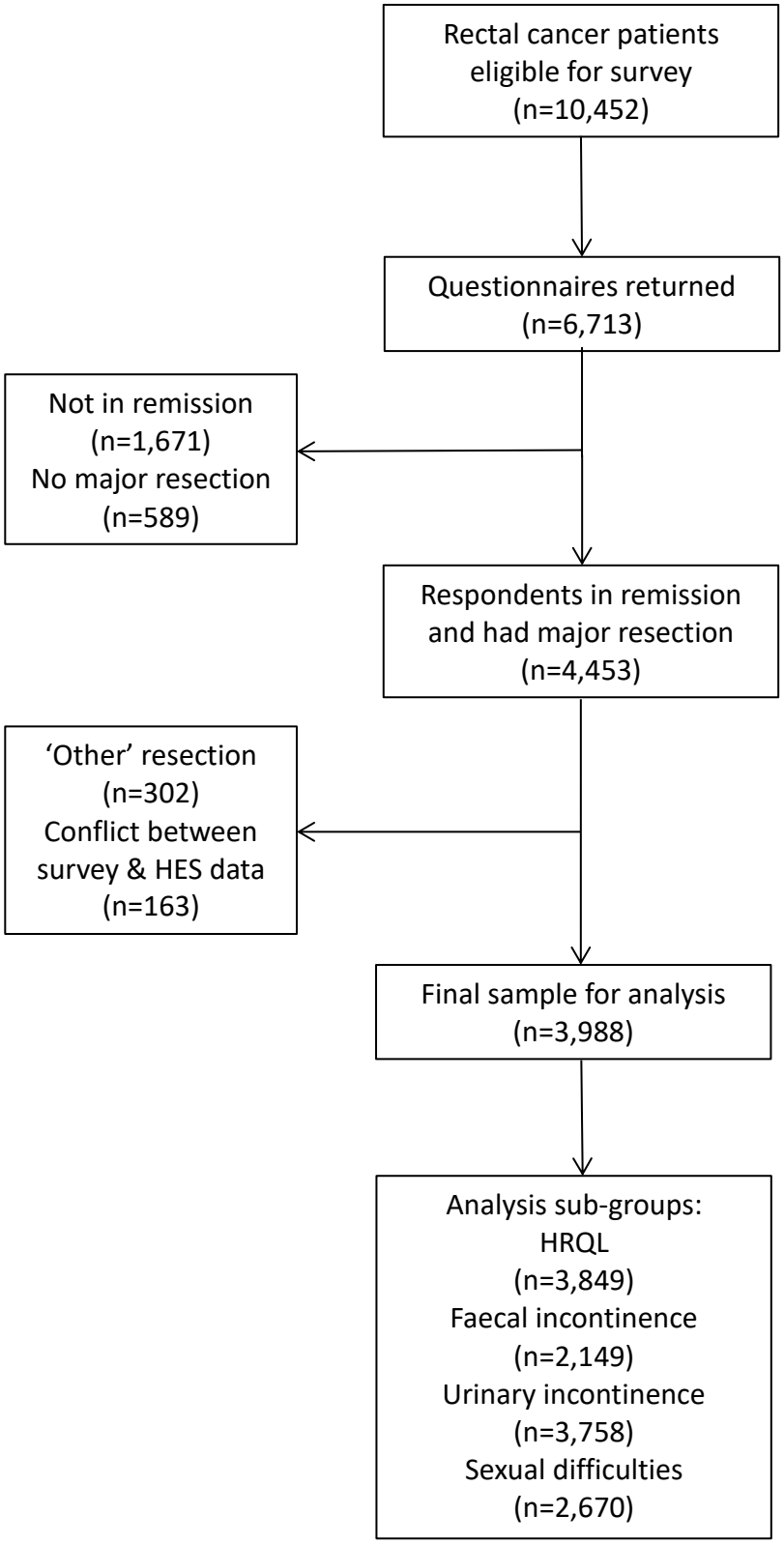
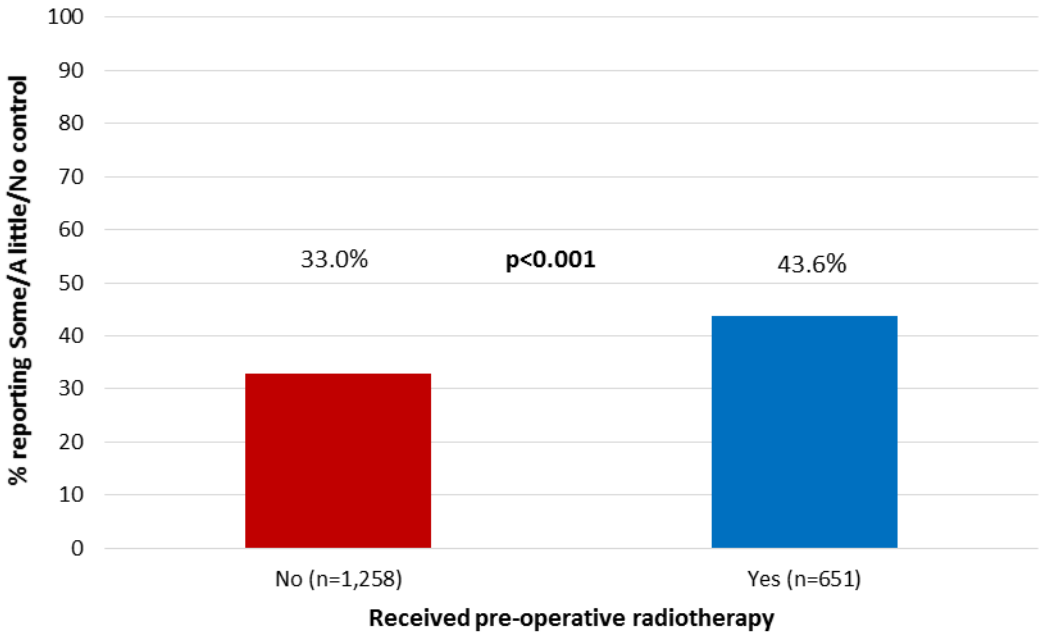
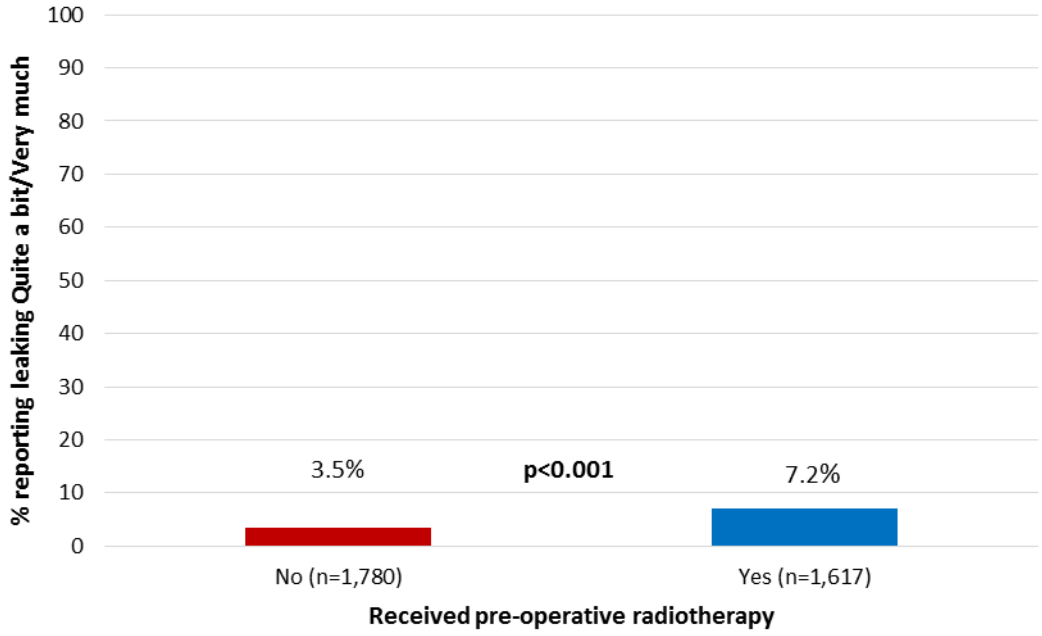


Figure 2: Functional outcomes in patients who did and did not receive pre-operative radiotherapy

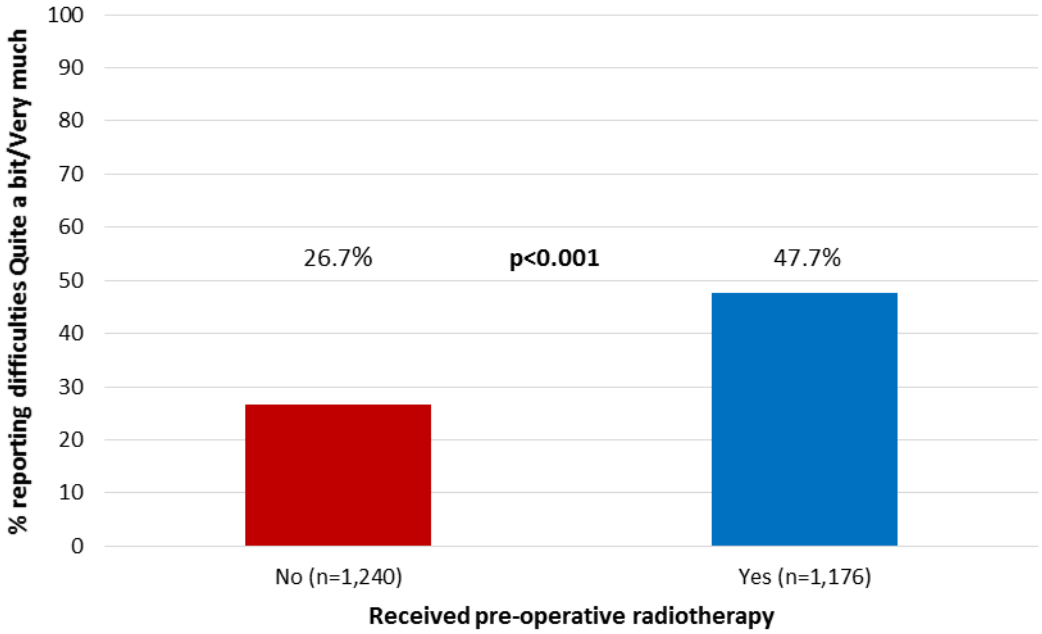
a: Faecal incontinence (non-stoma patients)



b: Urinary incontinence



c: Sexual difficulties



2a: Based on responses to FACT item 'I have control of my bowels'
2b: Based on responses to FACT item 'I leak urine'
2c: Based on responses to SDI item 'Have you had any difficulties concerning sexual matters?'

Supplementary file 1: Copy of the survey

Supplementary Table 1: Reported sexual difficulties in males and females

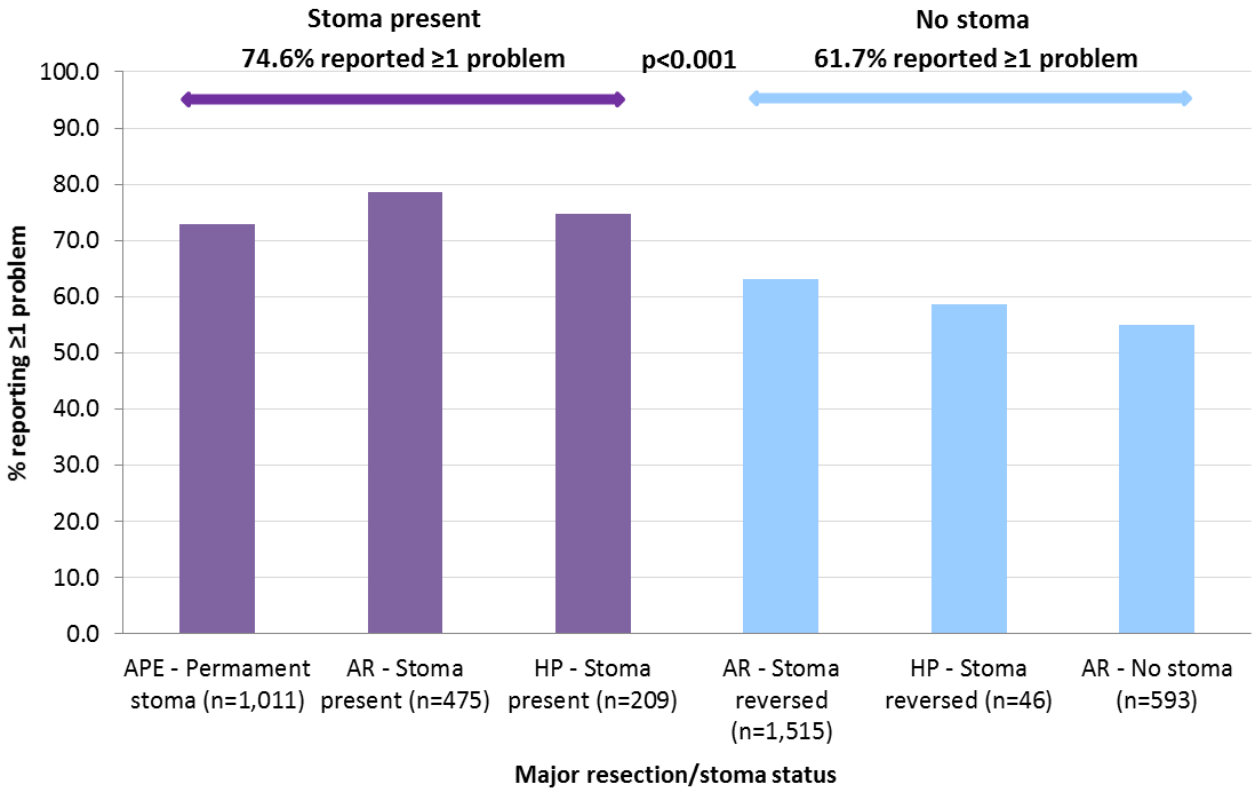
	None	A little	Quite a bit	Very much	Total	*Does not apply**
Males	765	345	296	536	1,942	*609*
	(39.4%)	(17.8%)	(15.2%)	(27.6%)	(100%)	*(23.9%)*
Females	431	126	72	99	728	*523*
	(59.2%)	(17.3%)	(9.9%)	(13.6%)	(100%)	*(41.8%)*
All respondents	1,196	471	368	635	2,670	*1,132*
	(44.8%)	(17.6%)	(13.8%)	(23.8%)	(100%)	*(29.8%)*

*The denominator for the percentages in this column is the total number of respondents plus the 'Does not apply' group

Supplementary Table 2: Functional outcomes and health-related quality of life according to number of fractions received in the long-course chemoradiotherapy group

No. fractions	**No. respondents** ***(total=1,214)***	**Severe faecal incontinence** ***(n=431)***		**Severe urinary incontinence** ***(n=1,151)***		**Severe sexual difficulties** ***(n=833)***		**≥1 EQ-5D problem** ***(n=1,176)***	
25	943	131		65		311		644	
	(77.7%)	(39.7%)		(7.3%)		(48.0%)		(70.7%)	
28	226	32	p=0.65	20	p=0.23	67	p=0.15	162	p=0.72
	(18.6%)	(37.7%)		(9.4%)		(43.8%)		(73.0%)	
30	45	8		1		20		32	
	(3.7%)	(50.0%)		(2.3%)		(62.5%)		(74.4%)	

Supplementary Figure 1: Health-related quality of life by surgical procedure and stoma status



APE: abdominoperineal excision; AR: anterior resection; HP: Hartmann's procedure
Based on responses to EQ-5D (reporting ≥1 problem on any domain)