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Keywords:	neoadjuvant radiotherapy, surgery, rectal adenocarcinoma, rectal cancer

Five-year oncological outcomes after selective neoadjuvant radiotherapy for resectable rectal cancer

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Abstract

Introduction

There is considerable variation in selection of patients for and type of neoadjuvant radiotherapy administered in the treatment of resectable rectal cancer. The aim of this study was to report outcomes for patients with resected rectal cancer from a unit with step-wise selection for surgery alone, short course radiotherapy (SCRT) or downstaging chemoradiotherapy (LCCRT).

Material and Methods

Cohort analysis of patients with rectal adenocarcinoma resected with curative intent between 2008 and 2012 at a specialist regional colorectal surgery centre. The primary endpoints were local recurrence, metastatic recurrence, disease-free survival and overall survival. Exploratory uni- and multi-variable regression analyses were performed to identify predictive factors.

Results

Two-hundred and forty patients were treated by surgery alone, 90 patients received SCRT and 91 patients received LCCRT. Five-year local recurrence was 10.8% in the surgery alone group, 3.3% in the SCRT and 18.7% with LCCRT. Metachronous distant metastasis was highest in the SCRT group (13.8% surgery alone, 25.6% SCRT, 15.4% LCCRT). Uni- and multi-variable regression analysis found that local and distant recurrence was attributable predominantly to adverse tumour biology.

Conclusion

Patients selected for SCRT had a lower rate of local recurrence than patients selected for surgery alone, but were more likely to develop distant metastasis. There was no difference in overall survival. With low local recurrence rates, distant metastasis is the predominant risk for patients with resectable rectal cancer.

Keywords: neoadjuvant radiotherapy, surgery, rectal adenocarcinoma, rectal cancer

Introduction

There is considerable world-wide variation in selection of patients for neoadjuvant radiotherapy in rectal cancer. 'Downstaging' long course chemoradiotherapy (LCCRT) is the most commonly used modality worldwide. In some centres it is given to all patients with stage II or III disease, in others reserved for locally advanced tumours with predicted surgical margin involvement to achieve operability with a negative circumferential resection margin (CRM). Short course radiotherapy (SCRT; 25Gy in five fractions over 1 week followed by immediate surgery) originated in Northern Europe, is easier to deliver and achieves similar local control to LCCRT [1-5]. However, surgery alone can achieve low rates of local recurrence in carefully selected patients with stage I-III disease [6, 7]. Even within the English National Health Service (NHS), the proportion of patients with surgically treated rectal cancer receiving some form of radiotherapy ranged from 5% to 78%, confirming considerable variation in practice between different hospital cancer multidisciplinary meetings (MDM) [8].

Neoadjuvant radiotherapy for rectal cancer is given to reduce local recurrence. Apart from the first Swedish trial, in which local recurrence in the control arm was exceptionally high, it has not been shown to improve cancer-related or overall survival. Furthermore, a non-selective approach to neoadjuvant radiotherapy carries a significant risk of over-treating patients with low risk tumours, exposing them to short and long term adverse effects on bowel and genitourinary function [9, 10].

Given the lack of consensus on management of rectal cancer it is important that clinical trial results are backed up by data from daily practice. Here we report 5-year outcomes for rectal

cancer surgery from a regional UK colorectal cancer centre in which patients are selected for surgery alone, SCRT or LCCRT based on clinico-radiological assessment and MDM discussion.

Material and Methods

Consecutive patients diagnosed with rectal adenocarcinoma and treated via the Lothian Colorectal Cancer MDM at the Western General Hospital, Edinburgh, between 1st January 2008 and 31st December 2012, were identified from the prospectively-compiled Southeast Scotland Cancer Network (SCAN) registry. This MDM is the sole centre for treatment of rectal cancers in Lothian region (population 850,000). Hospital electronic patient records were interrogated to retrieve additional data not provided by the database, including patient demographics, pre-operative staging, neoadjuvant and adjuvant treatment, operation type and histopathology. Tumour location within the rectum was determined by clinical measurement from the anal verge where this was recorded and dichotomised to upper rectum (≥10cm) or mid/lower rectum (<10cm); if absent, a determination of tumour location was made from clinical information (e.g. palpable tumours were deemed to lie in the mid/lower rectum) or MRI scan reports. Socioeconomic status quintiles were obtained from the Scottish Index of Multiple Deprivation Postcode Lookup function (http://www.gov.scot/Topics/Statistics/SIMD/SIMDPostcodeLookup). Primary outcomes were local recurrence, distant metastatic recurrence, disease- free survival and overall survival. Date of death was obtained from hospital electronic patient records, which are updated from National Records Scotland daily. Date of local or distant recurrence was determined from date of first radiological or clinical diagnosis.

Selection of patients for neoadjuvant radiotherapy was determined at a weekly MDM from clinical and radiological staging according to risk of local recurrence and proximity of tumour to the predicted CRM as per National Institute for Health and Clinical Excellence (NICE) guidelines. Patients deemed at high risk for local recurrence (tumour at or within 1mm of

predicted resection margin, involved resection margin, T4 disease, N2 disease, extra-mesenteric nodal disease, clinical fixity) received pre-operative LCCRT in the form of 45Gy in 25 fractions over 6 weeks with sensitising capecitebine, followed by re-staging and a delay of 8-12 weeks to surgical resection. Patients with contra-indications to chemotherapy agents but deemed high risk for local recurrence were treated with 20 fractions of radiotherapy over a four-week period (52.5 Gy) followed by delayed surgery. For the purposes of this analysis these patients were included in the LCCRT group. Patients with moderate risk of local recurrence (indicated by T3c/d tumour, and/orsuspicious mesorectal lymph nodes, and/orintramesenteric extramural vascular invasion) with non-threatened resection margins received SCRT (5x5Gy over 5 consecutive days) with resection 7-10 days after completion of treatment. Those deemed low risk (cT1-T3a disease, cN0) received surgery alone. Upper rectal tumours were treated as sigmoid colon cancers in most cases and were considered for neoadjuvant radiotherapy in only selected cases. All patients included in the main analysis had disease confined to the pelvis at the time of resection.

Selected patients with stage I rectal cancers were offered organ-preserving local resection by standard open transanal surgery or transanal endoscopic micro-surgery (TEMS) as their first line management. Patients were considered for local resection if the lesion was staged as T1, less than 3cm diameter, located in the mid- or distal rectum, with favourable histology (moderate to well differentiation, no evidence of lymphovascular invasion). Local resections were pre-dominantly reserved for patients with significant co-morbidities deemed unfit for major resection. Patients with polyp cancers (endoscopically completely excised adenomas containing a malignant focus) were managed depending on presence of conventional high risk features. Patients who underwent organ-preserving local resection are not included in these results. Patients who underwent local resection by any technique

followed immediately by radical resection are included in the cohort described in this report.

Adjuvant chemotherapy was offered to patients with pathological stage III disease and high-risk stage II disease (extramural vascular invasion, poorly differentiated or T4 primary tumour). Patients who had received downstaging LCCRT with significant or complete response were considered for adjuvant treatment based on clinicoradiological staging prior to radiotherapy.

Follow-up for patients managed with curative intent comprised 6-monthly clinic review for 4 years, two IV contrast-enhanced CT scans of the chest, abdomen and pelvis within the first 3 years, colonoscopic surveillance and 6-monthly serum carcinoembryonic antigen measurement. Patients with resectable metachronous metastatic disease were referred to the organ-specific MDM for further management, otherwise recurrent disease was managed with palliative intent.

A positive CRM was defined by histopathology as cancer <1mm from the ink-stained surgical resection margin (primary tumour or lymph node). Local recurrence was defined as tumour regrowth within the pelvis or perineum. Local recurrence analyses were performed on all eligible patients who underwent a macroscopically complete local resection.

Time-to-event analyses were calculated from date of diagnosis. Patients were censored at their last documented follow-up or hospital contact. Disease-free survival was calculated as time to first recurrence, local or distant. Overall survival was calculated as time from diagnosis to death by any cause using SPSS 24.0, comparing groups using Kaplan-Meier method and the log-rank test. Competing risk analysis was performed using methods proposed by Fine and Gray [11]. With death as a competing event, the cumulative incidence

rate was estimated for local recurrence, distant metastatic recurrence and disease-free survival. Gray's test was used to determine the significance of difference across patients treated by surgery alone, SCRT or LCCRT [11]. Univariable competing risk regression was used to estimate hazard ratios of variables known to be associated with recurrence/survival using data from the surgery alone and SCRT sub-groups only (n=330), excluding the LCCRT group because pathological variables are not representative of the pre-treatment primary cancer (the intention of radiotherapy being to downstage the tumour). Exploratory multi-variable regression was conducted using a backward stepwise model selection approach using two blocks to fit a competing risk model [12]. In this analysis, the BICcr criteria are modified based on Bayesian information criteria (BIC) to fit competing risk data where a log-transformed number of events instead of the sample size is used as the penalty parameter [13]. For overall survival, multi-variable analysis Cox proportional hazard regression backward stepwise (conditional LR) models were adopted. The first block comprised demographic (age, sex, SIMD quintile), surgical (operation: abdominoperineal excision of rectum (APER) v other; tumour location; plane of excision; positive CRM) and pathological data. The second block contained treatment variables (radiotherapy, chemotherapy). In order to overcome the issue of collinearity between multiple pathology variables, an 'Adverse Tumour' variable was created as a single composite categorical indicator of a poor prognosis tumour, defined by presence of any of the following adverse features: poor differentiation; T4; EMVI positive; N2/N2+. Analysis using an additive ordinal scale of these was explored but discarded due to a low number of cases scoring 3 or 4 points.

All competing risk analyses were performed in R (version 3.3.0) using the package 'cmprsk' [14]. With death as a competing event, the 5-year cumulative incidence rate was estimated and plotted for local recurrence and distant metastatic recurrence.

Results

Between 1st Jan 2008 and 31st December 2012 a total of 691 patients diagnosed with primary rectal adenocarcinoma were managed via the Lothian Colorectal Cancer MDM at the Western General Hospital, Edinburgh. Seventy-five (11%) patients underwent local excision via endoscopy, transanal polypectomy, or transanal endoscopic microsurgery (TEMS), and did not require, or were not fit for, subsequent radical resection. In all, 149 (22%) patients were treated with palliative intent from diagnosis, either as a consequence of metastatic disease at presentation, comorbidity which precluded surgical resection, or both. These patients were considered for defunctioning stomas, palliative radiotherapy, or supportive measures only depending on presentation.

Four hundred and sixty-seven patients underwent resection of the primary rectal cancer, of which 46 patients underwent resection in the presence of distant visceral or peritoneal metastasis, or clearly palliative resection of locally advanced/perforated disease. The remaining cohort of 421 patients (276 male (65.6%): 145 female) underwent surgical resection of the primary rectal cancer with curative intent. The mean age of the cohort was 66 years (SD 11.6, range 24-93 years).

Patient demographic, treatment and pathology variables by mode of neoadjuvant radiotherapy are shown in Table 1. Two hundred and forty (57%) patients were selected for surgery alone. Neoadjuvant short course radiotherapy (SCRT) was administered to 90 patients (22%) and neoadjuvant radiotherapy with down-staging intent (LCCRT) to 91 patients (21%). The overall permanent stoma rate (defined as a stoma which had not been reversed within 1 year of cancer resection) for the whole cohort was 35.2% (148/421). This number included a permanent stoma rate after initial restorative surgery of 15.5% (50/323).

Over half of the cohort was from the 4th and 5th SIMD quintiles (5=least deprived), indicating less deprivation, and hence better health status, than in some other regions of Scotland. There was no difference in SIMD quintile distribution in patients selected for surgical resection compared with the total cohort (p=0.712) and no relationship between SIMD quintile and oncological outcomes (Table 2 and Supplementary material).

Neoadjuvant radiotherapy was used much less frequently for upper rectal tumours compared to tumours in the middle and lower thirds of the rectum. A pathological positive resection margin (R1 resection) was identified in 38/421 (9.0%) patients. In 31 patients the positive resection margin was the primary tumour and in 7 patients a mesenteric lymph node. The rate of a positive resection margin was 4.4% (4/91) for upper rectal cancers and 10.3% (34/330) for cancers located in the mid/lower rectum (p=0.082).

There was complete pathological response to LCCRT in 13 of 91 (14.3%) patients. One patient had complete pathological response of the primary tumour but two positive lymph nodes were identified in the mesorectum.

In total 46 patients (10.9%) developed local recurrence. Of these, 16 patients had already developed metastatic disease prior to detection of local recurrence. Nine patients developed local recurrence (median interval from primary surgery to diagnosis of local recurrence 30 months, range 11-61 months) followed by distal metastatic disease after a further median interval of 14 months (range 4-53 months). True isolated recurrence without metastatic disease occurred in 21 patients (5%) after a median interval from primary surgery of 28 months (range 8-74 months).

The mean age (SD) of patients receiving adjuvant chemotherapy was 61.5 (10.6) years compared to 68.2 (11.5) years in those that did not.

Time-to-event survival analyses

Local recurrence was least frequent in the SCRT group compared to surgery alone or LCCRT (Figure 1). However, the SCRT group had the highest rate of distant metastasis (Figure 2). There was no difference in disease-free or overall survival between the groups.

Exploratory uni- and multi-variate competing risk regression analysis

In univariate analysis, pathology variables were much more strongly associated with oncological outcomes than treatment variables (Supplementary material).

In multivariate modelling, adverse tumour biology was the strongest predictive variable for local recurrence, distant metastasis, disease-free survival and overall survival. A positive CRM was an independent predictor of distant metastasis, disease-free survival and overall survival but not local recurrence. SCRT was predictive of reduced local recurrence. Male patients were more likely to develop distant metastases (Table 2).

Table 1: Demographic, treatment and histopathology data by mode of neoadjuvant treatment

		Surgery alone (n=240)	SCRT (n=90)	LCCRT (n=91)
Age (years) (median (range))		69 (33-93)	66.5 (40-82)	65 (24-83)
Male:female ratio		158: 82	58: 32	60: 31
Operation	Anterior resection	202 (84.2%)	68 (75.6%)	50 (54.9%)
	Abdomino-perineal excision	20 (8.3%)	19 (21.1%)	33 (36.3%)
	Hartmann's	10 (4.2%)	2 (2.2%)	5 (5.5%)
	Other*	8 (3.3%)	1 (1.1%)	3 (2.2%)
Tumour height	Upper third rectum	82 (34.2%)	3 (3.3%)	6 (6.6%)
	Mid/lower thirds of rectum	158 (65.8%)	87 (96.7%)	85 (93.4%)
Positive resection margin		13(5.4%)	9 (10.0%)	16 (17.6%)
Plane of surgery	Intramesorectal/ muscularis propria	36 (16.7%)	21 (23.3%)	20 (22.0%)
	Complete mesorectal fascia	180 (83.3%)	69 (76.7%)	71 (78.0%)
	Not reported	24	0	0
pT stage	y0	0	0	14 (15.4%)
	1	23 (9.6%)	3 (3.3%)	1 (1.1%)
	2	70 (29.2%)	19 (21.1%)	20 (22.0%)
	3	122 (50.8%)	62 (68.9%)	47 (51.6%)
	4	25 (10.4%)	6 (6.7%)	9 (9.9%)
pN stage	N0	149 (62.1%)	51 (56.7%)	58 (63.7%)
	N1	59 (24.6%)	26 (28.9%)	23 (25.3%)
	N2	32 (13.3%)	13 (14.4%)	10 (11.0%)
TNM stage	I	78 (32.5%)	17 (18.9%)	16 (17.6%)

	II	71 (29.6%)	34 (37.8%)	29 (31.9%)
	III	91 (37.9%)	39 (43.3%)	33 (36.3%)
	Complete pathological response	-	-	13 (14.3%)
EMVI positive		63 (26.3%)	31 (34.4%)	14 (15.4%)
Tumour grade	Poorly differentiated	16 (6.9%)	13 (14.6%)	9 (11.0%)
	Well/moderately differentiated	215 (93.1%)	76 (85.4%)	67 (88.2%)
	Missing/ not reported	9	1	15
Local recurrence		26 (10.8%)	3 (3.3%)	17 (18.7%)
Distant recurrence		33 (13.8%)	23 (25.6%)	14 (15.4%)
Adjuvant chemotherapy		65 (27.1%)	30 (33.3%)	52 (57.1%)

*1xProctectomy, 5xPanproctocolectomy and ileostomy, 2xPanproctocolectomy and IPAA, 3xPelvic exenteration, 1xTotal colectomy and ileorectal anastomosis.

Table 2: Exploratory multivariate regression analysis of rectal cancer variables in patients (n=330) receiving surgery alone or short-course radiotherapy (SCRT)

		HR, 95% CI	**P**
Local Recurrence	SCRT	0.274(0.082-0.914)	0.035
	'Adverse tumour'	2.924(1.387-6.165)	0.005
Distant Metastasis	Male sex	1.880(1.010-3.498)	0.046
	SCRT	1.918(1.127-3.265)	0.016
	CRM positive	2.491(1.239-5.018)	0.011
	'Adverse tumour'	2.992(1.644-5.446)	0.0003
Disease-free survival	CRM positive	3.044(1.571-5.898)	0.001
	'Adverse tumour'	2.768(1.651-4.642)	0.0001
Overall survival	Age	1.034 (1.014-1.053)	0.001
	CRM positive	2.696 (1.483-4.901)	0.001
	'Adverse tumour'	2.123 (1.382-3.256)	0.001

Discussion

This analysis reports the results of a consecutive cohort of rectal cancer patients treated over a 5-year period by surgical resection with curative intent, using a selective policy for short course or downstaging neoadjuvant radiotherapy. By definition, the groups that received surgery alone, SCRT, and LCCRT were not directly comparable because they were actively selected at the outset based on preoperative clinical/radiological staging. This analysis explores the relative contributions of radiotherapy, surgery, and tumour biology (pathology) to the overall outcomes.

Short course radiotherapy achieved significantly reduced local recurrence compared to patients selected for surgery alone. However, the SCRT group was more likely to develop distant metastatic disease than either the surgery alone group or the LCCRT group. Given that the SCRT group was selected on the basis that the primary tumour appeared more locally advanced on clinic-pathological staging than in the surgery alone group, it would be expected that systemic disease would be more likely than in the surgery alone group. However, that distant metastasis was greater than in the LCCRT group (the most locally advanced tumours) was unexpected. Selection for SCRT may have inadvertently identified a subgroup with greater propensity to systemic rather than local relapse, whereas those selected for LCCRT were perhaps more likely to advance locally than metastasise. It is also possible that the longer period of treatment required for LCCRT, and subsequent restaging, enriched this subgroup for more favourable tumour biology. However, only 7 patients received LCCRT with the intention of proceeding to surgery but were not resected due to local progression/non-response (3 patients) or development of systemic metastases (4 patients) during treatment (these patients are included in the 149 patients treated with

palliative intent). Twice as many LCCRT patients received adjuvant chemotherapy compared to SCRT patients, although the SCRT group contained some patients unfit for chemotherapy due to comorbidity.

Quality of surgery is a key determinant of outcome in rectal cancer surgery; indeed, new operations have arisen to overcome shortcomings in standard surgical technique (e.g. extra-levator perineal excision of rectum (ELAPE)) [15]. The surgical variables available in this dataset suggest that surgery was of reasonable quality: 80% of resections had a complete mesorectum and the overall positive resection margin was 9.0%. By comparison, the positive CRM rate was 15.2% in the UK MRC CLASICC study [16], 16% in the Dutch TME trial [17], 12% in a Danish short course radiotherapy registry report [18] and 10% in the CR07 trial [3]. A complete mesorectal excision, without defects, was achieved in 73.5% % in the COREAN study [19] and 52% in the CR07 trial [20]. Surgical factors which have been cited in previous reports as being associated with adverse outcomes, such as the type of operation (APER vs. anterior resection) [21], tumour location within the rectum (upper vs lower), or quality of mesorectal excision [20], were not risk factors for adverse survival outcomes in this cohort.

The main predictors of oncological outcome were pathological: poor differentiation, higher T and N stage and EMVI were all strongly associated with recurrence. As in the CR07 trial, a positive CRM was not independently predictive of local recurrence [20]. However, it was predictive of systemic disease recurrence, suggesting co-linearity of more locally advanced tumours with poor biological phenotype and therefore more difficult resection, rather than

poor quality surgery. In predicted medium-risk tumours, SCRT was effective in reducing local recurrence and hence negating a positive CRM as an independent risk factor.

The SCRT group had more advanced TNM staging and adverse histological features than patients selected for surgery alone. Nevertheless, over 50% of patients receiving SCRT were pathological stage I or II cancers, and hence over-staged by current assessment techniques. Although the surgery alone group contained a number of advanced tumours suggesting under-staging, many of these were upper rectal cancers which would not have been considered for neoadjuvant radiotherapy. As noted in other recent reports, preoperative nodal staging remains inaccurate [22]. This has implications if the Dutch TME subgroup analysis showing 10% survival advantage in node positive CRM negative patients that received radiotherapy is borne out in further analysis. Patients in the CR07 study that were CRM negative but node positive had local recurrence of 20% in 10 years. Better techniques for preoperative nodal staging are required.

A strength of this analysis is that it combines data granularity with a reasonably large cohort, and as the sole regional centre for management of rectal cancer there should be minimal loss of data for a retrospective study. We have reported the management of the entire rectal cancer cohort over this time period to set the cases selected for surgery in context. There was no association between socioeconomic status (SIMD) and selection for curative resection or oncological outcomes, suggesting that access to treatment across the region was equitable. However, it is difficult to overcome data collinearity: adverse pathological features tended to be aggregated in poor prognosis tumours and adjuvant treatments were selected based on clinical or pathological variables. Some variables (e.g.

Glasgow Prognostic Score, surgical complications) that have been shown to impact outcome were not available. Therefore, multivariate regression analyses should be interpreted with caution. Furthermore, no data on short- or long-term toxicity or treatment adjustments were available (other than reporting the number of cases that did not progress to surgery following LCCRT, see above). Our selection policy avoided neoadjuvant radiotherapy in >50% of the cohort; in the remainder we assume toxicities would be similar to existing data [9, 23].

In conclusion, neoadjuvant SCRT reduces local recurrence in resectable rectal cancer but selection remains suboptimal. Tumour biology has greater influence on outcomes than treatment variables. Distant metastasis is far more likely than local recurrence for patients with resectable disease, and a strategy of SCRT followed by immediate surgery allows prompt progression to systemic treatment when indicated.

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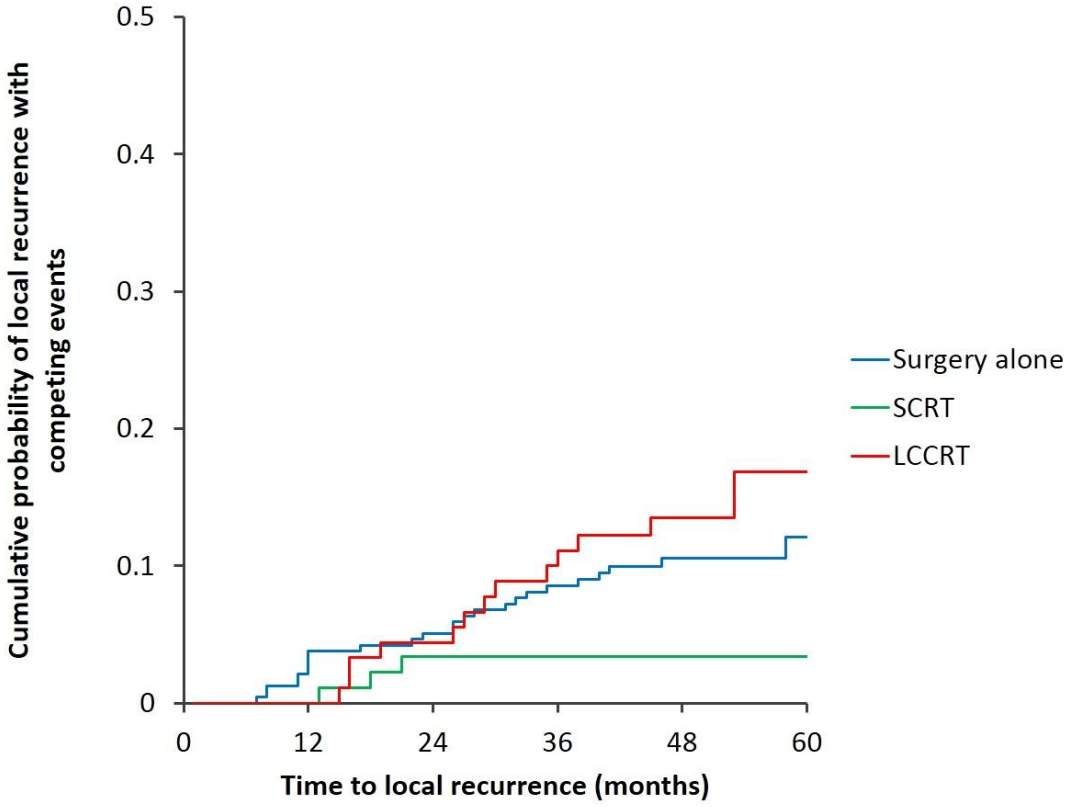
Figure 1: Cumulative probability of local recurrence with deaths as competing events

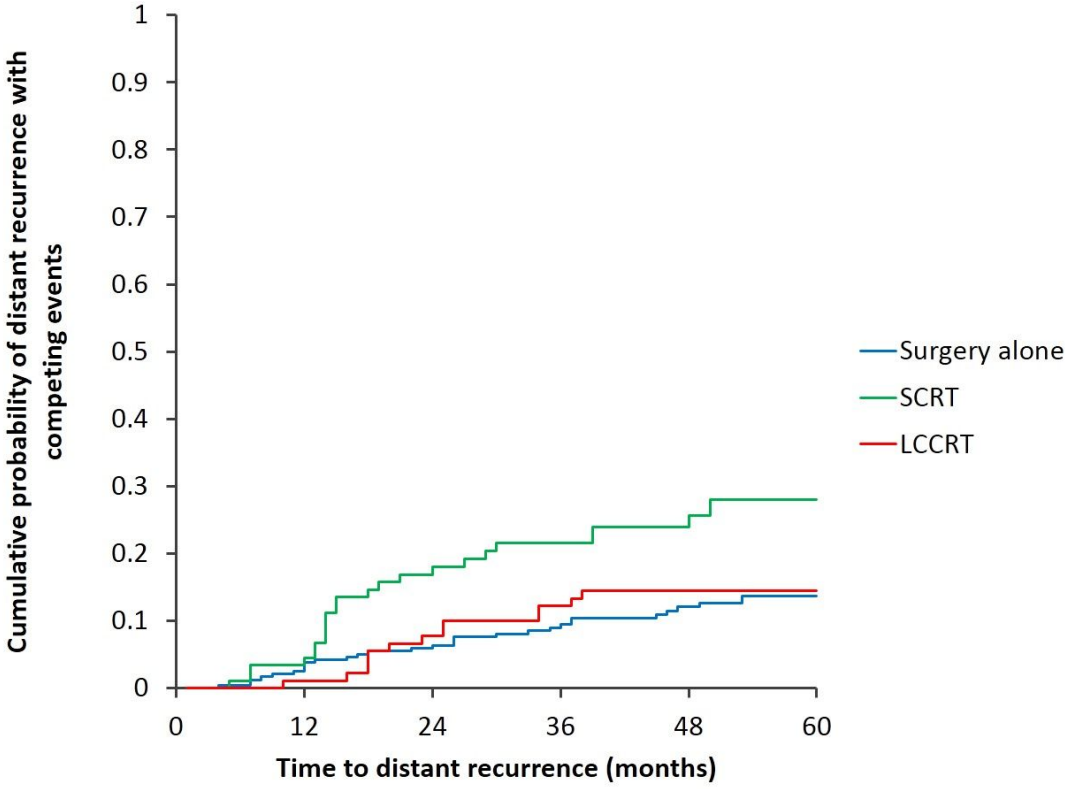


Number entering interval

Months:	0	12	24	36	48	60
Surgery alone	240	222	203	179	124	37
SCRT	90	86	79	69	44	16
LCCRT	91	90	80	72	56	27

Gray's test: Surgery alone v SCRT Chi2 4.553, p=0.033; Surgery alone v LCCRT Chi2 2.103, p=0.147; SCRT v LCCRT Chi2 8.839, p=0.003.

Figure 2: Cumulative probability of distant recurrence with deaths as competing events



Number entering interval

Months:	0	12	24	36	48	60
Surgery alone	240	224	202	180	124	38
SCRT	90	85	69	62	39	13
LCCRT	91	89	77	70	54	27

Gray's test: Surgery alone v SCRT: Chi2 7.223, p=0.007; Surgery alone v LCCRT: Chi2 0.014, p=0.905; SCRT v LCCRT Chi2 3.770, p= 0.052

Supplementary material: Univariate regression analysis of rectal cancer variables in patients (n=330) receiving surgery alone or short course radiotherapy (SCRT)

2.1 Local recurrence

		HR (95% CI)	p
Demographic	Age	0.992(0.960-1.020)	0.620
	Gender (male)	1.415(0.627-3.194)	0.400
	SIMD quintiles vs. most deprived		0.578
	2	2.105(0.243-18.245)	0.5
	3	2.175(0.240-19.713)	0.49
	4	3.864(0.493-30.310)	0.2
	5	2.243(0.277-18.136)	0.45
Treatment	SCRT vs. Surgery alone	**0.297(0.090-0.987)**	**0.047**
	Adjuvant chemotherapy	1.260(0.588-2.697)	0.55
	APER vs. other operation	0.523(0.126-2.164)	0.37
	Upper third vs. mid/lower	0.486(0.233-1.014)	0.055
	Incomplete mesorectal fascia	1.383(0.552-3.468)	0.49
Pathological	Positive CRM	2.385(0.808-7.044)	0.12
	Poor differentiation		
	Nodal status (vs. N0)	0.937(0.364-2.412)	0.89
	N1	**2.436(1.038-5.713)**	**0.041**
	N2	1.445(0.699-2.987)	0.32
	N+ vs. N-	**4.275(1.893-9.651)**	**0.00047**
	Lymphovascular invasion	**3.173(1.534-6.564)**	**0.0018**
	T3/4 vs. T0-2	**7.372(1.737-31.280)**	**0.0067**

2.2 Distant metastasis

		HR (95% CI)	p
Demographic	Age	**0.978(0.957-1.000)**	**0.05**
	Gender (male)	1.670(0.906-3.076)	0.1
	SIMD quintile vs. most deprived		
	2	1.328(0.430-4.102)	0.62
	3	1.658(0.542-5.073)	0.38
	4	1.246(0.421-3.681)	0.69
	5	0.889(0.293-2.704)	0.84
Treatment	SCRT vs. Surgery alone	**2.064(1.213-3.511)**	**0.0076**
	Adjuvant chemotherapy	**1.868(1.106-3.153)**	**0.019**
	APER vs. other operation	**1.998(1.037-3.847)**	**0.039**
	Upper third vs. mid/lower	0.917(0.522-1.608)	0.76
	Incomplete mesorectal fascia	0.750(0.353-1.594)	0.45
Pathology	Positive CRM	**4.239(2.143-8.383)**	**<0.0001**
	Nodal status (vs. N0)		
	N1	**2.479(1.342-4.577)**	**0.0037**
	N2	**4.201(2.174-8.117)**	**<0.0001**
	N+ vs. N-	**3.030(1.763-5.208)**	**<0.0001**
	Poor differentiation	**3.184(1.675-6.052)**	**0.00041**
	Lymph node ratio	**11.226(4.908-25.679)**	**<0.0001**
	Lymphovascular invasion	**3.162(1.879-5.319)**	**<0.0001**
	T3/4 vs. T0-2	**3.440(1.644-7.196)**	**0.001**

2.3 Disease-free survival

		HR (95% CI)	p
Demographic	Age	0.982(0.962-1.003)	0.092
	Gender (male)	1.246(0.868-1.791)	0.23
	SIMD quintile vs. most deprived		
	2	1.526(0.510-4.567)	0.45
	3	2.066(0.693-6.154)	0.19
	4	1.709(0.601-4.859)	0.31
	5	1.120(0.381-3.291)	0.84
Treatment	SCRT vs. Surgery alone	**1.414(1.069-1.870)**	**0.015**
	Adjuvant chemotherapy	**1.729(1.068-2.799)**	**0.026**
	APER vs. other operation	1.670(0.905-3.080)	0.1
	Upper third vs. mid/lower	0.827(0.494-1.387)	0.47
	Incomplete mesorectal fascia	0.905(0.472-1.736)	0.76
Pathology	Positive CRM	**4.635(2.499-8.597)**	**<0.0001**
	Nodal status vs. N0		
	N1	**1.781(1.007-3.153)**	**0.047**
	N2	**3.978(2.247-7.045)**	**<0.0001**
	N+ vs N-	**2.459(1.523-3.971)**	**0.00023**
	Poor differentiation	**4.056(2.333-7.051)**	**<0.0001**
	Lymph node ratio	**15.088(6.362-35.785)**	**<0.0001**
	Lymphovascular invasion	**3.092(1.926-4.965)**	**<0.0001**
	T3/4 vs. T0-2	**3.920(1.953-7.869)**	**0.00012**

2.4 Overall survival

		HR (95% CI)	p
Demographic	Age	1.036 (1.015-1.057)	**0.001**
	Gender (male)	1.131 (0.737-1.735)	0.573
	SIMD quintile vs. most deprived		
	2	1.361 (0.581-3.187)	0.478
	3	1.876 (0.805-4.374)	0.145
	4	0.956 (0.408-2.238)	0.917
	5	0.760 (0.324-1.780)	0.527
Treatment	SCRT vs. Surgery alone	0.931 (0.587-1.479)	0.763
	Adjuvant chemotherapy	0.693 (0.399-1.202)	0.192
	APER vs. other operation	1.563 (0.884-2.765)	0.125
	Upper third vs. mid/lower	0.927 (0.594-1.448)	0.740
	Incomplete mesorectal fascia	1.255 (0.757-2.079)	0.378
Pathology	Positive CRM	3.361 (1.899-5.948)	**<0.0001**
	Poor differentiation	3.615 (2.178-5.999)	**<0.0001**
	Nodal status vs. N0		
	N1	1.184 (0.727-1.930)	0.497
	N2	2.488 (1.515-4.085)	**<0.0001**
	N+ vs N-	1.592 (1.067-2.376)	**0.023**
	Lymph node ratio	10.593 (4.716-23.794)	**<0.0001**
	Lymphovascular invasion	2.271 (1.515-3.404)	**<0.0001**
	T3/4 vs. T0-2	2.169 (1.337-3.520)	**0.002**

SIMD, Scottish Index of Multiple Deprivation