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ORIGINAL ARTICLE

The Impact of Tumour Distance From the Anal Verge on Clinical Management and Outcomes in Patients Having a Curative Resection for Rectal Cancer

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Abstract

Aim The clinico-oncological significance of the distance of rectal cancer from the anal verge is unclear and not well reported. The aim of this study is to assess the influence of the rectal cancer distance from the anal verge on clinical management and long-term outcomes after curative resection in a specialised colorectal cancer unit.

Methods Prospectively collected data on patients who underwent primary rectal cancer treatment at our unit between January 2005 and December 2010 were analysed. Low rectal cancer (LRC) was defined as tumour < 5 cm from the anal verge on MRI scan. Recurrent cancer, palliative resections, perforated tumours and those requiring total pelvic exenteration were excluded.

Results Three hundred fifty-nine patients underwent surgery for rectal cancer (226 male/133 female). Of these, 149 (41.5%) patients had low rectal cancer (LRC). Compared to patients with mid/upper rectal cancer (M/URC), patients with low rectal cancers were significantly more likely to receive neo-adjuvant therapy (75.2 vs 38%; $p < 0.001$), to be associated with lower rate of restorative surgery (15.4 vs 79%; $p < 0.001$) and to have higher rates of pathological positive circumferential resection margin involvement (14.1 vs 7.1%; $p = 0.047$). There were however no significant difference in the rates of recurrent disease or survival among the two groups.

Conclusion Distance of rectal cancer from the anal verge does influence the use of neo-adjuvant treatment and ultimate R0 resection rate. It does not influence loco-regional or systemic recurrence rates.

Keywords Rectal tumour distance from anal verge · Circumferential resection margin · Rectal cancer · Anterior resection · Laparoscopic surgery · Restorative surgery · Abdominoperineal excision of the rectum (APER)

What Does This Paper Add to the Literature? Patients with low rectal cancers are significantly more likely to be treated with neo-adjuvant therapy, to be associated with non-restorative surgery and to have a higher incidence of positive circumferential resection margin compared to patients with mid/upper rectal cancers. However, the distance of rectal cancer from anal verge did not impact on the loco-regional or systemic recurrence rates and disease-free survival (DFS) and overall survival (OS).

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Introduction

The surgery for low rectal cancer is challenging. It can be associated with significant rates of positive circumferential resection margin (CRM) which can lead to recurrent disease, and a permanent stoma is not uncommon.[1–5] Therefore, the management of rectal cancer surgery has evolved in order to optimise clinical and oncological outcomes as much as possible. Advancements include total mesorectal excision (TME), neo-adjuvant chemo-radiotherapy, minimal access surgery, ultra-low restorative resection, extra-levator resection and transanal TME, all of which are underpinned by high-quality multidisciplinary team discussion.

In view of the challenges associated with low rectal cancer, intuitively one might expect outcomes to be worse than the mid/upper rectal cancer. However, there have been few studies assessing this specifically. The aim of this work was to assess the management and long-term outcomes after resection with curative intent for low rectal cancer (LRC)

compared with mid/upper rectal cancers (M/URC) in a major teaching unit.

Patients and Methods

This is a retrospective study from a prospectively maintained database on the Patient Pathway Manager (PPM) computerised system at the John Goligher Colorectal Unit in St James's University Hospital, Leeds. All elective rectal cancer resections undertaken with curative intent for adenocarcinoma of the rectum between January 2005 and December 2010 were identified. Patients having had local excision, emergency or palliative resections (R2 resection) and perforated tumours; those requiring total or multivisceral pelvic exenteration and those with distant metastasis (stage IV) were excluded. This data set was then cross referenced with the data from the UK Cancer Registry to ensure accurate numbers. Clinical data obtained as part of routine treatment was used for the purposes of this study, and therefore, no additional patient consent or ethical approval was required.

All the patients with rectal cancer were assessed clinically (including a digital rectal examination), by endoscopy, and a biopsy was taken. Assessment of the residual colon was undertaken either by colonoscopy or by computed tomography (CT) colonography. The staging of the cancer was carried out by using a high-resolution CT scan of the thorax, abdomen and pelvis and a high-resolution magnetic resonance imaging (MRI) of the pelvis. Low rectal cancer (LRC) was defined as a tumour < 5 cm from the anal verge. The tumour distance from the anal verge was assessed by high-resolution MRI scan as standard because this was formally measured and documented in every case. Mid to upper third rectal cancers (M/URC) were defined as rectal tumours between 5 and 15 cm from the anal verge on MRI scan.

It is our departmental protocol to discuss all patients diagnosed with rectal cancer in the colorectal multidisciplinary team meeting (MDTM) comprising surgeons, oncologists, radiologists, pathologists and specialist nurses. Patients were then assessed in clinic to discuss treatment options. Patients with locally advanced cancer, threatened circumferential resection margin (tumour within 1 mm of the CRM (mesorectal plane) on the pre-operative MRI scan) or suspected vascular or lymph node involvement were offered neo-adjuvant therapy (NAT) in the form of short-course radiotherapy (SCRT) or long-course chemo-radiotherapy (CRT) or SCRT with delay. Patients with SCRT underwent surgery within 1–2 weeks of completion of radiotherapy. Patients with long-course CRT or SCRT with delay were re-staged with CT scan of the thorax, abdomen and pelvis and MRI scan of the pelvis after 6 weeks and then re-discussed in the colorectal MDTM before undergoing resection within the next 2–4 weeks.

Restorative surgery was defined as anterior resection, ultra-low anterior resection and ileo-anal pouch surgery. Non-restorative surgery included abdomino-perineal excision of the rectum (APER), panproctocolectomy and Hartmann's procedure. Patients with direct tumour extension into adjacent organs or with multiple previous abdominal operations underwent open resection. The remaining patients were offered laparoscopic or open resection depending on the surgeon's practice. Post-operative management provided was similar for both open and laparoscopic surgery groups according to surgeon's preference. There were no enhanced recovery (ERAS) protocols in place during the study period, although these have subsequently been implemented.

The post-operative complications were defined as any significant complication occurred within 30 days from the immediate post-operative period. These include infection-related complications (wound, urinary, respiratory, intra-abdominal/pelvic collection, rectal stump leak and anastomotic leak), cardiac, thrombo-embolic, acute kidney injury, haemorrhagic, stoma-related, other organ injury and prolonged post-operative ileus/small bowel obstruction.

Patients were re-discussed in the colorectal MDTM after surgery. All post-operative resection specimens are examined by specialist GI pathologists. Tumours were staged according to the 5th Edition of the Union for International Cancer Control TNM staging system [6] in line with the recommendations of the Royal College of Pathologists in UK. The distance of the tumour from the surgical resection margin was measured macroscopically and microscopically and in addition the mode of involvement documented i.e. direct spread from the tumour or satellite deposit/lymph node involvement. Patients were classified according to the resection margin involvement into R0 (clear margin) and R1 (microscopic presence of tumour within 1 mm of a resection margin). When less than 12 lymph nodes were identified on initial assessment of the specimen, a further examination of the specimen was carried out to find all available lymph nodes.

Patients with lymph node metastases (stage III) and selected patients without lymph node metastases (stage II) but with adverse prognostic features (poorly differentiated cancers, extramural venous invasion, peritoneal and serosal involvement and positive CRM) were reviewed in an oncology clinic to assess and discuss the suitability for adjuvant chemotherapy.

Patients were followed up as per Yorkshire Cancer Network (YCN) guidelines. This included regular outpatient review (every 3 months for the 1st year, every 6 months for the 2nd year and then yearly for next 3 years), measurement of carcinoembryonic antigen (CEA) level at these visits, surveillance CT scans at years 1, 2, 3 and 5 years following resection and interval colonoscopy as per British Society of Gastroenterology (BSG) guidelines. If the CEA level was significantly high or found to be mildly raised persistently on two occasions, then patients were re-assessed clinically and

investigated as such with early colonoscopy, or CT scan of the thorax, abdomen and pelvis and MRI scan of the pelvis as deemed appropriate. Surveillance colonoscopy was undertaken at year 1 and then every 3 to 5 years following surgery. Recurrent disease was confirmed by radiological imaging (computed tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography (PET) scan) and if necessary by biopsy. Local or regional disease recurrence was defined as disease at or near the surgical resection site (pelvis) or within the draining lymphatic field. Systemic recurrence was defined as recurrent disease beyond this in other organs.

Statistical Analysis

Categorical variables were expressed as frequency and proportion (%), and continuous variables were presented as medians (range). Univariate analysis was carried out by using chi-square test or Fisher exact test to identify significant risk factors in relation to tumour distance from the anal verge and R1 resection margin; factors with statistical significance were then subjected to multivariate analysis using multimodal regression analysis to identify independent factors for R1 status. Kaplan-Meier survival curves were studied using log-rank statistics to assess which variables affected OS and DFS. The median survival time was extracted from the Kaplan-Meier survival curves and so was the 1-, 3-, 5- and 10-year DFS and OS. The variables which showed statistical significance (p value < 0.05) on Kaplan-Meier univariate analysis were subjected to multivariate analysis using Cox proportional hazards model and hazard ratio with 95% confidence interval calculated appropriately. The variables which were significant on multivariate analysis were considered as independent prognosticators of OS and DFS. The survival (DFS/OS) was measured from the date of initial surgical procedure. This was a non-randomised retrospective cohort study from a prospectively maintained data, and therefore, a power calculation was not undertaken. This was an intention-to-treat analysis mainly to assess the long-term oncological outcomes in relation to the tumour distance from the anal verge. All statistical analysis was carried out using SPSS for Windows version 20 (SPSS Inc., Chicago, IL, USA).

Results

Patient Demographics

There were 359 patients who underwent rectal cancer resection with curative intent over the study period. Of these, 226 (62.9%) were male and 133 (37.1%) were female. The median age was 68 years (range 21–93) and 70 years (range 28–91) in the low rectal cancer group and mid/upper rectal cancer groups respectively. The median number of lymph nodes retrieved was 15 (range 4–34) in the LRC group and 17 (range 2–60) in the M/URC group. Similarly, the retrieval of > 12 lymph nodes was achieved in 111/149 (74.5%) patients in the LRC group and 166/210 (79%) patients in the M/URC group. The post-operative complication rate was similar in the LRC group (33.6%) and the M/URC group (33.3%) of patients. The overall 90-day mortality was 5.8%. The median follow-up was 67 months (range 6–119 months). There were 12 (3.34%) patients who underwent partial excision of an adjacent organ (vaginal cuff = 8, sacrum = 3 and bladder wall = 1) with suspected direct tumour extension, and two of these cases were found to have an R1 resection. The demographics of the two groups and their associated factors are demonstrated in Table 1.

Post-operative complications identified were infection-related (n = 84, wound, urinary, sepsis, respiratory, pelvic including collection, rectal stump leak and anastomotic leak), cardiac (n = 6), thrombo-embolic (n = 4), acute kidney injury (n = 3), haemorrhagic (n = 3), stoma-related (n = 3), other organ injury (n = 6) and prolonged post-operative ileus/small bowel obstruction (n = 11). There were nine patients who underwent re-laparotomy due to anastomotic leak or small bowel obstruction.

Neo-Adjuvant Therapy and Disease Recurrence

There were a higher number of patients in the LRC group treated with neo-adjuvant therapy compared to the M/URC group (112/149 [75.1%] vs 80/210 [38.0%], p < 0.001) (Table 1). Among patients in the LRC group treated with neo-adjuvant therapy (n = 112), 51 (34.2%) received SCRT and 61 (41%) received long-course CRT (or SCRT with delay). In contrast, patients in the M/URC group (n = 80), that 47 (22.3%) received SCRT and 33 (15.7%) had long course CRT or SCRT with delay.

The incidence of isolated local recurrence, isolated systemic recurrence and combination of both local and systemic recurrence was 2.6, 16 and 8% in the LRC resection group and 1.9, 14 and 5.2% in the M/URC resection group, respectively. This was statistically insignificant (p = 0.339). However, an R1 resection had significant impact on the disease recurrence. In our cohort, 19/36 (52.8%) patients with an R1 resection had disease recurrence as compared to 67/323 (20.7%) patients with R0 resection (p < 0.001). The relationship of disease recurrence with tumour distance from the anal verge and circumferential resection margin involvement (R1) is shown in Table 2.

Type of Surgery

The type of surgery either restorative or non-restorative was influenced by the distance of rectal cancer from the anal verge. There were 126/149 (84.6%) patients in the LRC group who

Table 1 Demographics of low (LRC) and mid-upper third rectal cancer (M/URC) groups

Variables		Tumour < 5 cm (LRC) (n = 149)	Tumour > 5 cm (M/URC) (n = 210)	p value
Sex	Male	99	127	
	Female	50	83	0.297
Age	Age < 75	105	136	
	Age > 75	44	74	0.307
Neo-adjuvant therapy (NAT)	No	37	130	
	Yes	112	80	*< 0.001*
Type of surgery	Restorative	23	166	
	Non-restorative	126	44	*< 0.001*
Laparoscopic surgery	Yes	70	99	
	No	79	111	0.975
TNM stage	0–I	61	66	
	II	47	60	0.619
	III	41	84	0.108
CRM status	CRM negative (R0)	128	195	
	CRM positive (R1)	21	15	*0.047*
Tumour grade	Well-mod diff (G1–2)	134	189	
	Poor diff (G3)	15	21	0.983
Extramural vascular invasion	Absent	102	132	
	Present	47	78	0.324
Lymph node status	Negative	108	126	
	Positive	41	84	*0.019*
Post op chemotherapy	No	119	146	
	Yes	30	64	*0.038*
T stage	T0–2	76	79	
	T3	68	114	0.040
	T4	05	17	0.240
Lymph node count	< 12	38	44	
	> 12	111	166	0.376
Tumour recurrence	No	109	164	
	Yes	40	46	0.339
Complications	No	99	140	
	Yes	50	70	0.964

The italic entries are highlighting the significance only

had non-restorative surgery, compared to the M/URC group where 44/210 (20.9%) patients underwent non-restorative surgery ($p < 0.001$) (Table 1). Despite this, the oncological outcomes of DFS ($p = 0.199$) and OS ($p = 0.491$) were statistically insignificant in the restorative and non-restorative surgery groups. In a subgroup analysis of low rectal cancer only, again similar results were observed for DFS ($p = 0.103$) and OS ($p = 0.886$) in the restorative and non-restorative surgery groups.

The high incidence (n = 44/210, 20.9%) and indications of non-restorative surgery in M/URC group were multifactorial. Almost all the patients in the M/URC group who underwent non-restorative surgery were actually mid rectal tumours located within 6–8 cm from the anal verge. Non-restorative surgery was performed generally due to patient co-morbidities and concerns over high risk of anastomotic leak (n = 12), sphincter dysfunction (n = 3), intra-operative complication (n = 3), technical failure/misfired stapling device (n = 2), rectal cancer with polyposis (n = 8), locally advanced tumour (n = 7), intra-operative difficulties encountered due to body habitus and narrow pelvis (n = 6) and patient's choice (n = 3).

There were 27 patients identified in the LRC group who technically could have restorative surgery. However, non-restorative surgery was performed in these patients due to concerns over patients' multiple co-morbidities and high risk of anastomotic leak (n = 19), sphincter dysfunction (n = 4) and patient's choice (n = 4).

Table 2 Disease recurrence in relation to tumour distance from anal verge (LRC vs M/URC) and circumferential resection margin involvement (R0 vs R1)

	M/URC		*p* value[a]	LRC		*p* value[a]
Disease recurrence	R0 (*n* = 195)	R1 (*n* = 15)		R0 (*n* = 128)	R1 (*n* = 21)	
Local recurrence	4 (2%)	1 (6.7%)	0.312	3 (2.3%)	1 (4.8%)	0.459
Systemic recurrence	26 (13.3%)	4 (26.7%)	0.239	17 (13.3%)	7 (33.3%)	*0.047*
Local and systemic recurrence	8 (4.1%)	3 (20%)	*0.034*	9 (7%)	3 (14.3%)	0.377
Total	38 (19.5%)	8 (53.3%)	*0.005*	29 (22.7%)	11 (52.4%)	*0.007*

The italic entries are highlighting the significance only

M/URC mid to upper rectal cancer, *LRC* low rectal cancer, *R0* negative circumferential resection margin, *R1* positive circumferential resection margin

[a] *p* value by Fisher exact test

Mode of Surgery

Overall rectal cancer resection was laparoscopically completed in 156 (43.5%) patients, with laparoscopic converted to open surgery in 13 (3.6%) patients, while 190 (52.9%) patients had open surgery. Of the 149 patients with low rectal cancer, 68 (45.6%) had laparoscopically completed surgery with 2 (1.34%) patients having laparoscopic converted to open surgery, while 79 (53%) patients had open resection for LRC. There was no difference ($p = 0.975$) when compared to the 210 patients with mid-upper third rectal cancer, where surgery was laparoscopically completed in 88 (41.9%) patients with laparoscopic converted to open surgery in 11 (5.2%) patients, while 111 (52.9%) patients had open surgery.

Table 3 Patient demographics and risk factors for R1 resection margin

Variables		CRM negative (R0) *N* = 323	CRM positive (R1) *N* = 36	Univariate analysis	Multivariate analysis		
					OR	95% CI	*p* value
Sex	Male	204	22	0.856			
	Female	119	14				
Age	Age < 75	214	27	0.351			
	Age > 75	109	9				
Neo-adjuvant therapy	No	154	13				
	Yes	169	23	0.219			
Type of surgery	Restorative	176	13				
	Non-restorative	147	23	0.051			
Laparoscopic surgery	Yes	153	16				
	No	170	20	0.860			
TNM stage	0–I	127	0				
	II	96	11	*< 0.001*			
	III	100	25	*0.046*	0.30	0.12–0.74	*0.009*
Tumour grade	Well-mod diff (G1–2)	295	28				
	Poor diff (G3)	28	8	*0.017*	0.76	0.26–2.19	0.617
Extramural vascular invasion	Absent	224	10				
	Present	99	26	*< 0.001*	0.38	0.15–0.94	*0.037*
Lymph node status	Negative	223	11				
	Positive	100	25	*< 0.001*	0.14	0.01–0.29	*0.031*
T stage	T0–2	152	3				
	T3	151	31	*< 0.001*	2.27	0.47–10.8	0.305
	T4	20	2	0.540			
Tumour distance from anal verge	< 5 cm	109	21				
	> 5 cm	214	15	*0.005*	4.4	1.9–9.9	*< 0.001*

The italic entries are highlighting the significance only

CRM circumferential resection margin

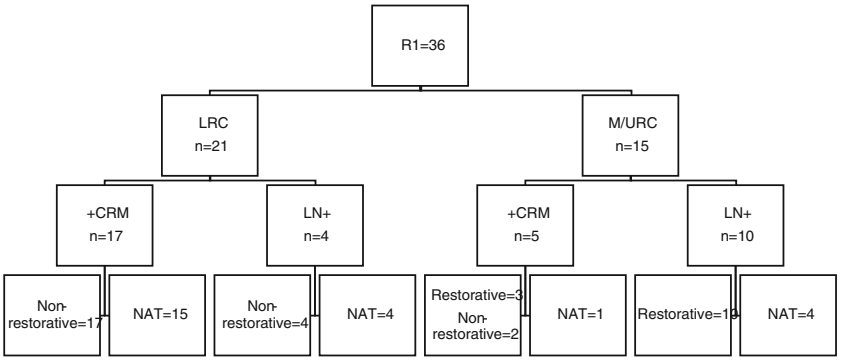

Fig. 1 R1 resections and their associations with tumour distance from the anal verge, neo-adjuvant therapy and type of surgery. *+CRM* circumferential resection margin less than 1 mm from the resection margin; *LN+* lymph node deposit < 1 mm from the resection margin; *LRC* rectal cancer at less than 5 cm from the anal verge; *M/URC* rectal cancer between 5 and 15 cm from the anal verge; *NAT* neo-adjuvant therapy

R1 Resections and Risk Factors

There were overall 36/359 (10.0%) R1 resections due to circumferential resection margin involvement. There was no case of proximal or distal resection margin involvement. The patient demographic data and analyses for risk factors for R1 resections are shown in Table 3. Patients with LRC were significantly associated with higher incidence of R1 resection compared to the M/URC group (21/149 [14.1%] vs 15/210 [7.1%], $p = 0.047$). On univariate analysis, the significant risk factors for R1 resection were advanced TNM stage (TNM II; $p < 0.001$ and TNM III; $p = 0.046$), increased tumour depth (T3–T4 tumour) ($p < 0.001$), poorly differentiated carcinoma ($p = 0.017$), presence of vascular invasion ($p < 0.001$), lymph node metastasis ($p < 0.001$) and low rectal tumour < 5 cm from the anal verge ($p = 0.005$). However, on multivariate analysis, only TNM stages II and III ($p = 0.009$), presence of vascular invasion ($p = 0.037$), lymph node metastasis ($p = 0.031$) and low rectal cancer < 5 cm from the anal verge ($p < 0.001$) were independent predictors.

There were two main types of R1 resections identified. Fourteen of 36 (38.9%) occurred due to lymph node deposit being < 1 mm from the resection margin. The remainders (22/36; 61.1%) occurred due to direct extension of the tumour. In the LRC group, the R1 resection was most frequently due to direct tumour extension (17/21; 81%) as compared to the M/URC group where an R1 resection was more common due to lymph node deposit (10/15; 66.7%) (Fig. 1). There was significantly higher incidence of administration of neo-adjuvant therapy (19/21; 90.5%) in patients with low rectal cancer as compared to mid-upper third rectal cancer (5/15; 33.3%) in R1 patients. Similarly, all patients ($n = 21$) with an R1 resection in LR cancer

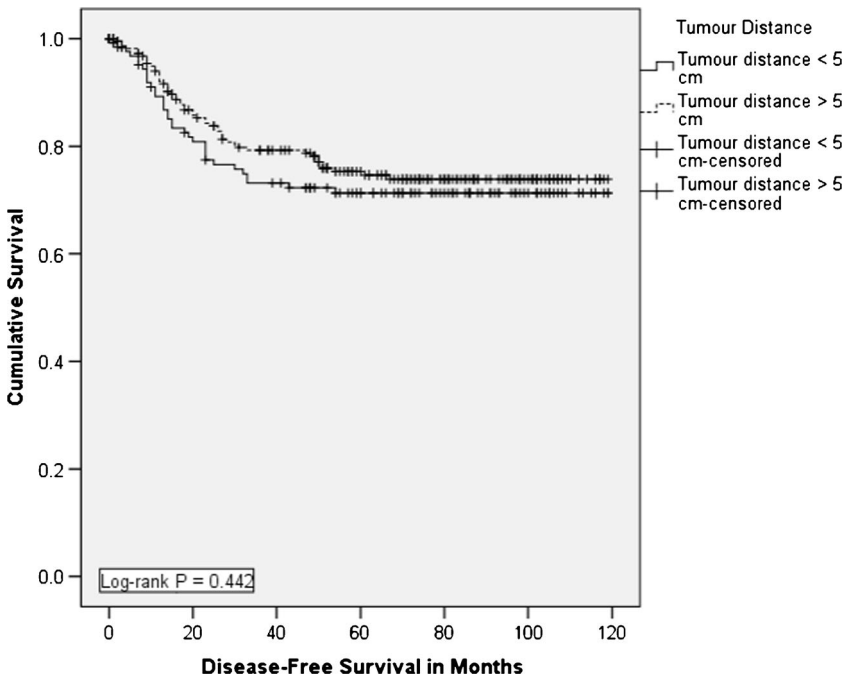

Fig. 2 DFS–LRC (tumour distance from the anal verge < 5 cm) vs M/URC (tumour distance from anal verge > 5 cm) groups

had non-restorative surgery in contrast to 2/15 (13.3%) patients in mid-upper third rectal cancer with an R1 resection who underwent non-restorative surgery.

Disease-Free Survival (DFS) and Overall Survival (OS)

The distance of tumour from the anal verge had no impact on the disease-free survival (DFS). The 1-, 3-, 5- and 10-year disease free survival (DFS) rates were 92, 74, 70 and 70% in the LRC resection group. These rates were similar to the DFS rates in the M/URC resection group (96, 80, 76 and 74%, $p = 0.442$) (Fig. 2). On univariate analysis, neo-adjuvant therapy (NAT), tumour depth (T stage), positive circumferential resection margin (R1), presence of vascular invasion, presence of lymph node metastasis, advanced TNM stage and post-operative adjuvant chemotherapy were predictors of DFS. On multivariate analysis, only NAT, positive CRM and positive lymph node (LN) status were independent predictors of DFS (Table 4).

Similar to the DFS, the distance of tumour from the anal verge had no impact on the overall survival (OS). The 1-, 3-, 5- and 10-year OS rates were 91, 78, 66 and 58% in the LRC resection group respectively. These rates were similar to the OS rates in the M/URC resection group (90, 79, 67 and 50%,

Table 4 Demographics and pathological features predicting disease-free survival (DFS)

Variables		Numbers	Disease-free survival (%)			
			Univariate analysis	Multivariate analysis		
				HR	95% CI	*p* value
Age	< 75 years	241				
	> 75 years	118	0.602			
Gender	Male	226				
	Female	133	0.397			
Tumour distance from anal verge	< 5 cm	130				
	> 5 cm	229	0.422			
Type of surgery	Restorative	189				
	Non-restorative	170	0.199			
Neo-adjuvant therapy (NAT)	No	167				
	Yes	192	*0.038*	0.62	0.39–0.98	*0.039*
Mode of surgery	Laparoscopic	169				
	Open	190	0.299			
TNM stage	0	17				
	I	110		0.66	0.13–3.34	0.618
	II	107		0.48	0.13–1.74	0.264
	III	125	*< 0.001*	0.58	0.26–1.26	0.166
Tumour depth	T0–T2	155				
	T3–T4	204	*< 0.001*	0.48	0.15–1.46	0.193
Lymph node stage	N0	234				
	N1	89				
	N2	36	*< 0.001*	0.48	0.25–0.94	*0.032*
Extramural vascular invasion	Absent	234				
	Present	125	*< 0.001*	0.61	0.36–1.05	0.075
CRM status	R0	323				
	R1	36	*< 0.001*	0.55	0.31–0.95	*0.031*
Tumour grade	Well-moderate (G1–2)	323				
	Poor (G3)	36	0.090			
Lymph node count	< 12	82				
	> 12	277	0.233			
Post-op chemotherapy	No	265				
	Yes	94	*0.022*	1.13	0.60–2.11	0.704
Complications	No	239				
	Yes	120	0.775			

The italic entries are highlighting the significance only

$p = 0.995$) (Fig. 3). On univariate analysis; age< 75 years, advanced TNM stage, tumour depth (T stage), presence of extramural vascular invasion (V1), positive surgical resection margin (R1), positive nodal status and post-operative complications were predictors of OS. On multivariate analysis, only age > 75 and incidence of post-operative complications were independent predictors of OS (Table 5).

Discussion

Historically, colon and rectal cancers have been considered the same diseases and hence they were often referred to as 'colorectal cancer'. In the recent era, it has been recognised that these are arguably separate diseases, supported by the American Joint committee on Cancer (AJCC) and the UK National Bowel Cancer Audit that the clinical management and outcome of colon and rectal cancer have been reported separately.[7–9] More interestingly, evidence has emerged that low rectal cancers have more pronounced adverse prognostic factors compared to high rectal cancers.[10] Here, we considered low rectal cancer (LRC) as a separate entity to mid/upper rectal cancer (M/URC).

In our patient cohort, there was significantly higher number of patients with low rectal cancer treated with neo-adjuvant therapy compared with patients with mid/upper rectal cancer. On preoperative staging, the LRC group was predicted to have more advanced disease, ± CRM involvement, compared to the M/URC group. This corresponded to a higher incidence of administration of NAT in the LRC group (75.2%) compared to the M/URC group (38.1%). The tumouricidal effect of NAT in our LRC group seems to have translated into favourable patient survival outcome, in that the DFS and OS between the LRC and M/URC groups were similar. In addition, this study also highlighted that there were 40% in the M/URC group with TNM III disease compared to 27.5% in the LRC group. This was probably due to the lower number of patients in the M/URC group receiving NAT. This may imply that potentially more patients in the M/URC group could have benefitted from NAT from an oncological perspective. Consequently, we have observed a significant higher number of patients with M/URC receiving post-operative adjuvant therapy (30.5 vs 20.1%, $p = 0.038$).

Although the distance of the rectal tumour from the anal verge does not influence disease recurrence, DFS and OS in this study, it does have an impact on the incidence of R1 resection rates. Our multivariate analysis showed that advanced TNM stage, lymph node metastasis, extramural vascular invasion and low rectal tumour were independent predictors of an R1 resection (Table 2). All these are markers of an aggressive tumour which are not uncommonly associated with local failure, non-restorative surgery, disease recurrence and poor outcome. These prognostic factors are similar to older series from our unit reported by Quirke et al.[11] In our cohort, the overall R1 rate was 10% (much improved from 25% reported by Quirke et al. in 1994).[11] The UK National Bowel Cancer Audit 2015 reported a lower incidence of 7.2% R1 after rectal cancer resection.[8] This difference could be due to under-reporting in NBOCAP as the CRM status was not reported in up to 25.6% of patients in the 2015 report, while the CRM status was recorded in all of our patients as standard of practice. Bhangu et al.[12] from a single surgeon outcome

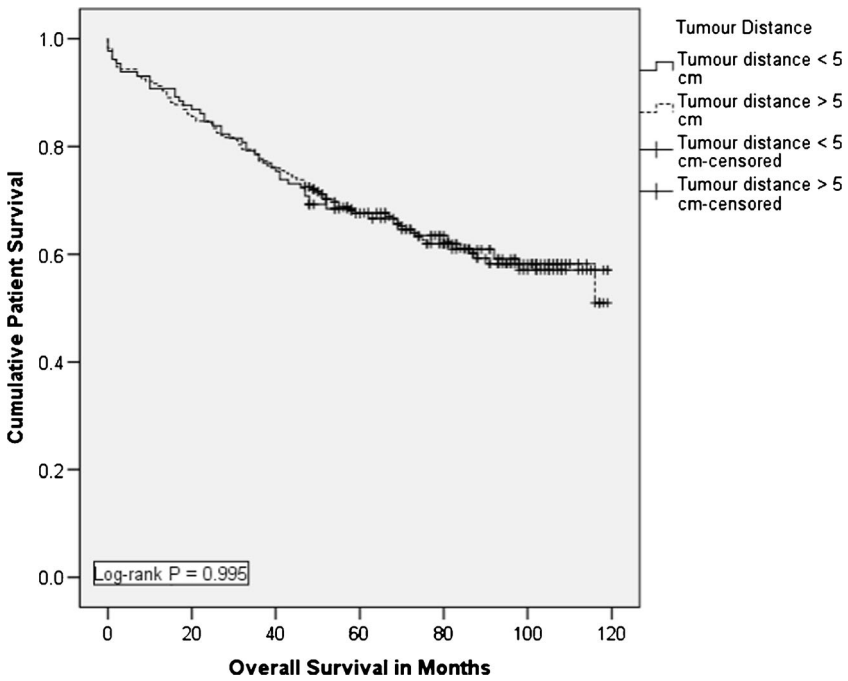

Fig. 3 OS–LRC (tumour distance from the anal verge < 5 cm) vs M/URC (tumour distance from the anal verge > 5 cm) groups

Table 5 Demographics and pathological features predicting overall survival (OS)

Variables		Numbers	Overall survival (%)			
			Univariate analysis	Multivariate analysis		
				HR	95% CI	*p* value
Age	< 75 years	241				
	> 75 years	118	*< 0.001*	0.53	0.37–0.76	*0.001*
Gender	Male	226				
	Female	133	0.143			
Tumour distance from anal verge	< 5 cm	130				
	> 5 cm	229	0.995			
Type of surgery	Restorative	189				
	Non-restorative	170	0.491			
Neo-adjuvant therapy (NAT)	No	167				
	Yes	192	0.472			
Mode of surgery	Laparoscopic	169				
	Open	190	0.171			
TNM stage	0	17				
	I	110		0.34	0.06–1.80	0.203
	II	107		1.03	0.37–2.83	0.958
	III	125	*0.015*	0.66	0.37–1.15	0.145
Tumour depth	T0–T2	155				
	T3–T4	204	*< 0.001*	0.53	0.21–1.31	0.170
Lymph node stage	N0	234				
	N1	89				
	N2	36	*0.007*	0.61	0.34–1.09	0.094
Extramural vascular invasion	Absent	234				
	Present	125	*0.002*	0.74	0.47–1.15	0.180
CRM status	R0	323				
	R1	36	*0.031*	0.75	0.44–1.27	0.288
Tumour grade	Well-moderate (G1–2)	323				
	Poor (G3)	36	0.451			
Lymph node count	< 12	82				
	> 12	277	0.991			
Post-op chemotherapy	No	265				
	Yes	94	0.340			
Complications	No	239				
	Yes	120	*0.001*	0.55	0.38–0.77	*0.001*

The italic entries are highlighting the significance only

study also reported an impressive overall very low positive CRM rate of 3.2% and that there was no difference in the positive CRM rate between low and mid to upper rectal tumours and between restorative and non-restorative surgery.

Anatomically, the mesorectum narrows in the distal rectum, before disappearing just above the anal canal, at the level of the levator plate. There is less surrounding tissue in the low rectum compared to the mid/upper rectum. Neo-adjuvant therapy does have a significant downstaging effect on the tumour as evident on final histology, but due to the relative paucity of mesorectal fat around the low rectum and narrow confines of the pelvis at this level, R0 resection can be more difficult to achieve potentially explaining higher R1 rates with lower tumours. R1 resection after LRC surgery is more likely due to direct tumour extension in this study. However, R1 resection after M/URC resection is more likely due to a lymph node at the mesorectal margin in keeping with this. In many cases, wide excision of the levator muscle (extra-levator abdominoperineal excision) reduces the risk of residual tumour, but the risk is not completely eliminated as there may still be exposed tumour cells at the CRM just above the levator muscle[13] or involved pelvic side wall nodes low in the pelvis that are not included in the standard resections.[14,15] These tend not to be issues for M/URC surgery. Presumably, the higher rates of NAT for LRC surgery offset the

adverse impact of R1 resection in the longer term and hence similar rates of LR and DFS/OS were seen in this study for all rectal tumours irrespective of distance from the anal verge.

The UK National Bowel Cancer Audit 2015 reported that just over 60% of patients with rectal cancer had restorative surgery in the form of anterior resection.[8] In our cohort, 52.6% of patients with rectal cancer had restorative surgery. More detailed analyses showed that a significantly higher number of patients with LRC had non-restorative surgery compared to patients with M/URC (84.6 vs 20.9%, $P < 0.001$). Multiple reasons for non-restorative surgery in this group were identified including patients with multiple co-morbidities and concerns regarding the impact of an anastomotic leak in this setting, patients with poor sphincter function and patient choice. It is interesting to note that no patient who had an R1 resection after LRC surgery had restorative surgery (90% of these had NAT). The implication here is that surgeons avoided a low anastomosis in patients with 'bad low tumours' after NAT where surgery was presumably challenging, hence an R1 resection.

There is good evidence in the literature to support high-volume surgical centres for complex diseases including rectal cancer.[16,17] We would concur with this as high-quality radiology; careful selection and delivery of NAT as well as appropriate surgical strategy and procedure underpin the outcomes in this study. This is delivered within our MDT discussion with interested radiologists, oncologists and surgeons, and we consider this to be pivotal to getting the best results for patients with rectal cancer both in the short and long terms.

In summary, our data showed that patients with low rectal cancers were significantly more likely to be treated with neo-adjuvant therapy, undergo non-restorative surgery and demonstrate a higher incidence of positive circumferential resection margin compared to patients with mid/upper rectal cancers. However, despite this, the DFS, OS and loco-regional or systemic recurrence rates are not significantly different between low rectal cancer (LRC) and mid/upper rectal cancer (M/URC) independent of an R1 resection margin. Presumably, this is due to the increased use of neo-adjuvant therapy in low rectal cancer.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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