Original article

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Evaluating the incidence of pathological complete response in current international rectal cancer practice: the barriers to widespread safe deferral of surgery

The 2017 European Society of Coloproctology (ESCP) collaborating group

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Abstract

Introduction The mainstay of management for locally advanced rectal cancer is chemoradiotherapy followed by surgical resection. Following chemoradiotherapy, a complete response may be detected clinically and radiologically (cCR) prior to surgery or pathologically after surgery (pCR). We aim to report the overall complete pathological response (pCR) rate and the reliability of detecting a cCR by conventional pre-operative imaging.

Methods A pre-planned analysis of the European Society of Coloproctology (ESCP) 2017 audit was performed. Patients treated by elective rectal resection were included. A pCR was defined as a ypT0 N0 EMVI negative primary tumour; a partial response represented any regression from baseline staging following chemoradiotherapy. The primary endpoint was the pCR rate. The secondary endpoint was agreement between post-treatment MRI restaging (yMRI) and final pathological staging.

Results Of 2572 patients undergoing rectal cancer surgery in 277 participating centres across 44 countries, 673 (26.2%) underwent chemoradiotherapy and surgery. The pCR rate was 10.3% (67/649), with a partial response in 35.9% (233/649) patients. Comparison of AJCC stage determined by post-treatment yMRI with final pathology showed understaging in 13% (55/429) and overstaging in 34% (148/429). Agreement between yMRI and final pathology for T-stage, N-stage, or AJCC status were each graded as 'fair' only (n = 429, Kappa 0.25, 0.26 and 0.35 respectively).

Conclusion The reported pCR rate of 10% highlights the potential for non-operative management in selected cases. The limited strength of agreement between basic conventional post-chemoradiotherapy imaging assessment techniques and pathology suggest alternative markers of response should be considered, in the context of controlled clinical trials.

Keywords Rectal surgery, rectal cancer, pathology, radiology, neoadjuvant therapy, surgical oncology, deferral of surgery

What does this paper add to the literature?
This paper highlights the potential for selective non-operative management of rectal cancer with long-course chemoradiotherapy. We report a complete pathological response rate of 10.3% in an international audit. There was limited agreement between basic conventional post-chemoradiotherapy imaging and pathological staging, demonstrating a need for better use of current markers or more sensitive markers of treatment response.

Introduction

Approximately 450 000 rectal cancers are diagnosed worldwide annually [1]. In developed countries, in which 55% of these diagnoses are made, 45–55% of electively managed patients will receive chemoradiotherapy prior to the cancer resection [2]. The surgical resection, performed according to the principles of total mesorectal excision (TME), is widely regarded as the mainstay of curative treatment for resectable rectal cancer [3]. However, rectal cancer resections have significant morbidity along with a 90-day mortality of approximately 4–5% [2,4]. Furthermore, the long-term consequences of treatment of pre-operative radiotherapy and surgery can profoundly impair quality of life, this may be attributed to bowel dysfunction following a restorative procedure [5,6], living with the challenges and complications of a permanent stoma [7], or genitourinary side effects of treatment [8].

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Over the past decade there has been increasing interest in avoiding the consequences of a TME procedure through organ preserving approaches [9,10]. This is on the proviso that equivalent or favourable oncological outcomes can be achieved with a lower overall morbidity. One approach has been to consider deferral of surgery, whereby patients who have responded favourably to pre-operative chemoradiotherapy do not undergo surgery if there is no evidence of detectable tumour by clinical, endoscopic and radiological surveillance. These patients are diagnosed with a clinical complete response (cCR), this approach is also termed "Watch and Wait" or 'Non-Operative Management' [11,12].

The original Watch and Wait concept was based on the observation of no residual tumour cells (a pathological complete response (pCR)) in up to 26.8% of rectal cancer specimens following chemoradiotherapy [10]. Furthermore, with optimal follow-up, selected patients who participate in these programmes were reported to have favourable oncological outcomes compared with patients who underwent surgery, with 5-year disease-free and overall survival exceeding 90% [10]. Deferral of surgery is increasingly reported as a feasible approach for rectal cancer management, with acceptable detection rates of regrowth and safe surgical salvage [13,14]. A meta-analysis of 17 studies, from centres with established surveillance protocols for deferral of surgery, reported a clinical complete response rate (cCR) of 22.4% (95% CI:14.3–31.8) [15]. However most of these centres pursue strategies thought to enhance the likelihood of a favourable response, including consolidation or induction chemotherapy sensitizing regimes [16] radiotherapy dose escalation of up to 66 Gy [17] and offering chemoradiotherapy to smaller tumours (over 25% of the tumours in the meta-analysis were cT2 or less) [15].

The aim of this study was to record the complete pathological response rate reported in a 'real world' setting in order to determine the potential for widespread uptake of non-operative rectal cancer management. We also aimed to determine whether conventional radiological assessment of response to chemoradiotherapy is sufficiently reliable to feasibly consider generalised implementation of non-operative management in current clinical practice.

Methods

Protocol

This prospective, observational, multi-centre study was conducted in line with a pre-specified protocol (http://www.escp.eu.com/research/cohort-studies). An external pilot of the protocol and data capture system was conducted in five international centres prior to launch, allowing refinement of the study tool and delivery. This data was not included within the main study analysis.

Centre eligibility

Any unit performing gastrointestinal surgery was eligible to register to enter patients into the study. No minimum case volume, or centre-specific limitations were applied. The study protocol was disseminated to registered members European Society of Coloproctology (ESCP), and through national surgical or colorectal societies. Units recruiting patients to rectal cancer trials were still eligible to participate in the study.

Patient eligibility

Adult patients ($\geq$ 16 years) undergoing elective resection for rectal cancer treated with long-course pre-operative chemoradiotherapy, with or without metastatic disease, were extracted from the main audit database. A rectal cancer was defined as an adenocarcinoma 0–15 cm from the anal verge on rigid sigmoidoscopy or MRI. Concomitant chemoradiotherapy was a mandatory inclusion criteria, however the dose of chemotherapy and the delivery of long-course radiotherapy was administered to according to unit and clinician preference. Patients undergoing palliative pre-operative therapy, chemotherapy alone or short course radiotherapy were excluded.

Data capture

Consecutive sampling was performed for eligible patients over an 8-week study period in each included centre. Local investigators commenced data collection on any date between the 1 February 2017 and 15 March 2017, with the last eligible patient being enrolled on 10 May 2017. Small teams of up to five surgeons or surgical trainees worked together to collect prospective data on all eligible patients at each centre. Quality assurance was provided by at least one consultant or attending-level surgeon. Data was recorded contemporaneously and stored on a secure, user-encrypted online platform (REDCap) without using patient identifiable information. Centres were asked to validate that all eligible patients during the study period had been entered, and to attain > 95% completeness of data field entry prior to final submission.

Demographic data including Age, Gender, American Society of Anaesthesiologists (ASA) classification grade, smoking history, body mass index, cardiovascular

disease, indication for surgery and disease location. The index operation, operative steps, approach, duration and morbidity were recorded. Tumour staging information (T-stage, N-stage, extramural vascular invasion), recorded at three different timepoints, were available: 1. Baseline pre-neoadjuvant treatment MRI staging; 2. Post-treatment MRI staging; 3. Post-treatment pathological staging. Staging was summarised according to IUCC/AJCC TNM 7 system [18]. The MRI Rectum was performed according to individual unit protocol. An MRI for baseline staging was mandatory for all rectal cancers included in the study, the post treatment MRI was encouraged but was not compulsory. A complete pathological response (pCR) has been defined previously as ypT0,N0 [19], our definition also required the ypEMVI status to be negative. Tumor regression was staged into three categories: a complete pathological response (no visible cancer cells), a partial response (regression from baseline MRI to pathology for one or more of T stage, N stage, EMVI status), and no change/progression from the baseline MRI staging. The circumferential rectal margin (CRM) was regarded as involved if the microscopic tumor extension reached ≤ 1 mm from the margin. Central quality control of surgical specimens by pathologic examination was not performed.

Outcome measures

The primary outcome measure was the rate of complete pathological response. The secondary outcome measure was the concordance of the TNM-based post-treatment MRI assessment and post-treatment pathological staging for T stage, N stage and overall AJCC TNM grade, assessed using Kappa agreement and the Intraclass Correlation Coefficient.

Statistical analysis

This report has been prepared in accordance to guidelines set by the STROBE (strengthening the reporting of observational studies in epidemiology) statement for observational studies [20]. Patient, disease and operative characteristics were compared using descriptive analysis and tests of normality were used to guide analysis. Chi-squared test was used for categorical data, Student's t-test for normally distributed continuous data and Mann-Whitney U test for non-parametric data. To explore associations between T-stage, nodal status, EMVI status and tumour height with pathological complete response univariable logistic regression models were fitted, described as odds ratios with 95% confidence intervals.

The reliability of post-treatment MRI restaging to assess response to neoadjuvant therapy was assessed by the Kappa agreement between the post-treatment MRI and pathology T-, N- and AJCC-staging [21]. A Kappa value of < 0.20 was interpreted as 'Poor', 0.21–0.40 as 'Fair', 0.41–0.60 as 'Moderate', 0.61–0.80 as 'Good', and 0.81–1.00 as 'Very good'. An estimate of the Intraclass Correlation Coefficient was also reported, with 95% exact confidence intervals (95% CI) derived using the variance components from a one-way ANOVA [22,23]. Data analysis was undertaken using R Studio V3.1.1 (R Foundation, Boston, MA, USA).

Ethical approval

All participating centres were responsible for compliance to local approval requirements for ethics approval or indemnity as required. In the UK, the National Research Ethics Service tool recommended that this project was not classified as research, and the protocol was registered as clinical audit in all participating centres.

Results

Figure 1 shows inclusion of patients within this study. A total of 2572 patients underwent surgery for rectal cancer in 277 participating centres across 44 countries. Of these, 673 (26.2%) underwent CRT and TME surgery. Twenty four patients were excluded due to missing MRI or pathology staging. The median (IQR) age of the remaining 649 patients was 65 years (56–71 years). 35% (229/649) were female.

pCR was reported in 10.3% (67/649) patients. An overall partial response occurred in 35.9% (233/649), with T stage regression in 42.8% (278/649), N stage regression in 71.6% of those with baseline node positivity (111/155), and EMVI regression in 82.5% with baseline mrEMVI positivity (33/40). No regression occurred in 53.8% (349/649) patients. Treatment failure with progression of T-staging was seen in 9.4% (53/562), N-staging in 8.9% (52/583) and EMVI-status in 17.6% (99/561).

Demographic and operative data are compared according to tumour response in Table 1. Overall the mean (SD) tumour height was 4.1 cm [1.9], whereas the pCR group were significantly closer to the anal verge (mean (SD) 3.2 cm [1.7], $P < 0.007$). Patients with a pCR were more likely to undergo a restorative resection 73.1% ($P = 0.004$) and a significantly higher proportion of robotic cases were performed on patients with a pCR (27%[13/48], $P < 0.001$) compared with 11.4% [38/333] and 6.0% [16/268] for laparoscopic and open approaches, respectively. Response was not

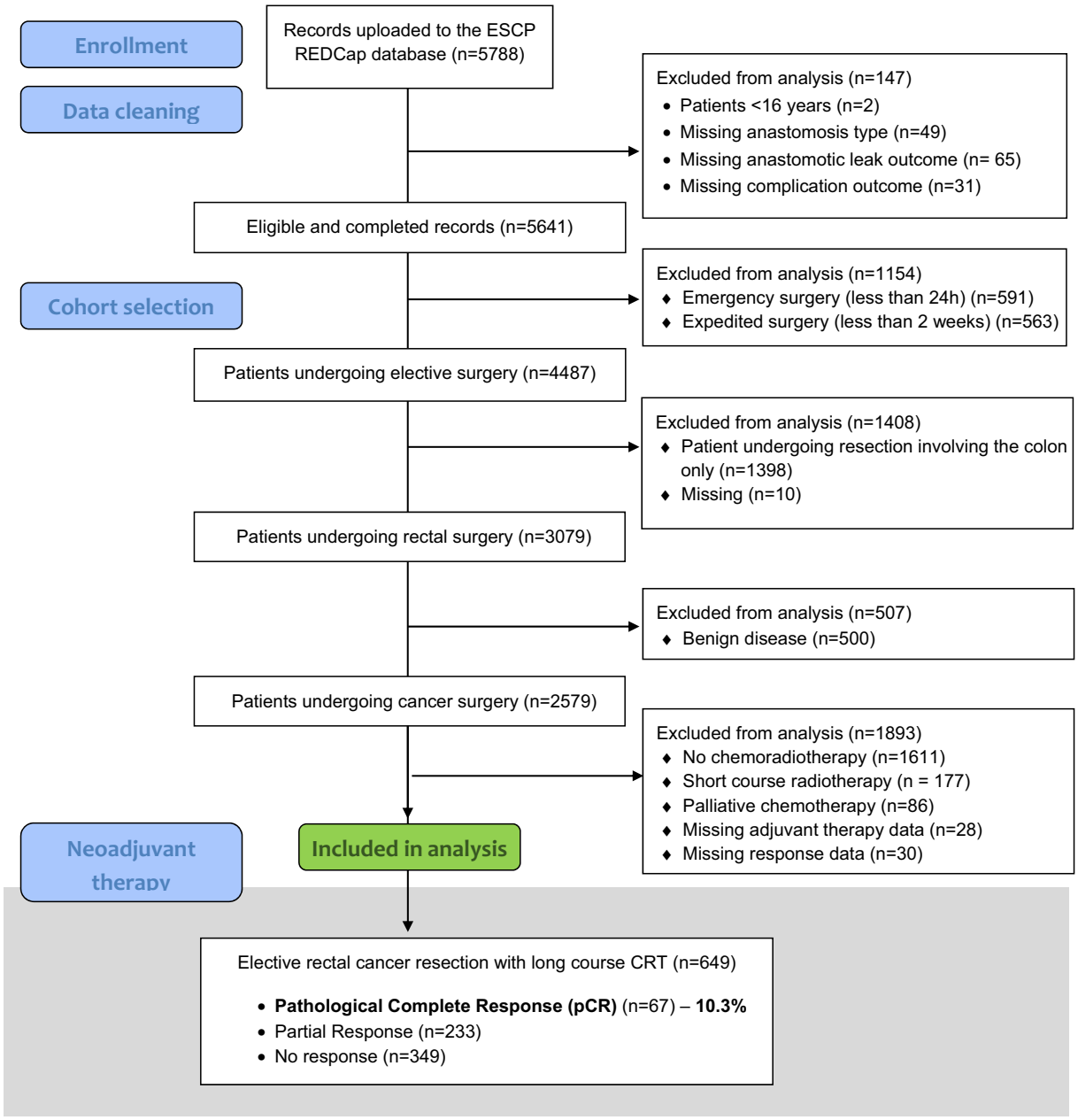


Figure 1 Flowchart for patients included in the analysis of pre-operative chemoradiotherapy followed by elective rectal cancer surgery.

influenced by age, gender and patient fitness in this series. The degree of regression did not influence Clavien Dindo reported complication rates.

Baseline MRI staging ($n = 649$), post-CRT MRI staging ($n = 429$), and pathological staging are compared against tumour response in Table 2. A post-treatment MRI was performed in 66.1% (429/649) of patients. According to the baseline MRI over 70% of tumours were T3 in all response groups, only 4.5% of pCR tumours were mrT4 and the highest proportion of T4 tumours were in the partial response group 23.6% (55/233). mrT1 were reported in 8 (1.2%) cases, these were mrEMVI or mrN2 +ve tumours and all patients were non-responders. Following CRT, ymrT1 was reported in 7.7% overall and in 20% of pCR group. Figure 2 displays response rates by tumour height and pre-treatment MRI T-stage. Complete response was more common in T1/T2 tumours than T3/T4

Table 1 Characteristics of patients undergoing long course neoadjuvant chemoradiotherapy.

				Pathological assessment of response to CRT			
Factor	Level	Total	%	Complete (%)	Partial (%)	None (%)	*P*-value
		649	100.0	67 (10.3)	233 (35.9)	349 (53.8)	
Patient and disease factors							
Age	< 55	131	20.2	12 (17.9)	44 (18.9)	75 (21.5)	0.61
	55–70	308	47.5	29 (43.3)	120 (51.5)	159 (45.6)	
	70–80	182	28.0	24 (35.8)	60 (25.8)	98 (28.1)	
	> 80	28	4.3	2 (3.0)	9 (3.9)	17 (4.9)	
Gender	Female	229	35.3	24 (35.8)	88 (37.8)	117 (33.5)	0.57
	Male	420	64.7	43 (64.2)	145 (62.2)	232 (66.5)	
ASA class	Low risk (ASA 1–2)	464	71.5	48 (71.6)	171 (73.4)	245 (70.2)	0.16
	High risk (ASA 3–5)	178	27.4	17 (25.4)	58 (24.9)	103 (29.5)	
	Missing	7	1.1	2 (3.0)	4 (1.7)	1 (0.3)	
BMI	Normal weight	237	36.5	21 (31.3)	87 (37.3)	129 (37.0)	0.67
	Underweight	16	2.5	0 (0.0)	7 (3.0)	9 (2.6)	
	Overweight	243	37.4	28 (41.8)	85 (36.5)	130 (37.2)	
	Obese	143	22.0	16 (23.9)	49 (21.0)	78 (22.3)	
	Missing	10	1.5	2 (3.0)	5 (2.1)	3 (0.9)	
Tumour height	High rectum	77	11.9	5 (7.5)	24 (10.3)	48 (13.8)	0.37
(measured from	Middle rectum	225	34.7	23 (34.3)	77 (33.0)	125 (35.8)	
anal margin) (cm)	Low rectum	347	53.5	39 (58.2)	132 (56.7)	176 (50.4)	
Tumour height (cm)	Mean (SD)			3.2 (1.7)	3.7 (2.1)	4.5 (3.5)	0.007
Operation factors							
Operative approach	Open	268	41.3	16 (23.9)	96 (41.2)	156 (44.7)	< 0.001
	Laparoscopic	333	51.3	38 (56.7)	127 (54.5)	168 (48.1)	
	Robotic	48	7.4	13 (19.4)	10 (4.3)	25 (7.2)	
Duration (minutes)	Mean (SD)			262.8 (97.5)	243.7 (95.8)	246.3 (97.2)	0.24
Approach	Anterior Resection	424	65.3	49 (73.1)	154 (66.1)	221 (63.3)	0.04
	Hartmanns	37	5.7	5 (7.5)	5 (2.1)	27 (7.7)	
	APE	121	18.6	7 (10.4)	45 (19.3)	69 (19.8)	
	ELAPE	67	10.3	6 (9.0)	29 (12.4)	32 (9.2)	
Defunctioning stoma	Yes	345	53.2	42 (62.7)	129 (55.4)	174 (49.9)	0.11
	No	304	46.8	25 (37.3)	104 (44.6)	175 (50.1)	
Outcomes							
Complication grade	None	364	56.1	38 (56.7)	135 (57.9)	191 (54.7)	0.75
	Grade 1–2	190	29.3	18 (26.9)	67 (28.8)	105 (30.1)	
	Grade 3–5	92	14.2	11 (16.4)	31 (13.3)	50 (14.3)	
	Missing	3	0.5	0 (0.0)	0 (0.0)	3 (0.9)	

CRT, chemoradiotherapy. Pathological assessment of response to CRT: complete response (ypT0,N0, EMVI-ve). Partial response (regression from baseline MRI T stage), none (no change or progression from baseline MRI T stage).

tumours (14.5% *vs* 9.7%), although this association was non-significant (T3/T4; OR: 0.64, 0.34–1.30, $P = 0.19$). Despite trends towards a higher pCR rate in low or middle rectal disease, neither tumour height (Low rectum; OR: 1.82, 0.76–5.43, $P = 0.22$, Middle rectum; OR: 1.64, 0.65–5.02, $P = 0.33$) or EMVI status (EMVI positive; OR: 1.26, 0.42–3.07, $P = 0.64$) were significantly associated with complete response. Node positivity at baseline was significantly associated with a lower rate of pCR (OR: 0.40, 0.17–0.81, $P = 0.02$).

The pathology data is also summarised in Table 2. There was no tumour in the pCR group and therefore the grade of differentiation could not be determined, however there was no difference in the tumour grade for partial and non-responders. Non-responders were significantly more likely than partial responders to be ypEMVI positive (12.9% [30/233] *vs* 24.4% [85/349], $P < 0.001$). The overall pCRM rate was 6.2% [40/649].

The post-CRT MRI staging ($n = 429$) is compared with pathology staging in Table 3. Overall understaging occurred in 14% (61/429) and 12.8% (55/429) of ypT

Table 2 Magnetic resonance imaging and pathological staging of included patients.

				Pathological Assessment of Response to CRT			
Factor	Level	Total	%	Complete (%)	Partial (%)	None (%)	*P*-value
		649	100.0	67 (10.3)	233 (35.9)	349 (53.8)	
Pre-treatment MRI staging							
mrT	T1	8	1.2	0 (0.0)	0 (0.0)	8 (2.3)	< 0.001
	T2	75	11.6	12 (17.9)	11 (4.7)	52 (14.9)	
	T3	479	73.8	52 (77.6)	167 (71.7)	260 (74.5)	
	T4	87	13.4	3 (4.5)	55 (23.6)	29 (8.3)	
mrN	N0	497	76.6	59 (88.1)	141 (60.5)	294 (84.2)	< 0.001
	N1	89	13.7	3 (4.5)	55 (23.6)	31 (8.9)	
	N2	66	10.2	5 (7.5)	37 (15.9)	24 (6.9)	
mrEMVI	No	561	86.4	58 (86.6)	194 (83.3)	309 (88.5)	0.389
	Yes	40	6.2	5 (7.5)	16 (6.9)	19 (5.4)	
	Missing	48	7.4	4 (6.0)	23 (9.9)	21 (6.0)	
mrAJCC	Stage 1	58	8.9	10 (14.9)	0 (0.0)	48 (13.8)	< 0.001
	Stage 2	408	62.9	43 (64.2)	119 (51.1)	246 (70.5)	
	Stage 3	121	18.6	7 (10.4)	65 (27.9)	49 (14.0)	
	Stage 4	62	9.6	7 (10.4)	49 (21.0)	6 (1.7)	
Post-treatment MRI re-staging							
Post treatment MRI performed	Yes	429	66.1	39 (58.2)	164 (70.4)	226 (64.8)	2.12
	No	220	33.9	28 (41.8)	69 (29.6)	123 (35.2)	
Of those restaged (n = 429)	T0/1	33	7.7	8 (20.5)	13 (7.9)	12 (5.3)	< 0.001
ymrT	T2	107	24.9	14 (35.9)	37 (22.6)	56 (24.8)	
	T3	226	52.7	14 (35.9)	78 (47.6)	134 (59.3)	
	T4	63	14.7	3 (7.7)	36 (22.0)	24 (10.6)	
ymrN	N0	229	53.4	27 (69.2)	102 (62.2)	100 (44.2)	< 0.001
	N1	141	32.9	11 (28.2)	40 (24.4)	90 (39.8)	
	N2	59	13.8	1 (2.6)	22 (13.4)	36 (15.9)	
ymrEMVI	No	346	80.7	35 (89.7)	133 (81.1)	178 (78.8)	0.376
	Yes	67	15.6	3 (7.7)	23 (14.0)	41 (18.1)	
	Missing	14	3.3	1 (2.6)	7 (4.3)	6 (2.7)	
ymr AJCC stage	Stage 1	99	23.1	16 (41.0)	41 (25.0)	42 (18.6)	< 0.001
	Stage 2	115	26.8	11 (28.2)	59 (36.0)	45 (19.9)	
	Stage 3	170	39.6	12 (30.8)	61 (37.2)	97 (42.9)	
	Stage 4	44	10.3	0 (0.0)	2 (1.2)	42 (18.6)	
	Missing	1	0.2	0 (0.0)	1 (0.6)	0 (0.0)	
Post-operative pathological staging							
ypT stage	T0	77	11.9	67 (100.0)	2 (0.9)	8 (2.3)	< 0.001
	T1	34	5.2	0 (0.0)	28 (12.0)	6 (1.7)	
	T2	181	27.9	0 (0.0)	121 (51.9)	60 (17.2)	
	T3	310	47.8	0 (0.0)	67 (28.8)	243 (69.6)	
	T4	47	7.2	0 (0.0)	15 (6.4)	32 (9.2)	
ypN stage	N0	431	66.4	67 (100.0)	212 (91.0)	152 (43.6)	< 0.001
	N1	150	23.1	0 (0.0)	15 (6.4)	135 (38.7)	
	N2	68	10.5	0 (0.0)	6 (2.6)	62 (17.8)	
ypEMVI	No	534	82.3	67 (100.0)	203 (87.1)	264 (75.6)	< 0.001
	Yes	115	17.7	0 (0.0)	30 (12.9)	85 (24.4)	
Differentiation grade	Poor	72	11.1	–	27 (11.6)	45 (12.9)	< 0.001
	Moderate	337	51.9	–	128 (54.9)	209 (59.9)	
	Well	161	24.8	–	75 (32.2)86 (24.6)		
	Missing	79	12.2	67	3	9	

Prefix notations: mr, MRI staging; p, pathology staging; y, staging following chemoradiotherapy (CRT). ymr, MRI staging following CRT; AJCC, American Joint Committee on Cancer; EMVI, extramural vascular invasion; N, node; T, tumour.

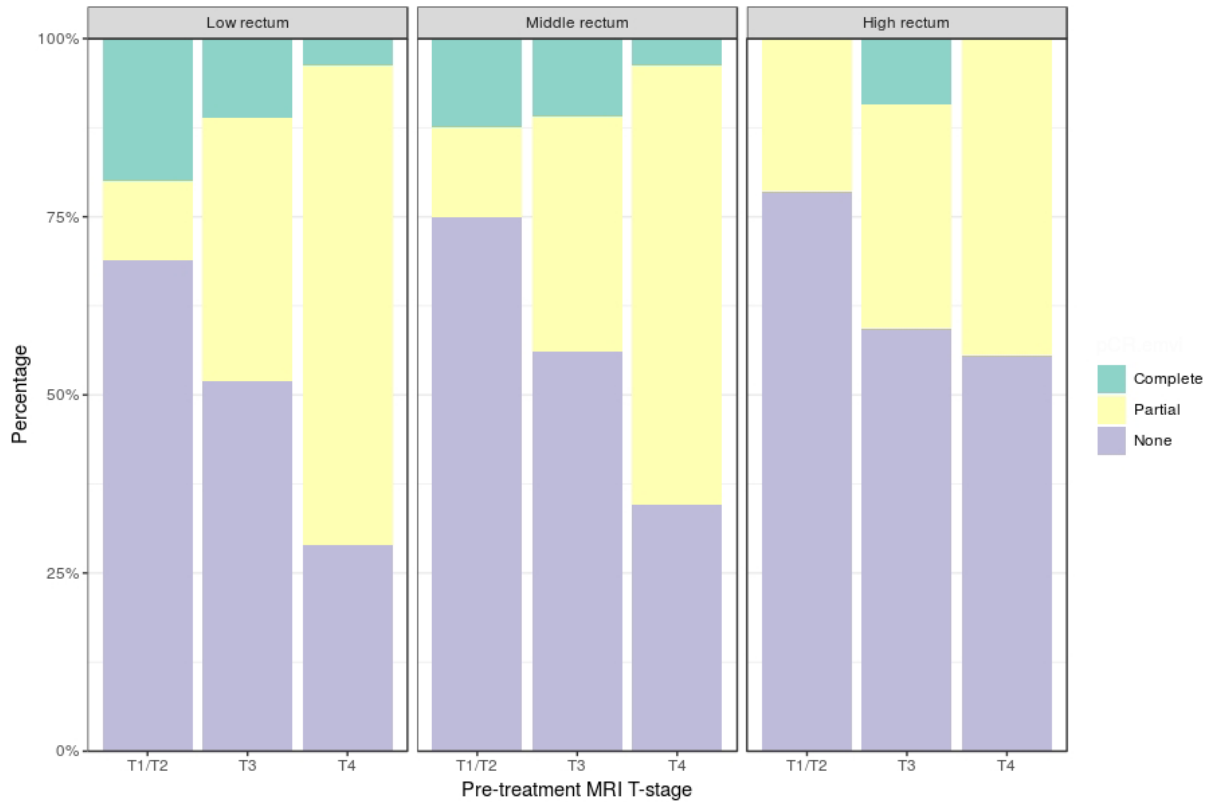


Figure 2 Differences in treatment response by tumour height.

Table 3 Comparison of post-treatment MRI and pathological staging. A post-treatment MRI was performed in 66.1% (429/649) cases. Under-staging (blue) indicated lower staging by post-treatment MRI than by pathology. Overstaging (yellow) indicated higher staging by post-treatment MRI than by pathology.

MRI tumor classification	pT0/1	pT2	pT3	pT4	Total (*n*)	Over staged, %	Under staged, %	Accuracy, %
Pathologic tumor classification – yT stage								
rT0/T1	14	5	6	0	25	-	44	56
rT2	21	44	30	1	96	22	32	46
rT3	14	57	129	14	214	33	7	60
rT4	3	8	31	16	58	72	–	28
Total (*n*)	52	114	196	31	393	34	14	52

MRI tumor classification	pN0	pN1	pN2	Total (*n*)	Over staged, %	Under staged, %	Accuracy, %
Pathologic tumor classification – yN stage							
rN0	167	32	8	207	–	19	81
rN1	65	46	22	133	49	16	35
rN2	21	15	17	53	68	–	32
Total (*n*)	253	93	47	393	26	16	58

stage and ypAJCC grade cancers respectively. Overstaging was reported in 35% (151/429) of ypT staging and 34% (148/429) of ypAJCC grading. Table 4 shows that the agreement between the post-treatment MRI and Pathology was graded 'fair' for T stage, N stage and AJCC status (Kappa 0.25, 0.26 and 0.35 respectively).

Table 4 Agreement between post-treatment MRI and pathological staging.

	ymr v pathology			
Pathological stage	Agreement (%)	Agreement (Kappa)	Kappa *P*-value	Intraclass correlation coefficient
ypT-stage	50.7	0.249	< 0.001	0.26 (0.09–0.84)
ypN-stage	58.8	0.264	< 0.001	0.25 (0.08–0.93)
ypAJCC stage	52.8	0.348	< 0.001	0.35 (0.14–0.88)

Agreement refers to the concordance of post-treatment MRI re-staging with pathological staging.

Discussion

This large, prospective international audit identified a pCR rate of 10.3% for patients with rectal cancer treated with preoperative chemoradiotherapy. This data was simultaneously collected from 262 units over a period of six weeks. It provides a unique and truly generalised 'snapshot' of the pathological response rate in current practice. Many regard a pathological response as a mixed blessing; on the one hand this reflects a favourable prognosis but on the other it may indicate an unnecessary operation with the sequelae that can follow. Consequently, there is increasing interest in trying to identify a complete response after chemoradiotherapy on clinical and radiological (cCR) grounds rather than by pathological assessment (pCR). However, this 'real-world' MRI staging data gives us an indication that if current basic staging tools are used in isolation, they will be inadequate for accurately identifying and safely monitoring 'deferral of surgery' patients.

The pCR rate reported in this study is consistent with outcomes reported in large trials that used single agent concomitant chemotherapy and a radiotherapy dose of at least 45 Gy. The FFCD 9203, EORTC 22921 and the German Rectal Cancer Study (CAO/ARO/AIO-94) trials have been described extensively elsewhere [24–26]. In summary these trials recruited cT3 or resectable cT4M0 adenocarcinoma of the rectum, located within 15, 15 and 16 cm from the anal verge respectively [24–26]. These trials reported pCR rates with pre-operative CRT of 11.4%, 14% and 8% respectively [24–26]. One review of phase II and III studies identified pCR rates ranging from 0–67% with an overall pCR rate of 13.5% [27].

This current study identified that a pCR was associated with a lower tumour height. This finding has been reported previously and authors postulate that lower tumours are fixed by the pelvic floor muscles allowing radiotherapy to be delivered more consistently which allows for a favourable response rate [28]. A significantly higher proportion of patients in the pCR group had a node negative tumour at baseline. As authors have previously discussed, this may indicate that earlier stage tumours are more likely to produce a complete clinical response or this may reflect a more biologically indolent tumour that is more likely to respond favourably to treatment [15,28,29]. The size of the tumour may also influence complete response rates [29], however in this study tumours were predominately mrT3 and the MRI baseline staging suggested CRT was given in order to downstage locally advanced tumours rather than to achieve a complete response in early stage tumours.

Other factors previously shown to be associated with an increased response rate include dual concomitant chemotherapy [27], induction chemotherapy [30], consolidation chemotherapy [31,32], allowing time for regression between CRT and surgery [33], and intensified pre-operative radiotherapy [17]. The pathological assessment can also influence the pCR rate. The more thorough the histopathology technician and the pathologist, the less likely they are to find a pCR. However recent guidelines for assessing post-CRT rectal cancer specimens provide recommendations on the number of levels that should be cut from each tumour block. These recommendations are likely to standardise the pathological assessment of response [34].

When the response to CRT is favourable and a pCR is achieved it can be regarded as an encouraging outcome. Many patients with a pCR will be reassured by the absence of a cancer. Furthermore, the longterm outcomes are highly favourable; the German Rectal Cancer trial reported a 10 year DFS of 89.5% with a pCR, compared with 63% when minimal tumour regression occurred (p = 0.008) [35]. On the other hand this represents a missed opportunity for organ preservation. In selected patients it is possible to avoid surgery. Thus much of the morbidity may be prevented along with the reported 90-day post-operative mortality of 4–5% [4]. Deferral of surgery has now been reported for 867 patients from 23 studies [13]. In highly selected cases, motivated centres with established surveillance protocols report no significant difference between 'deferral of surgery' for a cCR compared with surgery for a pCR [13]. They found no difference in non-regrowth recurrence

(RR 0.58, 95% CI 0.18–1.90), disease-free survival (HR 0.56, 95% CI 0.20–1.60), or overall survival (HR 3.91, 95% CI 0.57–26.72) [13].

The challenge that currently prevents widespread uptake of 'deferral of surgery' is the inability to reliably identify and monitor responders. In our study 'fair' Kappa agreements of 0.25, 0.26 and 0.35 were reported for ypT stage, ypN stage and ypAJCC grade respectively with understaging occurred in over 10% of cases and overstaging in over 30% of cases. These Kappa agreements exceed published agreements for other methods of assessing response such as mrRECIST [R*esponse Evaluation Criteria In Solid Tumors*] criteria and MR volumetric analysis (Kappa 0.12 and 0.36 respectively) [36]. However higher Kappa agreement scores of > 0.4 have been reported for ymr versus pT stage assessment in selected centres [36]. Nevertheless, these data suggests that the techniques used in a typical international surgical unit for post-treatment MRI staging are insufficiently reliable to allow for the safe delivery of deferral of surgery.

In selected centres, multidisciplinary team (MDT) orientated standardised protocols have contributed to significant improvements in the interpretation of response to chemoradiotherapy; multimodal assessment, with T2 weighted-MRI serving as the primary screening tool, in conjunction with clinical and endoscopic examination, is used to evaluate response [37–39]. This suggests that with optimal training and experience, current tools can be used effectively to select patients whose tumours have responded favourably to chemoradiotherapy. Nevertheless in a global setting we share the view of the authors of the MERRION study [40] and Putte *et al.* who suggested current imaging modalities have a low accuracy for predicting a true pathological complete response, indicating that deferral of surgery should not be offered outside of well-designed clincal trials [41]. Whilst we need to search for alternative methods for assessing response.

The actively recruiting TRIGGER randomised control trial is testing methods to identify, and safely monitor, clinical complete responders [42]. The trial, uses current MRI imaging in a smarter way, to identify clinical complete responders by applying a 5-point MRI tumour regression grade (mrTRG), which most closely resembles the Mandard pathologic TRG system [39]. The basic principle of both grading systems relate to the ratio of tumour to fibrosis following CRT. This is the first imaging technique that has been shown to assess the degree of tumour regression and to correlate the findings with pathology and with long-term survival [37,43]. A unique aspect of this trial is that participating units are trained to report mrTRG and may only take part when the unit radiologist completes a training dataset for mrTRG and achieves a high degree of agreement with the index radiologist (Kappa $\geq$ 0.7) [42]. TRIGGER may enable the dissemination of a standardised, reliable, evidence based technique for assessing post-chemoradiotherapy response.

There are a number of limitations with this study. There is a lack of detail in terms of treatment approach. We did not know the exact radiotherapy dose used, whether pre-operative 'consolidation' or 'induction' systemic chemotherapy was used in addition to CRT or the standard waiting time between completion of CRT (or short course radiotherapy) and surgery. Consequently we have not been able to perform a multivariate analysis to explore the key risk factors for predicting a favourable response to CRT. Although it was compulsory for data to be reviewed by a senior member of the department prior to submission, no external audit of the radiology or pathology was performed and we could not be certain that recogised standardised methods were performed [34,42]. For the purposes of this study we believe this to be acceptable because it simply reflects the 'real-world' data that we aimed to assess. Finally, only patients undergoing surgery were included in the study. It is possible that a number of units already practice deferral of surgery. However, for the reasons outlined above we would recommend that this is performed within the context of a clinical trial.

Conclusions

The pathological complete response (pCR) rate of 10% reported in this international audit is consistent with rates reported in clinical trials that used concomitant chemoradiotherapy. This highlights the potential for non-operative management in selected rectal cancer patients, however the number of eligible patients may be increased if treatment strategies that enhance the overall response rate are pursued. The second barrier to non-operative management is the limited strength of agreement between post-CRT imaging and pathology. This suggests that assessing response with crude measures such as post-treatment T stage and post-treatment AJCC grade are not reliable or generalisable. Alternative detection methods, such as mrTRG with serial assessment, need to be considered in the context of clinical trials in order to feasibly allow safe widespread uptake of deferral of surgery.

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Conflicts of interest

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