Population-based study of morbidity risk associated with pathological complete response after chemoradiotherapy for rectal cancer

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EUROPEAN COLORECTAL CONGRESS

Spotlight on the colon

1 – 5 December 2019, St.Gallen, Switzerland

Sunday, 1 Dec. 2019

MASTERCLASS

09.00
When the appendix plays nasty: intraoperative surprises, immediate solutions, and long-term treatment options
Justin Davies, Cambridge, UK

09.40
All the secrets of the pelvic floor - common disorders and proven solutions
Julie Cornish, Cardiff, UK

10.20
taTME in 2020 – when the dust settles: current and innovative indications, implementation, and practical advices
Roel Hompes, Amsterdam, NL

11.30
Complete mesocolic excision: indications, surgical approaches, and pitfalls
Paris Tekkis, London, UK

12.10
The views of an Editor and the wisdom of an Expert: contemporary publications with the potential to change and improve practice
Neil Mortensen, Oxford, UK

14.00
To ostomize or not and when? The value and downside of a diverting stoma versus virtual ileostomy versus no stoma
Gabriela Möslein, Wuppertal, DE

14.40
Extended lymph node dissection: indications, surgical anatomy, and technical approaches
Peter Sagar, Leeds, UK

15.20
Is the longer the new better - how to safely extend the interval after neoadjuvant chemoradiotherapy prior to surgery for rectal cancer
Ronan O'Connell, Dublin, IE

16:30
The colorectal anastomosis: time-proven wisdom, innovative configurations, and salvage techniques
André d'Hoore, Leuven BE

17.10
All you need to know about stomas but never dared to ask
Willem Bemelman, Amsterdam, NL

17.50
The EBSQ Coloproctology Examination
Michel Adamina, Winterthur, CH

18.00
Wrap-up
Michel Adamina, Winterthur, CH

Monday, 2 Dec. 2019

SCIENTIFIC PROGRAMME

09.45
Opening and welcome
Jochen Lange, St.Gallen, CH

10.00
Pathophysiology and non-operative management of symptomatic uncomplicated diverticular disease
Robin Spiller, Nottingham, UK

10.30
Surgery of acute diverticulitis – evidence, eminence and real life
Willem Bemelman, Amsterdam, NL

11.00
Management of atypical diverticulitis
Dieter Hahnloser, Lausanne, CH

11.30
Hartmann reversal: open, laparoscopic or transanal?
Roel Hompes, Amsterdam, NL

13.30
The surgeon personality – influence on decision making, risk-taking and outcomes
Desmond Winter, Dublin, IE

14.00
SATELLITE SYMPOSIUM
Medtronic

15.00
Clinical applications of image-guided cancer surgery
Cornelis van de Velde, Leiden, NL

16.00
Volvulus of the colon – a treatment algorithm
Peter Sagar, Leeds, UK

16.30
Hereditary colorectal cancer syndromes: tailored surgical treatment
Gabriela Möslein, Wuppertal, DE

17.00
Lars Pahlman and Herand Abcarian (2015)
Herand Abcarian, Chicago, US

17.20
Lars Påhlman Lecture
Steven Wexner, Weston, US

Tuesday, 3 Dec. 2019

09.00
Robotic-assisted versus conventional laparoscopic surgery for rectal cancer
Amjad Parvaiz, Poole, UK

09.30
Robotic multivisceral resection
Paris Tekkis, London, UK

10.00
SATELLITE SYMPOSIUM
Karl Storz

11.30
Neoadjuvant chemotherapy for advanced colon cancer: clinical and pathological Results
Dion Morton, Birmingham, UK
Philip Quirke, Leeds, UK

12.30
Cytoreductive surgery and hyperthermic intraoperative chemotherapy for intestinal and ovarial cancers: lessons learned from 2 decades of clinical trials
Vic Verwaal, Aarhus, DK

14.30
Mechanical bowel obstruction: rush to the OR or stent and dine
Neil Mortensen, Oxford, UK

15.00
Controversies in IBD surgery
André d'Hoore, Leuven, BE

16.00
How to deal with IBD and dysplasia
Janindra Warusavitarne, London, UK

16.30
Perianal Crohn – avoiding delay and best surgical practice
Justin Davies, Cambridge, UK

17.00
Perianal Crohn – stem cells therapy and current medical approach
Gerhard Rogler, Zürich, CH

Wednesday, 4 Dec. 2019

09.00
Is anastomotic leak an infectious disease
Ronan O'Connell, Dublin, IE

09.30
Is it time to invest in robotic surgery?
Antonino Spinelli, Milan, IT

10.00
SATELLITE SYMPOSIUM
Intuitive

11.00
New developments in robotic systems
Alberto Arezzo, Torino, IT

12.00
Posterior component separation for abdominal wall reconstruction: evolution from open to minimal invasive using the robotic platform
Filip Muysoms, Gent, BE

14.00
Coloproctology 4.0 – the networked surgeon
Richard Brady, Newcastle upon Tyne, UK

14.30
SATELLITE SYMPOSIUM
Olympus

15.30
The elderly colorectal patient – functional outcomes and patient reported outcomes
Isacco Montroni, Faenza, IT

16.30
The microbiome and colorectal cancer
Philip Quirke, Leeds, UK

17.00
Surgical management of rectal endometriosis
Eric Rullier, Bordeaux, FR

17.30
EAES Presidential Lecture 3D printing for the general surgeon
Andrea Pietrabissa, Pavia, IT

Thursday, 5 Dec. 2019

09.00
Management of locoregionally advanced colon cancer
Torbjörn Holm, Stockholm, SE

09.30
ROUNDTABLE
Herand Abcarian, Chicago, US
Bill Heald, Basingstoke, UK

10.30
Artificial intelligence in colorectal surgery
Michele Diana, Strasbourg, FR

11.30
The mesentery in colonic diseases
Calvin Coffey, Luimneach, IE

12.00
Technical pearls and typical mistakes in minimal invasive colectomy
Antonio Lacy, Barcelona, ES

12.30
Choosing the right anastomotic technique in colon surgery
Roberto Persiani, Rom, IT

13.00
Precision surgery: past, present and future
Brendan Moran, Basingstoke, UK

13.30
Poster award
Michel Adamina, Winterthur, CH

Information & Registration

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Original article

Population-based study of morbidity risk associated with pathological complete response after chemoradiotherapy for rectal cancer

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Background: **Neoadjuvant chemoradiotherapy (nCRT) for locally advanced rectal cancer may induce a pathological complete response (pCR) but increase surgical morbidity due to radiation-induced fibrosis. In this study the association between pCR and postoperative surgical morbidity was investigated.**
Methods: **Patients in the Netherlands with rectal cancer who underwent nCRT followed by total mesorectal excision between 2009 and 2017 were included. Data were stratified into patients who underwent resection with creation of a primary anastomosis and those who had a permanent stoma procedure. The association between pCR and postoperative morbidity was investigated in univariable and multivariable logistic regression analyses.**
Results: **pCR was observed in 976 (12·2 per cent) of 8003 patients. In 3472 patients who had a primary anastomosis, the presence of pCR was significantly associated with surgical complications (122 of 443 (27·5 per cent) *versus* 598 of 3029 (19·7 per cent) in those without pCR) and anastomotic leak (35 of 443 (7·9 per cent) *versus* 173 of 3029 (5·7 per cent) respectively). Multivariable analysis also showed associations between pCR and surgical complications (adjusted odds ratio (OR) 1·53, 95 per cent c.i. 1·22 to 1·92) and pCR and anastomotic leak (adjusted OR 1·41, 1·03 to 2·05). Of 4531 patients with a permanent stoma, surgical complications were observed in 120 (22·5 per cent) of 533 patients with a pCR, compared with 798 (20·0 per cent) of 3998 patients with no pCR (adjusted OR 1·17, 0·94 to 1·46).**
Conclusion: **Patients with a pCR in whom an anastomosis was created were at increased risk of developing an anastomotic leak.**

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Introduction

In the Netherlands, patients with locally advanced rectal cancer (cT3 with distance to the mesorectal fascia of 1 mm or less, or cT4, and/or high likelihood of four or more positive lymph nodes within the mesorectum or positive lymph nodes outside the mesorectum based on MRI) are treated according to national guidelines (http://www.oncoline.nl/colorectaalcarcinoom). The mainstay of curative treatment for high-risk and locally advanced rectal cancer is neoadjuvant chemoradiotherapy (nCRT) followed by surgical resection according to total mesorectal excision (TME) principles. The majority of patients have a low anterior resection (LAR) with a primary anastomosis. In patients in whom sphincter preservation is not feasible, an abdominoperineal resection (APR) is performed. In recent years, a wait-and-see policy in patients with a clinical complete response (cCR) has gained more acceptance[1–4]. This strategy is increasing in popularity when a cCR is observed, especially in elderly and frail patients.

The relationship between tumour response to nCRT and morbidity related to the surgical procedure is still unclear. Both increased and decreased morbidity have been reported in the literature[5–8]. Horisberger and colleagues[6] reported markedly enhanced rates of major surgical complications (anastomotic leak) in patients with histopathological regression grades 3 and 2. In contrast, Maggiori and co-workers[5] described a lower anastomotic leak rate among patients with a pathological complete response (pCR). In the populations described by Landi *et al.*[7] and Duldulao

and colleagues[8] no associations were found between pathological response and postoperative complications.

When considering a more conservative treatment strategy for a patient with a cCR, it is important to know whether response to nCRT is related to an increased or decreased postoperative complication rate. Preoperative risk assessment based on individual patient characteristics allows for a more accurate consideration of potential harm and benefit of the different treatment strategies.

Because of discordant results in the postoperative morbidity associated with response to nCRT and its potential influence on clinical decision-making, the present authors aimed to clarify whether there is a causal relationship between response to nCRT and surgical complications. To investigate this, surgical complication rates were compared between patients with and without pCR in a nationwide and unselected cohort that underwent TME after nCRT. Because the nature of surgical complications differs markedly between patients with or without construction of a primary anastomosis (risk of anastomotic leak), these groups were analysed separately.

Methods

Data were obtained from the Dutch ColoRectal Audit (DCRA) (www.dica.nl/dcra) database. The DCRA was initiated by the Association of Surgeons of the Netherlands to monitor, evaluate and improve colorectal cancer care. Because participation in the DCRA is made mandatory by the Dutch Health Care Inspectorate, all 92 hospitals that perform colorectal cancer surgery in the Netherlands participate in data delivery to this nationwide database. As a consequence, data are recorded in this database on all patients who undergo colorectal cancer surgery in the Netherlands. Data are recorded on over 200 parameters including: demographic characteristics, preoperative work-up, preoperative clinical staging, procedures performed, postoperative complications encountered and results of pathological examination. Validity of the data is safeguarded by control tools in the web-based data entry program. Feedback is sent whenever data are missing or appear to be improbable. Furthermore, an annual comparison is made with the National Cancer Registry on completeness and accuracy[9].

Patients were selected from the database when they met the following criteria: they had undergone surgical resection of a single primary carcinoma of the rectum between 1 January 2009 and 31 December 2017, and they had received nCRT before surgery. Minimum data requirements for inclusion in the study were data completeness on: postoperative tumour staging; detailed information on the exact procedure performed; and whether or not a primary anastomosis had been constructed. Patients were divided into two groups: those who had undergone TME without construction of a primary anastomosis (APR and LAR without anastomosis) and those who had had TME with construction of a primary anastomosis. As this was an observational study, and study data could not be traced back to individual patients, the study received ethical review board exemption status.

Treatment

In the Netherlands, patients with a locally advanced rectal carcinoma are treated with nCRT according to current national guidelines. According to these guidelines, radiotherapy is given at a total dose of 45–50 Gy (delivered in daily 1·8–2-Gy fractions 5 days per week). During radiotherapy, chemotherapy is given on a daily basis (capecitabine 825–1000 mg/m^2 5–7 days per week). Usually, surgical resection according to the TME principle is performed 8–12 weeks after completion of radiotherapy. The procedures performed are done in either a laparoscopic or open fashion depending on surgeon preference and tumour characteristics.

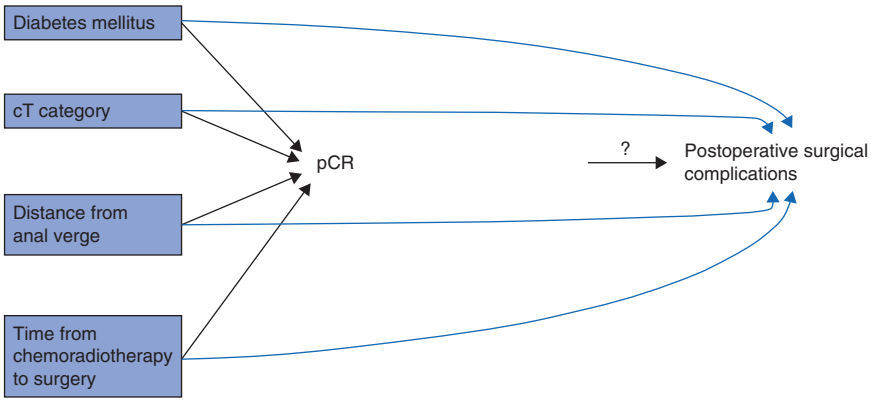
Outcome parameters

The primary outcome parameter was the occurrence of one or more surgical complications within 30 days of surgery or during the hospital admission (including mortality). Surgical complications were defined as complications directly related to the procedure performed. Complications that were scored were: anastomotic leak, pelvic abscess, surgical-site infection, postoperative haemorrhage, ileus requiring surgical intervention, fascial dehiscence, and iatrogenic injury of bowel or urinary tract.

Secondary outcome parameters investigated were: the occurrence of one or more postoperative complications regardless of cause within 30 days of surgery or during the hospital admission, anastomotic leakage, one or more invasive procedures performed for a postoperative complication (including both surgery and placement of percutaneous drains), anastomotic take-down resulting in secondary stoma construction, and the occurrence of one or more non-surgical complications within 30 days of surgery or during the hospital admission.

Anastomotic leak was defined as requiring either radiological or surgical intervention (International Study Group of Rectal Cancer grade B and C). Because no routine imaging was performed, patients with grade A anastomotic leakage were not scored and were thus automatically analysed as having no anastomotic leakage.

Fig. 1 Graphical presentation of confounding in a directed acyclic graph



Arrows are drawn based on prior knowledge of causal relationships between parameters. Boxed parameters are related to both pathological complete response (pCR) and postoperative surgical complications, and are outside the causal chain. Therefore, boxed parameters are considered to be confounders. The research question is indicated with a question mark above the arrow from exposure (pCR) to outcome (postoperative surgical complication).

Non-surgical complications were scored and defined as complications of either cardiac, respiratory, thromboembolic, infectious (other than surgical site) or neurological nature. Mortality was defined as death from any cause within 30 days of surgery or during the hospital admission.

Predictors and confounders

The main predictor investigated was pathological response to nCRT. For this, pathological response was categorized into two groups: patients with and patients without pCR. pCR was defined as the absence of histological evidence of viable tumour cells at the primary tumour site or in locoregional lymph nodes in the resected specimen (ypT0 N0). No detailed information was available on tumour regression grade. Patients with a moderate, minimal and poor response were therefore grouped together as having no pCR.

Confounders were defined as parameters that are associated both with pCR and the primary outcome parameter of surgical complications, without being in the causal path. Four parameters were considered to be potential confounders. *Fig. 1* depicts the relationships between the confounders, exposure and outcome. Parameters considered to be confounders were: diabetes mellitus[10–13] (dichotomous variable); tumour size reflected by cT status[14,15] (analysed as a categorical variable; 4 subgroups); distance from the anal verge[16,17] (analysed as a categorical variable, defined as low (0–5 cm), mid (more than 5 to 10 cm) and high (more than 10 cm) tumours); and weeks from nCRT to surgery[18,19] (analysed as a continuous variable). Potential confounders that contained missing values were investigated on whether missing data could be assumed to be missing completely at random. For these variables, Little's missing completely at random (MCAR) test was performed.

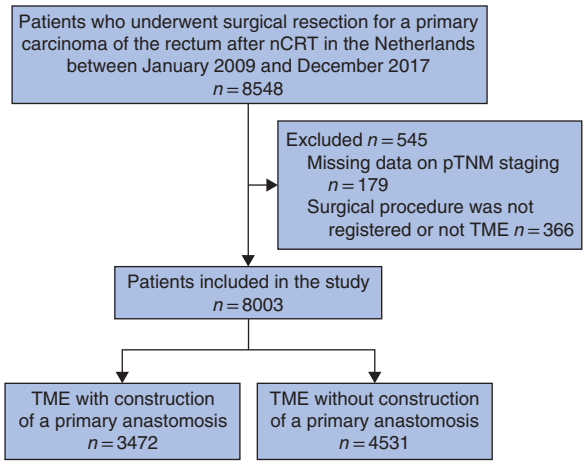
Statistical analysis

The study population was divided into patients with and without the construction of a primary anastomosis after TME. These groups were described and analysed separately. Within these groups, overall and specified complication rates were stratified by pathological response. The association of pCR with each of the outcomes of interest was analysed using univariable and multivariable logistic regression models. In the multivariable models, all of the parameters identified in the directed graph (*Fig. 1*) were included regardless of statistical significance. In this way, odds ratios (ORs) and 95 per cent confidence intervals were estimated. $P < 0{\cdot}050$ was considered statistically significant. All calculations were performed using SPSS® version 23 (IBM, Armonk, New York, USA).

Results

Between 1 January 2009 and 31 December 2017, a total of 8548 patients who underwent resection of colorectal cancer were identified in the DCRA database. Minimum data requirements were met for 8003 patients. All of these patients received nCRT before resection of the tumour by either TME with anastomosis (3472 patients, 43·4 per cent) or TME without anastomosis (4531 patients, 56·6 per cent) (*Fig. 2*). Overall, pCR was observed in 976 patients

Fig. 2 Inclusion of patients in the study



nCRT, neoadjuvant chemoradiotherapy; TME, total mesorectal excision.

(12·2 per cent). The majority of patients (in both groups) were men (5102 patients, 63·8 per cent), 2959 patients (37·0 per cent) were aged between 60 and 70 years, 4897 (61·2 per cent) had ASA grade 2, and 7076 patients (88·4 per cent) had resection for a clinically (pretreatment) staged T3–4 adenocarcinoma. Overall, the in-hospital mortality rate was 1·2 (94 patients) and did not differ between patients with and without a pCR ($P = 0·171$). More complications (surgical and non-surgical) were observed in patients who had a pCR (319 of 976, 32·7 per cent) than in patients without a pCR (2103 of 7027, 29·9 per cent); this difference was not statistically significant ($P = 0·083$). Surgical complications were observed more frequently when there was a pCR (242 of 976 (24·8 per cent) *versus* 1396 of 7027 (19·9 per cent) in patients without pCR; $P < 0·001$).

Characteristics of patients who had TME with or without anastomosis are summarized in *Table 1*. Apart from mean distance from the anal verge and surgical procedure performed, baseline parameters were comparable between the two groups. Mean distance from the anal verge was shorter in the TME without anastomosis group (4·3 cm *versus* 8·4 cm in patients with an anastomosis).

Handling of missing data

Three of the confounders entered in the multivariable analyses contained missing data: distance from the anal verge (missing in 975 patients, 12·2 per cent), cT category (missing in 310 patients, 3·9 per cent) and time from nCRT to surgery (missing in 694 patients, 8·7 per cent). Data were complete for all of these variables in 6211 patients (77·6 per cent).

Table 1 Patient and disease characteristics

	TME with anastomosis ($n = 3472$)	TME without anastomosis ($n = 4531$)
Age (years)*	62·4(10·1)	65·7(10·3)
Male sex	2192 (63·1)	2910 (64·2)
Type of procedure		
LAR with anastomosis	3472 (100)	–
LAR without anastomosis	–	1235 (27·3)
APR	–	3296 (72·7)
Laparoscopic (assisted) procedure	2288 (65·9)	2441 (53·9)
Creation of defunctioning stoma	2601 (74·9)	–
ASA grade		
1	1016 (29·3)	1002 (22·1)
2	2134 (61·5)	2763 (61·0)
3	302 (8·7)	717 (15·8)
4	8 (0·2)	26 (0·6)
Missing	12 (0·3)	23 (0·5)
Medical history		
Diabetes mellitus	383 (11·0)	651 (14·4)
Cardiac disease	404 (12·7)	806 (17·8)
Pulmonary disease	323 (9·3)	499 (11·0)
Preoperative anaemia‡	357 (10·3)	567 (12·5)
BMI (kg/m^2)		
< 20	171 (4·9)	253 (5·6)
20–24	1334 (38·4)	1584 (35·0)
25–34	1754 (50·5)	2286 (50·5)
≥ 35	94 (2·7)	168 (3·7)
Missing	119 (3·4)	240 (5·3)
Distance from anal verge (cm)		
0–5	616 (17·7)	2820 (62·2)
> 5	2446 (70·4)	1146 (25·3)
Missing	410 (11·8)	565 (12·5)
Time from nCRT to surgery (weeks)†	15	15
pT category		
pT0	629 (18·1)	768 (16·9)
pT1	217 (6·3)	289 (6·4)
pT2	833 (24·0)	1169 (25·8)
pT3	1654 (47·6)	1968 (43·4)
pT4	139 (4·0)	337 (7·4)
pN category		
pN0	2265 (65·2)	3081 (68·0)
pN1	795 (22·9)	967 (21·3)
pN2	412 (11·9)	483 (10·7)
pM status		
pM0	3266 (94·1)	4149 (91·6)
pM1	206 (5·9)	382 (8·4)
pCR	443 (12·8)	533 (11·8)
Histological subtype		
Adenocarcinoma	3229 (93·0)	4062 (89·6)
Mucinous carcinoma	124 (3·6)	233 (5·1)
Other/unspecified	119 (3·4)	236 (5·2)

Values in parentheses are percentages unless indicated otherwise; values are *mean(s.d.) and †median. ‡Defined as preoperative haemoglobin level lower than 11·3 g/dl in men and below 10·5 g/dl in women. TME, total mesorectal excision; LAR, low anterior resection; APR, abdominoperineal resection; nCRT, neoadjuvant chemotherapy.

Table 2 Postoperative outcomes stratified for pathological response

	After TME with primary anastomosis ($n = 3472$)		After TME without primary anastomosis ($n = 4531$)	
	No pCR ($n = 3029$)	pCR ($n = 443$)	No pCR ($n = 3998$)	pCR ($n = 533$)
Surgical complications	598 (19·7)	122 (27·5)	798 (20·0)	120 (22·5)
In-hospital mortality	26 (0·9)	2 (0·5)	63 (1·6)	3 (0·6)
All complications	873 (28·8)	159 (35·9)	1230 (30·8)	160 (30·0)
Anastomotic leak (ISREC grade B/C)	173 (5·7)	35 (7·9)	–	–
Invasive procedure owing to complication	353 (11·7)	60 (13·5)	361 (9·0)	57 (10·7)
Anastomotic take-down	125 (4·1)	23 (5·2)	–	–
Non-surgical complications	500 (16·5)	71 (16·0)	717 (17·9)	76 (14·3)
Length of hospital stay (days)*	7 (2–191)	7 (2–65)	8 (2–185)	7 (2–80)

Values in parentheses are percentages unless indicated otherwise; *values are median (range). TME, total mesorectal excision; pCR, pathological complete response; ISREC, International Study Group of Rectal Cancer.

Table 3 Univariable analysis of association between pathological complete response and postoperative outcomes

	After TME with primary anastomosis ($n = 3472$)		After TME without primary anastomosis ($n = 4531$)	
	Odds ratio*	*P*	Odds ratio*	*P*
Surgical complications	1·55 (1·23, 1·94)	0·001	1·17 (0·94, 1·45)	0·169
Mortality	0·52 (0·12, 2·20)	0·379	0·35 (0·11, 1·13)	0·080
All complications	1·38 (1·12, 1·71)	0·002	0·97 (0·79, 1·17)	0·726
Anastomotic leak (ISREC grade B/C)	1·51 (1·05, 2·17)	0·037	–	–
Invasive procedure owing to complication	1·19 (0·89, 1·59)	0·252	1·21 (0·90, 1·62)	0·213
Anastomotic take-down	1·27 (0·81, 2·01)	0·301	–	–
Non-surgical complications	0·97 (0·74, 1·27)	0·799	0·76 (0·59, 0·98)	0·036

Values in parentheses are 95 per cent confidence intervals. *Estimated based on results of univariable logistic regression analysis with no pathological complete response as reference group. TME, total mesorectal excision; ISREC, International Study Group of Rectal Cancer.

Little's MCAR test was performed to investigate whether missing data could be assumed to be MCAR. As Little's MCAR test was not significant ($\chi^2 = 33{\cdot}62$, 0 d.f., $P = 0{\cdot}001$), missing data could not be assumed to be MCAR. Because missingness was over 5 per cent and data could not be considered to be MCAR, complete case analysis was considered to be an unacceptable approach[20]. For this reason, multiple imputation by fully conditional specification was performed to impute estimated values for the three variables containing missing data that were considered to be potential confounders.

Total mesorectal excision with primary anastomosis

A total of 3472 patients had anterior resection with creation of a primary anastomosis after nCRT during the study period. In the large majority of these patients, a defunctioning stoma was also created (2601 patients, 74·9 per cent). Overall, postoperative complications were observed more often in patients with a pCR than in those without a pCR (difference 7·1 per cent) (*Table 2*). More surgical complications were observed in the pCR group than in the no-pCR group (27·5 *versus* 19·7 per cent respectively); this difference was statistically significant in the univariable analysis ($P = 0{\cdot}003$). A more detailed exploration of specific surgical complication rates revealed that anastomotic leak was found more frequently when pCR was present (7·9 per cent *versus* 5·7 per cent in patients with no pCR). In addition, surgical reintervention and secondary stoma construction were required more frequently in the pCR group.

Univariable logistic regression analysis found that surgical complications were observed more often when there was a pCR (OR 1·55, 95 per cent c.i. 1·23 to 1·94), but there was no significant difference for non-surgical complications (*Table 3*).

Table 4 gives the ORs of pCR (with no pCR as the reference, OR 1·00) for each outcome of interest adjusted for the predefined potential confounders. pCR was a statistically significant predictor of surgical complications (lower-bound c.i. OR greater than 1·00) and

Table 4 Multivariable analysis of the association between pathological complete response and outcome parameters after total mesorectal excision with construction of a primary anastomosis

	Odds ratio*	*P*
Surgical complications	1·53 (1·22, 1·92)	0·001
All complications	1·38 (1·12, 1·70)	0·003
Anastomotic leak	1·41 (1·03, 2·05)	0·040
Invasive procedure owing to complication	1·17 (0·87, 1·57)	0·296
Anastomotic take-down	1·24 (0·78, 1·96)	0·359
Non-surgical complications	0·97 (0·74, 1·28)	0·838

Values in parentheses are 95 per cent confidence intervals. *Estimated with no pathological complete response (pCR) as reference group for each outcome. Parameters entered in multivariable logistic regression analysis: pCR, distance to anal verge, time from chemoradiotherapy to surgery, cT status and diabetes mellitus.

Table 5 Multivariable analysis of association between pathological complete response and outcome parameters after total mesorectal excision without construction of a primary anastomosis

	Odds ratio*	*P*
Surgical complications	1·17 (0·94, 1·46)	0·154
All complications	0·98 (0·80, 1·19)	0·806
Invasive procedure owing to complication	1·22 (0·91, 1·65)	0·183
Non-surgical complications	0·80 (0·62, 1·04)	0·096

Values in parentheses are 95 per cent confidence intervals. *Estimated with no pathological complete response (pCR) as reference group for each outcome. Parameters entered in multivariable logistic regression analysis: pCR, distance to anal verge, time from chemoradiotherapy to surgery, cT status and diabetes mellitus.

anastomotic leak. There was no significant relationship with non-surgical complications.

Total mesorectal excision without primary anastomosis

A total of 4531 patients had resection without anastomosis. Overall, similar complication rates were found in the pCR and no-pCR response groups (*Table 2*). More surgical complications were observed in the pCR group (22·5 per cent *versus* 20·0 per cent in the no-pCR group). Interventions were also required slightly more often in the pCR group (10·7 *versus* 9·0 per cent respectively). In contrast (and compared with the results in the primary anastomosis group), more non-surgical complications were observed in patients without a pCR (17·9 per cent *versus* 14·3 per cent in patients with a pCR). In the no-pCR group the proportion of patients with ASA grade III/IV status was also higher than that of patients with ASA grade III/IV in the pCR group (17·0 *versus* 13·0 per cent respectively).

In the univariable analysis, for overall surgical complications the 95 per cent c.i. of the OR included 1·00, indicating no statistically significant effect of pCR on the occurrence of surgical complications (*Table 3*). For non-surgical complications, a statistically significant OR in favour of no pCR was found. Similarly in multivariable analysis, the effect of pCR on surgical complications was not statistically significant (*Table 5*). Again, there was a statistically significant relationship only between pCR and non-surgical complications.

Discussion

Patients who underwent TME and anastomosis had a greater likelihood of postoperative surgical complications in the presence of a pCR. In-depth analysis demonstrated that this increase in surgical complications was due partly to an increased risk of anastomotic leakage. Possibly as a result, surgical reinterventions and anastomotic take-down were observed more frequently when there was a pCR in this patient group. There was no evident relationship between surgical complications and pCR when no primary anastomosis was created.

To the authors' knowledge, four studies[5–8] have been published on postoperative morbidity in relation to response to nCRT. Those of Landi and colleagues[7] and Duldulao *et al.*[8] found no differences in terms of major postoperative complications between patients with and without a pCR. In the population described by Maggiori and co-workers[5] significantly more Clavien–Dindo grade III/IV complications were seen in the no-pCR group. In the study of Horisberger *et al.*[6] an increased risk of anastomotic leak was found in patients with histological regression grade 2 and 3 (tumour regression grading as defined by the Japanese Society for Cancer of the Colon and Rectum[21]). The database did not contain information on histopathological response grade, but the presence of pCR was recorded.

Increasing the interval between nCRT and TME to a minimum of 8 weeks appears to increase pCR and downstaging rates, and improve disease-free survival[22]. It is unclear whether an increased interval leads to more tissue reaction and consequently complications. Data from the GRECCAR-6 study[23] suggested that more complications are encountered when the interval between nCRT and surgery is longer. In contrast, the Stockholm III trial[24] found in a pooled analysis of the two short-course radiotherapy regimens (5 × 5-Gy radiation dose with surgery within 1 week *versus* 5 × 5-Gy radiation dose with surgery after 4–8 weeks) that the risk of postoperative complications was significantly lower after short-course radiotherapy with delay.

The nCRT protocols currently being described in the literature[25–27] demonstrate significant tumour downsizing in up to two-thirds of patients, and pCR rates ranging between 14 and 25 per cent. The overall pCR rate observed in the present study was somewhat lower (12·2 per cent). The higher pCR rates described in the literature are all documented in subpopulations rather than a nationwide sample. A meta-analysis[28] in which patients with pCR were compared with non-responders found that pCR was associated with fewer local recurrences, less frequent distant failure, and a greater likelihood of being alive and disease-free at 5 years. In addition, owing to improved tumour downstaging, relatively more sphincter-preserving procedures may be performed after nCRT[29]. In contrast to this improved oncological outcome, nCRT followed by TME has been associated with increased postoperative surgical morbidity[30] and decreased long-term functional outcome[31]. Furthermore, anastomotic leak has been associated with an increased risk of local recurrence, reduced long-term survival and decreased disease-free survival[32–35].

An alternative treatment strategy is organ preservation through local excision after a good response to nCRT[36,37]. In the GRECCAR-2 study[38], patients who responded well to nCRT (estimated residual tumour less than 2 cm) were randomized between TME and local resection only. A relatively large proportion of patients in the local excision group had completion TME resection. Probably because of this, surgical morbidity was increased and compromised the potential advantages of local excision. No short-term superiority of local excision over TME could be established, and long-term oncological outcome remains to be determined[38]. A similar observation was made by Debove and colleagues[39]; in a study of the results of local excision, they also observed relatively high incomplete oncological treatment results. These findings underline the importance of accurate staging following nCRT when making decisions about subsequent resection strategies.

The present study has several limitations. Although the database was based on a large nationwide population, resulting in high statistical significance, the presented results should be interpreted with caution. Response to nCRT was evaluated based on the results of pathological examination of the resected specimen. Unfortunately, it is still difficult to estimate whether pCR is present after nCRT based on clinical parameters. Several studies have investigated the role of imaging modalities such as transrectal endoscopic ultrasound imaging, MRI and integrated PET. None of these modalities has been proven to diagnose pCR accurately[40–43]. The time sequence of events makes it impossible to use pCR clinically when deciding whether or not to operate on a particular patient.

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