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Neoadjuvant Radiation Therapy Prior to Total Mesorectal Excision for Rectal Cancer is Not Associated with Postoperative Complications Using Current Techniques

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Abstract

Background—Neoadjuvant radiation therapy (RT) downstages rectal cancer but may increase postoperative morbidity. This study aims to quantify 30-day complication rates after total mesorectal excision (TME) using current techniques and to assess for an association of these complications with neoadjuvant RT.

Methods—Stage I–III rectal cancer patients who underwent TME from 2005 to 2010 were identified. Complications occurring within 30 days after TME were retrieved from a prospectively maintained institutional database of postoperative adverse events.

Results—The cohort consisted of 461 patients. Median age was 59 years (range 18–90), and 274 patients (59 %) were male. Comorbid conditions included obesity ($n = 147$; 32 %), coronary artery disease ($n = 83$; 18 %), diabetes ($n = 65$; 14 %), and inflammatory bowel disease ($n = 19$; 4 %). A low anterior resection (LAR) was performed in 383 cases (83 %), an abdominoperineal resection (APR) was performed in 72 cases (16 %), and a Hartmann's procedure was performed in 6 cases (1 %). Preoperative RT was delivered to 310 patients (67 %; median dose of 50.4 Gy, range 27–55.8 Gy). The 30-day incidence of postoperative mortality was 0.4 % ($n = 2$), any complication 25 % ($n = 117$), grade 3 or more complication 5 % ($n = 24$), intra-abdominal infection 3 % ($n = 12$), abdominal wound complication 9 % ($n = 42$), perineal wound complication after APR 11 % ($n = 8/72$), and anastomotic leak after LAR 2 % ($n = 6/383$). These events were not associated with neoadjuvant RT.

Conclusion—In a cohort undergoing TME using current techniques, neoadjuvant RT was not associated with 30-day postoperative morbidity or mortality.

Neoadjuvant chemoradiation and total mesorectal excision (TME), the standard of care in locally advanced rectal cancer, provide excellent local disease control but may result in significant morbidity.¹ Postoperative complications within 30 days after TME are an important aspect of treatment-related toxicity. Previous studies have identified multiple

factors that increase the risk of postoperative morbidity, including duration of surgery, diagnosis of inflammatory bowel disease, and other comorbidities.^{2,3} Some groups have identified an association between neoadjuvant radiation therapy (RT) and postoperative adverse events. At our institution, patients undergoing TME from the late 1980s to mid-1990s were at increased risk of perineal morbidity after abdominoperineal resection (APR),⁴ and pelvic abscess formation after low anterior resection (LAR),⁵ if they received preoperative RT. While some groups have corroborated an association between neoadjuvant RT and surgical site infections (SSIs),^{6–8} others have found none.^{2,9}

Practice patterns have changed since the publication of these reports. National quality improvement initiatives were implemented in the early 2000s to reduce the risk of SSIs. Initiatives such as the Surgical Care Improvement Project (SCIP) emphasize prophylactic antibiotic use, perioperative glucose control, normothermia, and clipper hair removal. These measures reduce rates of superficial, deep, and organ space infections after colorectal surgery.¹⁰ As part of the effort to monitor and reduce surgical morbidity at our institution, a prospectively maintained database of surgical secondary events was established in 2001, facilitating accurate quantification of postoperative morbidity with minimal bias. In recent years, neoadjuvant therapy regimens at our institution have also changed. Patients undergoing concurrent chemoradiation now receive capecitabine or protracted infusion, rather than bolus, 5-fluorouracil (5-FU).^{11,12} Based on promising preliminary results, selected patients receive induction systemic chemotherapy (CT), with or without RT.¹³

These changes in practice may influence the detected association between neoadjuvant RT and postoperative complications. This study was designed to quantify the current incidence of complications, within 30 days after TME, for non-metastatic rectal cancer, and to identify risk factors for postoperative morbidity, with a particular focus on the association of neoadjuvant RT with SSI.

Methods

Patients

After obtaining a waiver of authorization from our Institutional Review Board, patients undergoing surgery for stage I–III rectal cancer between January 2005 and December 2010 were identified retrospectively. Those undergoing standard TME or tumor-specific mesorectal excision were included. Patients were excluded if they had recurrent disease, underwent pelvic exenteration, or received intraoperative RT. A total of 461 patients met the eligibility criteria.

Treatment Information

All patients underwent APR, LAR, or Hartmann's procedure at the discretion of the surgeon. Patients with clinical stage I rectal cancer had surgery alone. Neoadjuvant therapy, followed by surgery in 4–8 weeks, was recommended for stage II–III patients.

For most stage II–III patients, the recommended neoadjuvant therapy was pelvic RT with concurrent infusional 5-FU or capecitabine. RT was provided with a conventional three-field technique or intensity-modulated RT (IMRT), according to institutional practice. The three-

field treatments used PA and opposed lateral fields to treat the entire pelvis to 45 Gy, followed by 5.4 Gy boost to the rectal tumor, for a total dose of 50.4 Gy at 1.8 Gy per fraction. With IMRT, the pelvis was treated to 45 Gy at 1.8 Gy per fraction, and the rectal tumor was treated to 50 Gy at 2 Gy per fraction, using an integrated boost. Contouring was performed according to the Radiation Therapy Oncology Group (RTOG) consensus guidelines.¹⁴ Some stage II–III patients received induction CT alone or in addition to RT. The most commonly used induction CT was 5-FU+oxaliplatin (FOLFOX)±bevacizumab. Other regimens were used less frequently, as detailed in the results section.

Patient Follow-Up and Toxicity Assessment

During the first postoperative month, patients were seen at least once in the colorectal surgery clinic. All complications were recorded in a prospectively maintained database and graded as follows: grade 1, resolved with oral medication or bedside medical care; grade 2, resolved with IV medical therapy; grade 3, resolved with procedure(s) performed by a surgeon or interventional radiologist; grade 4, resulted in chronic deficit(s) or disability; grade 5, resulted in death. A 2010 blinded audit of the database supported >95 % reporting of grade 3 or more events. SSIs were defined according to criteria published by the Centers for Disease Control.¹⁵

Statistical Analysis

Characteristics of patients who received RT versus those who did not were compared using the Chi-squared test for categorical variables and the independent samples *t*-test for continuous variables. Univariate and multivariate logistic regression analysis was used to assess the association between postoperative complications and demographic, tumor, and treatment characteristics. *p*-values < 0.05 were considered significant.

Results

Patient, Disease, and Treatment Characteristics

The cohort comprised 461 patients with a median age of 59 years (range 18–90). Fifty-nine percent (*n* = 274) were male and 41 % (*n* = 187) were female. Comorbidities included obesity (147; 31 %), diabetes (65; 14 %), coronary artery disease (83; 18 %), peripheral vascular disease (16; 3 %), and IBD (19; 4 %).

At the time of diagnosis, 92 patients (20 %) had clinical stage I disease, 104 (23 %) had clinical stage II disease, and 265 (57 %) had clinical stage III disease. Rectal cancer histology was adenocarcinoma (458; 99 %), squamous cell carcinoma (1; 0.2 %), adenosquamous (1; 0.2 %), and large cell neuroendocrine (1; 0.2 %). For patients with non-adenocarcinoma histology, neoadjuvant therapy consisted of induction 5-FU+cisplatin, then RT with concurrent 5-FU+mitomycin C (squamous cell); RT with concurrent 5-FU (adenosquamous); induction cisplatin+irinotecan, then RT with concurrent cisplatin+irinotecan (large-cell neuroendocrine).

LAR was performed in 383 cases (83 %), APR was performed in 72 cases (16 %), and Hartmann's procedure was performed in 6 cases (1 %). A loop ileostomy was created in 243

of the LAR patients (243/383; 63 %). In APR patients, perineal reconstruction with a rectus abdominis myocutaneous (RAM) flap was performed in 7 of 72 patients (10 %). The length of operation was a median of 240 min (range 51–604). Surgery was performed laparoscopically in 38 cases (8 %). Ninety-one patients (20 %) underwent multivisceral resection; additional organs most commonly resected were the uterus, posterior vaginal wall, or prostate. Twelve patients (3 %) required blood transfusions intraoperatively.

Preoperative RT was delivered to 310 patients (67 %). Of these, 304 (98 %) received concurrent 5-FU or capecitabine. Median RT dose was 50.4 Gy (range 27–55.8 Gy). The technique used was IMRT for 39 patients (13 %) and conventional three-field RT for 271 patients (87 %). Fourteen patients (5 %) required treatment breaks or could not complete the intended therapy. Median time from completion of RT to surgery was 7 weeks (range 2–39). Three patients had longer intervals between RT and surgery (19, 22, 39 weeks) because they received induction CT after RT.

Patients receiving RT were less likely to undergo laparoscopic surgeries (4 vs. 18 %; $p < 0.001$) and more likely to receive a loop ileostomy if they had LAR (72 vs. 40 %; $p < 0.001$) [Table 1]. There was no difference between the two groups in frequency of RAM flap perineal reconstruction during APR (5/51 [10 %] for RT vs. 2/17 [12 %] for no-RT; $p = 0.82$). Patients in the RT group had significantly higher stages of rectal cancer: a majority (70 %) had stage III disease, and in the no-RT group, a majority (54 %) had stage I disease ($p < 0.001$). Patients with locally advanced disease not receiving RT often received induction CT. This practice pattern explains the significantly higher use of neoadjuvant CT in patients not receiving RT (8 % for RT vs. 27 % for no-RT; $p < 0.001$).

Induction CT with or without RT was administered to 67 patients (15 %). The CT regimen was FOLFOX ($n = 27$; 6 %), FOLFOX+bevacizumab ($n = 27$; 6 %), 5-FU+cetuximab ($n = 9$; 2 %), FOLFOX+irinotecan+bevacizumab ($n = 1$; 0.2 %), 5-FU+irinotecan+bevacizumab ($n = 11$; 0.2 %), 5-FU+cisplatin ($n = 11$; 0.2 %), cisplatin+irinotecan (1; 0.2 %). For 26 patients who received both induction CT and RT, CT preceded RT in 23 patients (88 %), and followed RT in 3 patients (12 %). Median time from completion of CT to surgery was 5 weeks (range 2–28).

Complication Rates

The overall 30-day postoperative mortality rate was 0.4 % ($n = 2$). There was one death from aspiration on postoperative day 3, and one from sepsis due to *Clostridium difficile* enteritis on day 16. There were two grade 4 complications: one acute respiratory distress syndrome (postoperative day 0), and one anastomotic leak resulting in acute peritonitis (postoperative day 6). In the cohort of 461 patients, 117 (25 %) had at least one complication within 30 days after TME; 24 (5 %) had a grade 3 or more complication (Table 2).

Table 3 compares the 30-day complication rates of patients who did or did not receive neoadjuvant RT. RT was not significantly associated with incidence of any complication, any grade 3 or more complication, intraabdominal infection or abscess, abdominal wound

complication, perineal wound complication after APR, anastomotic leak after LAR, or postoperative mortality.

Univariate and multivariate analyses were performed to assess for association between the risk of postoperative complications and patient, disease, and treatment characteristics listed in Table 1. The only variable associated with risk of any grade 3 or more complication was longer duration of surgery (HR 1.00; 95 % CI 1.00–1.01; $p = 0.03$) [Table 4]. There was no association between grade 3 or more complications and neoadjuvant RT or CT, on univariate or multivariate analysis.

The risk of SSI was assessed separately, given the previously reported association with neoadjuvant RT. Two classes of SSI were considered: superficial and/or deep wound infections, and organ space infections, defined as intra-abdominal infection or abscess, rectovaginal fistula, and/or anastomotic leak. The only independent risk factor for superficial and/or deep wound infection was obesity (HR 2.72, 95 % CI 1.46–5.50; $p < 0.01$) [Table 5]. Organ space infections were more common in patients undergoing longer surgeries (HR 1.01; 95 % CI 1.00–1.01; $p = 0.01$). There was no association of superficial/deep or organ space infections with neoadjuvant RT or CT.

Discussion

This study of 461 non-metastatic rectal cancer patients undergoing TME from 2005 to 2010 found no association between preoperative RT and postoperative complications. On multivariate analysis, the only patient, disease, or treatment variable independently associated with increased risk of any grade 3 or more morbidity was longer duration of surgery, which may be a surrogate for technical difficulty of the operation. The risk of SSI was considered separately, given the previously reported association with neoadjuvant RT. For this analysis, two classes of SSI were considered: superficial and/or deep wound infections, and organ space infections. The only variable independently associated with increased risk of wound infections was obesity (HR 2.72; $p < 0.01$), and the only variable independently associated with organ space infections was longer duration of surgery (HR 1.01; $p = 0.01$).

Although some researchers have identified an association between SSI and preoperative RT,^{4,6,7} others have not.^{2,3,9} These discrepant findings may be due to differences in neoadjuvant therapy, surgical technique, patient follow-up, or definition and classification of toxicity. Interestingly, studies of patients undergoing TME at our institution from the late 1980s to mid-1990s did identify a significant association of SSIs with neoadjuvant RT. In a population of 681 patients undergoing LAR at our institution between 1987 and 1995, Enker et al.⁵ detected an increased risk of pelvic abscess formation in those receiving neoadjuvant RT (3 vs. 0.2 %; $p = 0.03$). In the current cohort, the incidence of pelvic infection or abscess was slightly higher in patients receiving RT; however, this association did not reach statistical significance (4 vs. 0.6 %; $p = 0.07$). Other groups have identified an increased risk of anastomotic leakage after LAR in patients receiving preoperative RT (relative risk 2.861; $p = 0.003$).^{8,16} In the current study, there was no association between RT and anastomotic leakage within 30 days postoperatively (1 % RT vs. 2 % no-RT; $p = 0.40$). However, pelvic

infections and anastomotic leaks were rare events in our cohort, so the statistical power may have been insufficient to detect an association.

Wound infections were also associated with RT in a previous cohort from our institution. In a group of patients undergoing APR from 1987 to 1997, those receiving pre-operative RT ($n = 100$) were compared with others who had not ($n = 159$). The 30-day incidence of perineal wound infection and failure of perineal wound healing was significantly higher in the RT group (34 vs. 13 %, and 51 vs. 19 %, respectively; $p < 0.05$).⁴ In the current study, there was no association between RT and perineal wound morbidity in patients who underwent APR ($n = 72$). The 30-day incidence of perineal wound complications was 11 % for both the RT and no-RT groups ($p = 0.93$). Furthermore, the incidence of perineal morbidity in the modern cohort was lower than in the historical cohort, even when considering only patients who did not receive RT.

In our study, obesity was the only variable independently associated with increased risk of wound infections (HR 2.72; $p < 0.01$). This finding corroborates a large body of data showing that obesity negatively affects wound healing.¹⁷ In fact, one group calculated a 10 % increase in the risk of perineal wound complication for each point increase in a patient's BMI.³ Zorcolo et al.⁹ recently published their experience treating 157 patients with long-course preoperative RT and APR. Their results corroborate those of the current study, identifying obesity as the only risk factor for postoperative perineal morbidity. No association between perineal wound complications and neoadjuvant RT was identified.

The results of the current study, considered in combination with previous reports from our institution, suggest that RT was formerly associated with an increased risk of SSI, but that this association does not currently exist. Multiple variables may have contributed to this shift. There have been changes in surgical practice following implementation of initiatives such as SCIP. RT may lose its association with postoperative morbidity when SSI prevention is emphasized. Differences in neoadjuvant therapy may also have influenced postoperative complication risk. In previous reports, most patients received bolus 5-FU during weeks 1 and 5 of RT; currently, patients receive continuous infusional 5-FU or oral capecitabine throughout 5 weeks of RT. Bolus 5-FU causes significantly worse myelosuppression than infusional 5-FU.¹¹ Therefore, it may be hypothesized that patients undergoing surgery are at greater risk of infection after receiving bolus rather than infusional 5-FU. In previous studies, neoadjuvant RT information was not available for all patients, and duration of time between completion of RT and surgery was not reported. These variables may significantly affect complication rates.¹⁸ Lastly, postoperative complications for the current cohort, but not for those in previous studies, were recorded in and retrieved from a prospectively maintained database. This methodological change may affect the detected rates of surgical adverse events and their association with demographic variables.

This study is subject to the limitations inherent in any retrospective work. However, every attempt was made to select a homogeneous patient population. Only non-metastatic rectal cancer patients who underwent TME at our institution during a 5-year period were eligible. Information regarding postoperative complications was retrieved from a prospectively maintained institutional database, limiting bias. A blinded audit of the database performed in

2010 supported >95 % reporting of grade 3 or more events (personal communication). Thus, it is unlikely that any of these clinically significant complications were missed. However, it is possible that lower grade events were less reliably captured in the database, and may not be accounted for in this analysis.

Conclusions

Although TME results in excellent oncologic outcomes, it is a challenging operation with significant potential morbidity. The clinician must understand factors that predispose to toxicity in order to make appropriate treatment recommendations. This study demonstrates no association between neoadjuvant RT and 30-day morbidity or mortality, in the current era.

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Table 1
Patient, disease, and treatment characteristics

	RT (n = 310)	No RT (n = 151)	p-value
<i>Patient characteristics</i>			
Age at surgery [years (range)]	59 (26–88)	59 (18–90)	0.957
Gender (male:female) [n (%)]	192 (62):118 (38)	82 (54):69 (46)	0.117
<i>Comorbid conditions [n (%)]</i>			
Obesity	93 (30)	54 (36)	0.213
Diabetes	41 (13)	24 (16)	0.440
Coronary artery disease	57 (18)	26 (17)	0.759
Peripheral vascular disease	11 (4)	5 (3)	0.896
Inflammatory bowel disease	10 (3)	9 (6)	0.166
<i>Surgery [n (%)]</i>			
APR	53 (17)	19 (14)	0.456
Hartmann's	4 (0.6)	2 (0.6)	
LAR	253 (82)	130 (86)	
Loop ileostomy in LAR patients	182 (72)	61 (40)	<0.001
<i>Surgical details</i>			
Laparoscopic [n (%)]	11 (4)	27 (18)	<0.001
Multivisceral resection [n (%)]	65 (21)	26 (17)	0.343
Length of operation [min (range)]	244 (51–604)	230 (88–520)	0.170
<i>Tumor histology [n (%)]</i>			
Adenocarcinoma	307 (99)	151 (100)	1.000
<i>Clinical stage [n (%)]</i>			
I	10 (3)	82 (54)	<0.001
II	82 (26)	22 (15)	
III	218 (70)	47 (31)	
<i>Neoadjuvant treatment [n (%)]</i>			
Induction chemotherapy	26 (8)	41 (27)	<0.001

RT radiation therapy, APR abdominoperineal resection, LAR low anterior resection

Table 2

30-day complications (*n* = 461 patients)

	Grade [<i>n</i> (%)]				
	1	2	3	4	5
<i>Surgical complications</i>					
Intra-abdominal infection or abscess (<i>n</i> = 12; 3 %)	1 (0.2)	2 (0.4)	9 (2)		
Abdominal wound complication (<i>n</i> = 42; 9 %)	31 (7)	8 (2)	3 (0.7)		
Perineal wound complication after APR (<i>n</i> = 8/72; 11 %)	3 (4)	5 (7)			
Anastomotic leak after LAR (<i>n</i> = 6/383; 2 %)			5 (1)	1 (0.2)	
Rectovaginal fistula (<i>n</i> = 2; 0.4 %)			2 (0.4)		
Small bowel perforation (<i>n</i> = 1; 0.2 %)			1 (0.2)		
Ileus (<i>n</i> = 8; 2 %)	2 (0.4)	6 (1)			
Small bowel obstruction (<i>n</i> = 3; 0.6 %)	2 (0.4)	1 (0.2)			
Urological complication (<i>n</i> = 7; 2 %)	4 (0.8)	1 (0.2)	2 (0.4)		
Bleeding (<i>n</i> = 6; 1 %)	3 (0.6)	3 (0.6)			
Dehydration and/or failure to thrive (<i>n</i> = 9; 2 %)	2 (0.4)	7 (2)			
<i>General complications</i>					
Cardiac (<i>n</i> = 9; 2 %)		5 (1)	4 (0.8)		
Vascular (<i>n</i> = 9; 2 %)	1 (0.2)	6 (1)	2 (0.4)		
Pulmonary (<i>n</i> = 4; 0.9 %)		1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Neurological (<i>n</i> = 3; 0.6 %)	3 (0.6)				
Infectious, excluding SSI (<i>n</i> = 9; 2 %)	1 (0.2)	7 (2)			1 (0.2)

APR abdominoperineal resection, LAR low anterior resection, SSI surgical site infection

Table 3
Complications stratified by neoadjuvant radiation therapy receipt

	Neoadjuvant RT (<i>n</i> = 310) [<i>n</i> (%)]	No neoadjuvant RT (<i>n</i> = 151) [<i>n</i> (%)]	<i>p</i> -Value
Any complication	77 (25)	40 (26)	0.70
Any grade 3 or more complication	14 (5)	10 (7)	0.34
Intra-abdominal infection or abscess	11 (4)	1 (0.6)	0.07
Abdominal wound complication	23 (7)	19 (13)	0.07
Perineal wound complication after APR (<i>n</i> = 72 ^a)	6/53 (11)	2/19 (11)	0.93
Anastomotic leak after LAR (<i>n</i> = 383 ^a)	3/253 (1)	3/130 (2)	0.40
Death	1 (0.3)	1 (0.6)	0.60

RT radiation therapy, APR abdominoperineal resection, LAR low anterior resection

^aThe remaining six patients had a Hartmann's procedure

Table 4
Risk factors for any grade 3 or more complication ($n = 24$)

	Univariate HR (95 % CI)	Univariate p -value	Multivariate HR (95 % CI)	Multivariate p -value
<i>Patient characteristics</i>				
Age at surgery (years)	1.01 (0.98–1.04)	0.73	–	–
Male:Female	1.05 (0.46–2.42)	0.91	–	–
<i>Comorbid conditions</i>				
Obesity	1.56 (0.68–3.61)	0.29	–	–
Diabetes	1.23 (0.41–3.73)	0.77	–	–
Peripheral vascular disease	1.22 (0.16–9.67)	0.85	–	–
Coronary artery disease	1.96 (0.78–4.88)	0.15	–	–
Inflammatory bowel disease	2.25 (0.49–10.34)	0.30	–	–
<i>Surgery</i>				
APR vs. LAR/Hartmann's	1.31 (0.38–4.52)	0.67	–	–
Laparoscopic	1.64 (0.47–5.77)	0.44	–	–
Stoma created	1.72 (0.63–4.69)	0.29	–	–
Multivisceral resection	1.73 (0.70–4.31)	0.24	–	–
Length of operation (min)	1.00 (1.00–1.01)	0.03	1.00 (1.00–1.01)	0.03
<i>Clinical stage</i>				
I	1.00	Ref	–	–
II	1.90 (0.71–5.06)	0.20	–	–
III	1.41 (0.51–3.93)	0.51	–	–
<i>Neoadjuvant treatment</i>				
Neoadjuvant radiation	0.67 (0.29–1.54)	0.34	0.60 (0.25–1.43)	0.25
Induction chemotherapy	0.83 (0.24–2.87)	0.77	0.75 (0.21–2.70)	0.65

HR hazard ratio, CI confidence interval, APR abdominoperineal resection, LAR low anterior resection

Table 5
Risk factors for surgical site infections, categorized as superficial and/or deep abdominal or perineal wound infection ($n = 50$) and organ space infection ($n = 16$)

	Wound infection ($n = 50$)				Organ space infection ($n = 16$)			
	Univariate HR (95 % CI)	Univariate p -value	Multivariate HR (95 % CI)	Multivariate p -value	Univariate HR (95 % CI)	Univariate p -value	Multivariate HR (95 % CI)	Multivariate p -value
<i>Patient characteristics</i>								
Age at surgery (years)	0.99 (0.97–1.02)	0.55	-	-	0.96 (0.93–1.00)	0.05	0.96 (0.93–1.01)	0.09
Male: Female	1.07 (0.59–1.94)	0.83	-	-	0.88 (0.31–2.45)	0.80	-	-
<i>Comorbid conditions</i>								
Obesity	3.12 (1.72–5.68)	<0.01	2.72 (1.46–5.05)	<0.01	1.70 (0.62–4.64)	0.31	-	-
Diabetes	1.19 (0.53–2.65)	0.68	-	-	0.40 (0.05–3.06)	0.38	-	-
Peripheral vascular disease	0.54 (0.07–4.17)	0.55	-	-	-	-	-	-
Coronary artery disease	1.00 (0.47–2.15)	1.00	-	-	0.64 (0.14–2.88)	0.56	-	-
Inflammatory bowel disease	0.45 (0.06–3.41)	0.44	-	-	1.58 (0.2–12.70)	0.67	-	-
<i>Surgery</i>								
APR vs. LAR/Hartmann's	2.10 (1.05–4.18)	0.04	1.77 (0.85–3.68)	0.13	1.26 (0.35–4.53)	0.73	-	-
Laparoscopic	0.96 (0.33–2.84)	0.95	-	-	0.74 (0.09–5.72)	0.77	-	-
Stoma created	1.64 (0.81–3.31)	0.17	-	-	1.33 (0.42–4.21)	0.62	-	-
Multivisceral resection	1.50 (0.76–2.96)	0.24	-	-	2.54 (0.90–5.72)	0.08	-	-
Length of operation (min)	1.00 (1.00–1.01)	0.03	1.00 (1.00–1.01)	0.27	1.01 (1.00–1.01)	<0.01	1.01 (1.00–1.01)	0.01
<i>Clinical stage</i>								
I	1.00	Ref	-	-	1.00	Ref	-	-
II	1.20 (0.48–3.00)	0.69	-	-	0.88 (0.17–4.48)	0.88	-	-
III	1.13 (0.52–2.49)	0.76	-	-	1.16 (0.31–4.32)	0.82	-	-
<i>Neoadjuvant treatment</i>								
Neoadjuvant radiation	0.64 (0.35–1.16)	0.14	0.66 (0.35–1.24)	1.09	2.16 (0.61–7.70)	0.24	2.27 (0.59–8.73)	0.23
Induction chemotherapy	1.14 (0.51–2.54)	0.76	1.09 (0.47–2.55)	0.84	1.37 (0.38–4.96)	0.63	1.51 (0.36–644)	0.57

Organ space infection is defined as intra-abdominal infection or abscess and/or rectovaginal fistula and/or anastomotic leak

HR hazard ratio, CI confidence interval, APR abdominoperineal resection, LAR low anterior resection