



## ORIGINAL ARTICLE

# Risk factors for anastomotic leakage after anterior resection for rectal cancer (RALAR study): A nationwide retrospective study of the Italian Society of Surgical Oncology Colorectal Cancer Network Collaborative Group

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## Abstract

**Aim:** Anastomotic leakage after restorative surgery for rectal cancer shows high morbidity and related mortality. Identification of risk factors could change operative planning, with indications for stoma construction. This retrospective multicentre study aims to assess the anastomotic leak rate, identify the independent risk factors and develop a clinical prediction model to calculate the probability of leakage.

<sup>†</sup>The members of the Italian Society of Surgical Oncology Colorectal Cancer Network Collaborative Group are listed in [Appendix 1](#).

**Funding information**

This study had no financial support or funding.

**Methods:** The study used data from 24 Italian referral centres of the Colorectal Cancer Network of the Italian Society of Surgical Oncology. Patients were classified into two groups, AL (anastomotic leak) or NoAL (no anastomotic leak). The effect of patient-, disease-, treatment- and postoperative outcome-related factors on anastomotic leak after univariable and multivariable analysis was measured.

**Results:** A total of 5398 patients were included, 552 in group AL and 4846 in group NoAL. The overall incidence of leaks was 10.2%, with a mean time interval of 6.8 days. The 30-day leak-related mortality was 2.6%. Sex, body mass index, tumour location, type of approach, number of cartridges employed, weight loss, clinical T stage and combined multiorgan resection were identified as independent risk factors. The stoma did not reduce the leak rate but significantly decreased leak severity and reoperation rate. A nomogram with a risk score (RALAR score) was developed to predict anastomotic leak risk at the end of resection.

**Conclusions:** While a defunctioning stoma did not affect the leak risk, it significantly reduced its severity. Surgeons should recognize independent risk factors for leaks at the end of rectal resection and could calculate a risk score to select high-risk patients eligible for protective stoma construction.

**KEYWORDS**

colorectal fistula, colorectal leakage, rectal cancer, rectal surgery, stoma

**INTRODUCTION**

Anastomotic leakage (AL) represents a frequent and severe complication after resection for rectal cancer (RC), with reported incidence and related mortality ranging from 0.0% to 36.3% and from 2% to 9%, respectively [1]. Additionally, many AL-related complications, such as intra-abdominal abscesses, wound infections, diffuse peritonitis and sepsis, can lead to lengthened hospital stay (LoS), reoperation, increased mortality and worsened survival outcomes [2].

In a review by Bruce et al. [3], 56 different definitions of AL were documented; several studies have tried to define the characteristics of AL and its grades of severity [2,4]. The most recurrent definition described AL as 'a communication between the intraluminal and extraluminal compartments owing to a defect of the integrity of the intestinal wall at the anastomosis between the colon and rectum or the colon and anus' [2]. Usually, AL is diagnosed between postoperative days 1 and 14 [1]; however, late leaks, occurring after patient discharge or even after the 30th postoperative day, have frequently been described [5].

Management of AL is primarily based on the patient's clinical stability; treatment can be conservative, with antibiotics associated with total parenteral nutrition in the case of subclinical leaks. While endoscopic treatment with colonic stenting, clip placement and endoluminal vacuum therapy or percutaneous drainage can be performed in stable patients with no signs and symptoms of incoming sepsis [6–8], surgery with abdominal and pelvic revision, together with bowel diversion, is mandatory in the case of otherwise unmanageable abdominal sepsis [9]. Ultimately, AL negatively affects

**What does this paper add to the literature?**

This study identified nine independent risk factors for colorectal anastomotic leak. The construction of a defunctioning stoma was documented to be a protective factor for clinical severity of leaks. A specific score (RALAR score) available online can help surgeons to intra-operatively select patients who may benefit from protective ostomy.

patients' overall and disease-specific survival, as well as local recurrence [10,11].

Based on the results of univariate and multivariate analysis of patient- and procedure-related variables, several independent factors to predict AL incidence and severity, such as the distance of the anastomosis from the anal verge, male sex and obesity [12,13], have been identified in recent years. Unfortunately, retrospective and other observational studies have several limitations, primarily due to their small sample size [4,14].

A recent, large sample size meta-analysis developed a specific score to predict the hazard of AL. Notwithstanding, this study also included data from secondary care facilities with variations in technologies and skills, which may have affected AL incidence [15,16].

Considering the lack of accurate assessment of risk factors for AL in the literature, the purpose of this study was to estimate the overall anastomotic leak rate after restorative resection for RC, identify the independent risk factors, and develop a clinical prediction model to calculate the probability of AL occurrence.

## METHODS

### Study design and oversight

This nationwide, multicentre, retrospective study involved 24 Italian referral centres for colorectal surgery; the guidelines set out in the STROBE statement [17] were followed. Central Ethics Committee approval was obtained by the AOU San Luigi Gonzaga human research institutional review board (approval date 23 October 2018, protocol number 15525). Individual sites not covered by central approval obtained the local committee's approval.

All consecutive patients with RC within 15 cm from the anal verge, submitted to resection surgery for rectal cancer between January 2000 and December 2016, were included in the study. Inclusion and exclusion criteria are detailed in Table S1. Based on their postoperative course, patients were classified into two groups: patients with anastomotic leak, AL; or patients without anastomotic leak, NoAL.

Most patients (93.9%) had a minimum follow-up of at least 5 years.

### Study variables, staging procedures and preoperative treatments

Patient-, disease-, treatment- and postoperative progress-related variables were analysed. Leak-related factors included radiological leak rate, clinical leak rate (presence of clinical signs confirmed by CT scan), AL severity grading (type A, B and C according to the International Study Group of Rectal Cancer [ISGRC] grading [2]), early and late leak rate (diagnosis at <20 or >20 postoperative days, respectively) and related reoperation rate, morbidity and mortality.

All included patients were submitted to the same staging workup, which encompassed endoscopy with biopsy, a carcinoembryonic antigen serum test and a CT scan. Rigid rectoscopy and high-resolution MRI or transrectal ultrasound were subsequently administered to assess tumour height (tumours were classified as high, middle or low when located 10–15 cm [upper rectum], 5–10 cm [middle rectum] or <5 cm [low rectum] from the anal verge, respectively) and cT/cN stage.

Weight loss was defined as the loss of 10% or more of body weight over the last 6 months.

After a multidisciplinary team evaluation, patients were submitted to neoadjuvant treatment or upfront surgery according to clinical tumour stage, following updated oncological guidelines. Emergency surgery was defined as an unplanned procedure performed in patients referred to the Emergency Department due to perforation, severe bleeding or bowel obstruction unsuitable for endoscopic stenting; planned surgical procedures performed for uncomplicated disease at presentation were defined as elective surgery.

### Surgical techniques

Surgery following preoperative treatment was performed within 1–12 weeks, depending on administration, duration and dose of

radiotherapy and/or chemotherapy. Three different types of procedures were initially considered for inclusion in the study: rectal anterior resection (RAR), intersphincteric resection and total proctocolectomy. However, after completion of the dataset, patients submitted to intersphincteric resection or total proctocolectomy were excluded from statistical analysis due to their small number compared to that of RAR.

RAR involves resecting the sigmoid or descending colon and rectum and removing the mesorectum (partially or totally), depending on tumour location; the anastomosis was made between the remaining colon and the rectum. Each surgeon decided at his own discretion to create a protective stoma at the end of the RAR procedure, based on his own criteria of measuring the risk of a leak in each specific patient.

The type of approach adopted was classified into three groups: open surgery, minimally invasive (laparoscopic/robotic) surgery (MIS) not converted, and MIS converted.

### Clinical staging and pathology

Both clinical and pathological staging were performed according to the American Joint Committee on Cancer staging system. We proceeded to reclassify all cases referring to the 8th edition of the TNM classification [18]. Mandard classification was used to categorize the specimen of patients submitted to preoperative treatment [19].

### Anastomotic leak diagnosis and grading

Diagnosis was made based on the presence of clinical (pain, fever, tachycardia, peritonitis, or feculent, enteric or purulent drainage) and radiological (fluid- or gas-containing collections during the CT scan or water-soluble contrast enema) signs, as well as intraoperative findings (gross enteric spillage or anastomotic disruption). Subclinical AL diagnosis was based solely on radiological signs; ISGRC grading was used to assess AL severity [2]. Briefly, ISGRC type A leak corresponds to a radiological leakage which is not associated with clinical symptoms and does not require any interventional procedure; type B AL is a leakage requiring active intervention without the need for reoperation (antibiotics, radiological or endoscopic procedures) and type C ALs are severe leakages requiring reoperation.

### Main outcomes and measures

The primary end-point of this study was the detection of any independent risk factors for anastomotic leak after anterior resection for rectal cancer in a large sample size multicentre retrospective study with the aim of developing a new specific risk score (RALAR score).

Secondary end-points included the overall rate of AL in the study population; the distribution of leaks according to ISGRC clinical

severity grading; the relationship between defunctioning -ostomy, leak occurrence and leak clinical severity grade; the rate of overall morbidity, 30-day mortality and reoperation in patients with and without AL.

## Statistical analysis

Primary analysis was performed by comparing variables between groups with and without AL. A secondary analysis assessed AL severity by comparing variables between types A/B and type C anastomotic leaks.

For the primary analysis we performed a series of univariable analyses to compare the two groups with respect to demographics, clinical and pathological data and postoperative outcomes.

Based on tests of normality, all continuous distributions (i.e., age, body mass index [BMI] and LoS) were non-normal and, accordingly, a nonparametric Wilcoxon rank-sum test was used to compare median values. The chi-squared test with Yates's continuity correction was used to compare categorical data across groups.

All eight demographics, clinical, surgical and pathological covariates significantly related to AL (sex, weight loss, number of cartridges, type of approach, combined multiorgan resection, operating time, cancer location and clinical T stage [cT]) together with BMI (for clinical relevance) were selected and multiple imputation on these variables was performed (given the high number of missing values in some of them) using data from the same set of covariates to handle missing data and improve the power of the analysis. Missing data were assumed to be missing at random, and the R mice procedure was used to impute the missing data. A total of 20 imputed datasets were created to account for sampling variability from the imputation process. For each dataset, a backward stepwise procedure was used to identify the most relevant variables; following the majority method, we did not remove any of the nine variables for the final model because all of them appeared in at least half of the models. A pooled multivariate logistic regression analysis of the 20 datasets was made to evaluate the impact of all the nine risk factors for anastomotic leak.

Predictive accuracy was assessed by averaging in the 20 imputed datasets the area under the receiver operating curve, the sensitivity and specificity to predict AL risk and the best threshold to maximize sensitivity and specificity. A nomogram was created, based on this model. All statistical analyses were performed using R version 4.0.5 (© The R Foundation); statistical significance was set at  $P < 0.05$ .

## RESULTS

### Patient characteristics and perioperative outcomes

Between January 2000 and December 2016, 5398 patients submitted to restorative surgery for RC across 24 Italian referral centres with expertise in colorectal resections were entered into this study. Half of the hospitals reported more than 30 cases per year during the study period. Patients were included in one of two groups based on their postoperative progress: AL group ( $n = 552$  patients, 10.2%) and

NoAL group ( $n = 4846$  patients, 89.8%). Clinical and demographic characteristics of the included patients are detailed in [Table 1](#); patients' median age was 67.1 years (58.7–74.7), with no significant difference between the two groups.

Patients who developed AL were significantly more likely to be men ( $P < 0.001$ ), had a higher BMI and experienced greater weight loss ( $P = 0.045$ ). By contrast, the American Society of Anesthesiologists score, Charlson Comorbidity Index score and smoking/alcohol habits did not correlate with AL.

The surgical approach adopted significantly influenced the incidence of AL ([Table 2](#)), and the proportion of AL was higher after minimally invasive surgery ( $P = 0.003$ ).

In univariate analysis, stapled rectal resection using more than one cartridge ( $P < 0.001$ ), combined multiorgan resections ( $P = 0.004$ ) and longer operating times ( $P < 0.001$ ) were strictly related to a higher risk of AL ([Table 2](#)).

In the same univariate analysis a stoma set-up was not identified as an independent protective factor of AL occurrence ( $P = 0.066$ ) ([Table 2](#)). Mobilization of the splenic flexure, site of central vascular ligation (low vs. high), type of anastomosis and pelvic drain positioning were not related to the risk of AL.

However, ALs identified after stapled anastomoses showed more severe complications than those observed after manual procedures.

### Clinical staging and pathological characteristics

Clinical T stage was recognized as significantly related to AL, while cN and cM were not ([Table 3](#)).

Tumour distance from the anal verge (and cancer location in upper, middle or lower rectum) and (y)pT/(y)pN stages of the disease were significantly related to AL. A complete response to neoadjuvant treatment was identified as not protective for AL ( $P = 0.379$ ) in this study, but the evidence of this result is strongly limited by the amount of missing data regarding both neoadjuvant treatment and tumour response grade.

### Postoperative outcomes

All postoperative complications, including medical complications ( $P = 0.006$ ) and Clavien–Dindo grade  $\geq 3$ , occurred more frequently in the AL than the NoAL group. Consequently, the reoperation rate ( $P < 0.001$ ), LoS ( $P < 0.001$ ) and 30-day mortality ( $P < 0.001$ ) were also significantly higher in AL patients ([Table 4](#)). 30-day postoperative mortality and median LoS were 2.6% versus 0.7% and 19 versus 9 days in the AL versus NoAL group.

### Anastomotic leak

[Table 5](#) details the distribution of AL according to ISGRC grading. The overall incidence of AL was 10.2%, and a severe (type C) leak was identified in 54% of cases. Most cases occurred before the

TABLE 1 Patient population

Patient characteristics		No AL	AL	95% CI	Total	P
Age	Median (IQR)	67.0 (58.8–74.8)	67.4 (58.3–74.1)		67.1 (58.7–74.7)	0.624
Sex	Female	1966 (92.3)	164 (7.7)	6.6–8.9	2130 (100)	<b>&lt;0.001</b>
	Male	2879 (88.1)	388 (11.9)	10.8–13	3267 (100)	
	(Missing)	1 (100.0)	0 (0.0)		1 (100)	
BMI	Median (IQR)	25.2 (22.9–27.8)	25.6 (23.3–28.4)		25.3 (23.0–27.8)	0.054
CCI	2	2103 (90.6)	218 (9.4)	n.a.	2321 (100)	0.602
	3	867 (89.8)	99 (10.2)	10.8–13	966 (100)	
	4–5	515 (89.4)	61 (10.6)	8.4–12.3	576 (100)	
	6+	140 (88.1)	19 (11.9)	8.2–13.4	159 (100)	
	(Missing)	1221 (88.7)	155 (11.3)		1376 (100)	
ASA score	I	564 (91.0)	56 (9.0)	9.6–13.1	620 (100)	0.279
	II	1950 (89.0)	242 (11.0)	6.9–11.6	2192 (100)	
	III	1068 (88.0)	146 (12.0)	9.8–12.4	1214 (100)	
	IV	55 (90.2)	6 (9.8)	10.3–14	61 (100)	
	(Missing)	1209 (92.2)	102 (7.8)		1311 (100)	
Weight loss <sup>a</sup>	No	2789 (91.0)	276 (9.0)	6.4–9.4	3065 (100)	<b>0.045</b>
	Yes	277 (87.4)	40 (12.6)	8–10.1	317 (100)	
	(Missing)	1780 (88.3)	236 (11.7)		2016 (100)	
Smoking habits	No	2395 (90.5)	250 (9.5)	10.3–13.2	2645 (100)	0.290
	Yes	903 (89.3)	108 (10.7)	8.4–10.6	1011 (100)	
	(Missing)	1548 (88.9)	194 (11.1)		1742 (100)	
Alcohol habits	No	3008 (90.3)	324 (9.7)	9.7–12.7	3332 (100)	0.724
	Yes	254 (89.4)	30 (10.6)	8.7–10.8	284 (100)	
	(Missing)	1584 (88.9)	198 (11.1)		1782 (100)	
Perioperative treatment	No	1216 (90.7)	124 (9.3)		1340 (100)	0.851
	Short-course RT	113 (92.6)	9 (7.4)	n.a.	122 (100)	
	Long-course RT	146 (91.2)	14 (8.8)	n.a.	160 (100)	
	Short-course RT + CT	189 (89.2)	23 (10.8)	7.8–10.9	212 (100)	
	Long-course RT + CT	1394 (89.9)	156 (10.1)	3.4–13.5	1550 (100)	
	CT	377 (91.1)	37 (8.9)	4.9–14.3	414 (100)	
	(Missing)	1411 (88.2)	189 (11.8)		1600 (100)	
Neoadjuvant treatment	No	1216 (90.7)	124 (9.3)	8.6–11.7	1340 (100)	0.680
	Yes	2219 (90.3)	239 (9.7)	6.4–12.1	2458 (100)	
	(Missing)	1411 (88.2)	189 (11.8)		1600 (100)	

Bold indicated significance value ( $P < 0.05$ ).

Abbreviations: AL, anastomotic leak; ASA, American Society of Anesthesiologists; BMI, body mass index; CCI, Charlson Comorbidity Index; CT, chemotherapy; IQR, interquartile range; RT, radiation therapy.

<sup>a</sup>Weight loss: reduction of more than 10% of body weight within the last 6 months.

20th postoperative day, with a mean time interval of 6.8 days. In clinically asymptomatic patients with normal laboratory tests (type A leak), no treatment was necessary. Endoscopic and radiological procedures were the first-line treatments for type B AL; these patients were frequently submitted to endoscopic stent or clip placement, endoscopic vacuum therapy or percutaneous pelvic drain positioning.

Table 6 describes the variation of the distribution of treatment- and postoperative progress-related factors in patients with a type A/B or a type C leak. The analysis was done in 494 patients, as the clinical severity grade was not available for 58 of them (Table 5). More than half of patients underwent surgery due to a severe leak (type C AL). Reoperation was also performed after non-surgical treatment failures (30.6%), mostly in type B AL. The overall 30-day

TABLE 2 Treatment-related variables

		No AL	AL	95% CI	Total	P
No. procedures/year	<10	18 (78.3)	5 (21.7)	7.5–43.7	23 (100)	0.296
	10–19	397 (89.0)	49 (11.0)	8.6–11	446 (100)	
	20–29	543 (89.8)	62 (10.2)	10.3–13.5	605 (100)	
	30+	3888 (89.9)	436 (10.1)	7.8–10.9	4324 (100)	
Emergency surgery	No	4630 (89.8)	526 (10.2)	8.2–14.3	5156 (100)	0.734
	Yes	82 (88.2)	11 (11.8)	8–12.9	93 (100)	
	(Missing)	134 (89.9)	15 (10.1)		149 (100)	
Number of cartridges	1	1651 (92.0)	143 (8.0)	9.4–11.1	1794 (100)	<0.001
	>1	1108 (87.7)	155 (12.3)	6.1–20.2	1263 (100)	
	(Missing)	2087 (89.1)	254 (10.9)		2341 (100)	
Type of approach	Open surgery	2222 (91.1)	218 (8.9)	6.8–9.3	2440 (100)	0.003
	MIS not converted	2232 (88.9)	280 (11.1)	10.5–14.2	2512 (100)	
	MIS converted	191 (85.3)	33 (14.7)	9.6–12.2	224 (100)	
	(Missing)	201 (90.5)	21 (9.5)		222 (100)	
Type of procedure	Down to up	4660 (89.8)	530 (10.2)	9.9–12.4	5190 (100)	0.883
	Up to down	182 (89.2)	22 (10.8)	10.4–20.1	204 (100)	
	(Missing)	4 (100.0)	0 (0.0)		4 (100)	
Splenic flexure mobilization	No	955 (91.2)	92 (8.8)	6.9–15.9	1047 (100)	0.273
	Yes	3482 (90.0)	386 (10.0)	9.4–11.1	3868 (100)	
	(Missing)	409 (84.7)	74 (15.3)		483 (100)	
Site of vascular ligation	High tie	3922 (90.2)	424 (9.8)	7.1–10.7	4346 (100)	0.454
	Low tie	605 (91.3)	58 (8.7)	9.1–11	663 (100)	
	(Missing)	319 (82.0)	70 (18.0)		389 (100)	
Type of anastomosis	End to end	4260 (89.5)	501 (10.5)	8.9–10.7	4761 (100)	0.101
	Side to end	554 (91.7)	50 (8.3)	6.7–11.2	604 (100)	
	(Missing)	32 (97.0)	1 (3.0)		33 (100)	
Type of anastomosis	Mechanical	4670 (89.8)	529 (10.2)	9.7–11.4	5199 (100)	0.526
	Manual	163 (88.1)	22 (11.9)	6.2–10.8	185 (100)	
	(Missing)	13 (92.9)	1 (7.1)		14 (100)	
Protective -ostomy	No	2219 (89.3)	267 (10.7)	9.4–11	2486 (100)	0.066
	Ileostomy	1976 (90.6)	206 (9.4)	7.6–17.5	2182 (100)	
	Colostomy	400 (87.1)	59 (12.9)	0.2–33.9	459 (100)	
	(Missing)	251 (92.6)	20 (7.4)		271 (100)	
Combined multiorgan resection	No	3767 (90.8)	380 (9.2)	8.3–10.8	4147 (100)	0.004
	Yes	788 (87.7)	111 (12.3)	9.9–16.3	899 (100)	
	(Missing)	291 (82.7)	61 (17.3)		352 (100)	
Operative time (h)	<3 h 00	992 (92.3)	83 (7.7)	6.2–9.5	1075 (100)	<0.001
	3 h 00–4 h 59	2252 (89.8)	255 (10.2)	9.0–11.4	2507 (100)	
	5 h 00+	1052 (85.5)	178 (14.5)	12.6–16.6	1230 (100)	
	(Missing)	550 (93.9)	36 (6.1)		586 (100)	
Pelvic drain	No	71 (91.0)	7 (9.0)	7.4–10	78 (100)	0.978
	Yes	4486 (90.3)	483 (9.7)	10.9–13.3	4969 (100)	
	(Missing)	289 (82.3)	62 (17.7)		351 (100)	

Bold indicated significance value ( $P < 0.05$ ).

Abbreviations: AL, anastomotic leak; MIS, minimally invasive surgery.



**TABLE 3** Clinical staging and pathological data

		No AL	AL	95% CI	Total	P
Tumour distance from the AV (cm)	Median (IQR)	9.0 (6.0–12.0)	8.0 (5.0–11.0)		9.0 (6.0–12.0)	<b>0.042</b>
Cancer location (anatomical subdivision)	Upper rectum	1482 (91.5)	137 (8.5)	3.7–17.6	1619 (100)	<b>0.004</b>
	Middle rectum	2153 (89.1)	263 (10.9)	8.9–11.6	2416 (100)	
	Lower rectum	984 (87.8)	137 (12.2)	13.8–22.1	1121 (100)	
cT	(Missing)	227 (93.8)	15 (6.2)		242 (100)	
	cT0–1–2	1146 (92.2)	97 (7.8)		1243	<b>0.043</b>
	cT3–4	2161 (90.2)	236 (9.8)		2397	
cN	(Missing)	1539 (87.5)	219 (12.5)		1758	
	cN0	1880 (92.2)	159 (7.8)		2039	0.166
	cN1	499 (89.9)	56 (10.1)		555	
cM	cN2	154 (93.3)	11 (6.7)		165	
	(Missing)	2313 (87.6)	326 (12.4)		2639	
	cM0	3299 (91.1)	321 (8.9)		3620	0.750
(y)pT stage	cM1	136 (91.9)	12 (8.1)		148	
	In situ	85 (94.4)	5 (5.6)	9.7–12.2	90 (100)	<b>&lt;0.001</b>
	0	388 (91.5)	36 (8.5)	10.4–14.3	424 (100)	
(y)pN stage	1	560 (93.6)	38 (6.4)	3.5–10	598 (100)	
	2	1190 (90.8)	121 (9.2)	6–11.6	1311 (100)	
	3	2210 (88.5)	286 (11.5)	4.5–8.6	2496 (100)	
	4	302 (85.6)	51 (14.4)	7.7–10.9	353 (100)	
	(Missing)	111 (88.1)	15 (11.9)		126 (100)	
	0	3100 (91.0)	307 (9.0)	11–18.6	3407 (100)	<b>&lt;0.001</b>
pM stage	1	1047 (88.4)	138 (11.6)	1.8–12.5	1185 (100)	
	2	612 (86.2)	98 (13.8)	6.8–18.9	710 (100)	
	(Missing)	87 (90.6)	9 (9.4)		96 (100)	
R grade	0	4210 (89.9)	475 (10.1)	9.9–13.6	4685 (100)	0.371
	1	470 (88.5)	61 (11.5)	11.4–16.6	531 (100)	
	(Missing)	166 (91.2)	16 (8.8)		182 (100)	
Mandard TRG No.	0	4279 (90.5)	449 (9.5)	9.3–11	4728 (100)	0.708
	1	82 (89.1)	10 (10.9)	8.9–14.5	92 (100)	
	2	143 (88.8)	18 (11.2)	5.1–13.9	161 (100)	
(Missing)	(Missing)	342 (82.0)	75 (18.0)		417 (100)	
	Median (IQR)	3.0 (2.0–4.0)	3.0 (2.0–4.0)		3.0 (2.0–4.0)	0.379
(Missing)	(Missing)	3355 (89.8)	382 (10.2)		3737 (100)	

Bold indicated significance value ( $P < 0.05$ ).

Abbreviations: (y)pN, pathological N stage according to the 8th edition of the TNM classification after neoadjuvant treatment (Y) when administered; (y)pT, pathological T stage according to the 8th edition of the TNM classification after neoadjuvant treatment (Y) when administered; AL, anastomotic leak; AV, anal verge; IQR, interquartile range; pM, pathological M stage according to the 8th edition of the TNM classification; R grade, residual tumour classification (R0 corresponds to resection for cure or complete remission; R1 to microscopic residual tumour and R2 to macroscopic residual tumour).

leak-related mortality was 2.6%, mainly due to grade C AL (92.9%). Postoperative mortality of type C leak was 5.2%, which was more than 7-fold higher than that of patients without AL (0.7%).

Although a defunctioning stoma did not reduce the risk of leak occurrence, it significantly decreased leak severity ( $P < 0.001$ ), enabled conservative treatment in most cases and allowed for quicker stoma reversal.

### Multivariable analysis and nomogram

The pooled multivariable analysis of risk factors for AL is reported in [Table 7](#). Body mass index, sex (male), tumour location (middle and low vs. high), type of approach (MIS vs. open), number of cartridges employed (1 vs. >1), weight loss, clinical T and combined multiorgan resection were identified as independent risk factors in a pooled set

**TABLE 4** Postoperative outcomes

		No AL	AL	Total	P
Medical complication	No	3946 (90.0)	439 (10.0)	4385 (100)	<b>0.006</b>
	Yes	630 (86.5)	98 (13.5)	728 (100)	
	(Missing)	270 (94.7)	15 (5.3)	285 (100)	
Surg compl CD	I-II	333	140	473	<b>&lt;0.001</b>
Surg compl CD	III+	156	360	516	
	Missing	41	52	93	
Reoperation	No	3883 (95.4) [97.0] <sup>*</sup>	189 (4.6) [37.0] <sup>*</sup>	4072 (100)	<b>&lt;0.001</b>
	Yes	123 (27.6) [3.0] <sup>*</sup>	323 (72.4) [63.0] <sup>*</sup>	446 (100)	
	(Missing)	840 (95.5)	40 (4.5)	880 (100)	
30-day mortality	No	3453 (86.7) [99.3] <sup>*</sup>	531 (13.3) [97.4] <sup>*</sup>	3984 (100)	<b>&lt;0.001</b>
	Yes	26 (65.0) [0.7] <sup>*</sup>	14 (35.0) [2.6] <sup>*</sup>	40 (100)	
	(Missing)	1367 (99.5)	7 (0.5)	1374 (100)	
Length of stay (days)	Median (IQR)	9.0 (7.0–11.0)	19.0 (12.0–27.0)	9.0 (7.0–12.0)	<b>&lt;0.001</b>

Bold indicated significance value ( $P < 0.05$ ).

Abbreviations: AL, anastomotic leak; CD, Clavien–Dindo classification; IQR, interquartile range; Surg compl, surgical complication.

<sup>\*</sup>indicates that the percentage in brackets is referred to the population of the column.

**TABLE 5** Anastomotic leak grade

	N	%	N
Total	5398	100	5398
No AL	4846	89.8	4846
Total AL	552	10.2	552
AL grade A <sup>a</sup>	91	1.7 (18.5) <sup>b</sup>	494
AL grade B <sup>a</sup>	136	2.5 (27.5) <sup>b</sup>	
AL grade C <sup>a</sup>	267	5.0 (54.0) <sup>b</sup>	
AL grade missing	58	(10.5) <sup>b</sup>	58

Abbreviation: AL, anastomotic leak.

<sup>a</sup>AL severity grade: grade according to the International Study Group of Rectal Cancer scoring system.

<sup>b</sup>Percentages referred to the group of patients with AL and severity grade available (total number of patients 494).

of 20 logistic regression models with anastomotic leak as dependent variable. The average area under the receiver operating curve calculated on the 20 datasets was 0.617 (95% CI 0.615–0.619). With an average threshold value corresponding to 0.1030 (95% CI 0.1027–0.1033), average sensitivity and specificity of the model's probability to identify anastomotic leak were 57.8% (95% CI 57.4%–58.1%) and 57.8% (95% CI 57.5%–58.1%) respectively.

To predict AL occurrence, we created a digital nomogram including all these covariates significantly correlated with the occurrence of a postoperative leak; based on this nomogram, a specific risk score (RALAR score) is now available online (<http://www.marianotomatis.it/RALARscore>) and could help surgeons in decision-making concerning the creation of a protective stoma.

## DISCUSSION

The present study showed an AL incidence of 10.2%, consistent with currently published data; conversely, the AL-related mortality of 2.6% is much lower than that reported in the literature, primarily because patients were treated in referral centres with adequate skill and experience also for management of complications.

Risk assessment of AL is crucial for early decision-making; thus, several preoperative and intra-operative factors should be considered: male sex, greater BMI, locally advanced tumour, lymph-node metastases and tumour proximity to the anal verge were identified as preoperative independent risk factors in this study, together with the minimally invasive approach, a longer operating time, the number of cartridges employed during a stapled procedure, and a combined multivisceral resection. To our knowledge, male sex is significantly related to increased AL risk, probably due to the narrower male pelvis, as well as androgens that may affect the bowel microcirculation acting on intestinal endothelial function [20,21].

Greater BMI and weight loss are both modifiable, independent risk factors for AL. Nevertheless, while patients with severe slimming could benefit from preoperative nutritional improvement, rapid weight loss in obese patients could further increase the risk of leak, as consequent malnutrition significantly affects tissue healing [22].

Consistent with previous data, we observed that the risk of AL rises in advanced stage cancer (both in clinical and pathological T3–4 stage) with metastatic nodes. This may be explained by the more technical complexity of such cases [1].

Neoadjuvant treatment was not found to be associated with AL in this study; while some authors showed a relationship between preoperative chemotherapy and AL occurrence, several others



AL characteristics		AL A/B	AL C	Total	P
Total		227 (46.0)	267 (54.0)	494 (100)	
Medical complication	No	182 (46.3)	211 (53.7)	393 (100)	1.000
	Yes	40 (46.0)	47 (54.0)	87 (100)	
	(Missing)	5 (35.7)	9 (64.3)	14 (100)	
Clavien–Dindo grade	I–II	130 (96.3)	5 (3.7)	135 (100)	<b>&lt;0.001</b>
	III+	93 (26.3)	261 (73.7)	354 (100)	
	(Missing)	4 (80.0)	1 (20.0)	5 (100)	
Protective ostomy	No	80 (32.5)	166 (67.5)	246 (100)	<b>&lt;0.001</b>
	Ileostomy	121 (61.1)	77 (38.9)	198 (100)	
	Colostomy	16 (50.0)	16 (50.0)	32 (100)	
	(Missing)	10 (55.6)	8 (44.4)	18 (100)	
Reoperation for leak	No	161 (94.2)	10 (5.8)	171 (100)	<b>&lt;0.001</b>
	Yes	50 (16.4)	255 (83.6)	305 (100)	
	(Missing)	16 (88.9)	2 (11.1)	18 (100)	
30-day mortality	No	225 (47.3)	251 (52.7)	476 (100)	<b>0.007</b>
	Yes	1 (7.1)	13 (92.9)	14 (100)	
	(Missing)	1 (25.0)	3 (75.0)	4 (100)	
Timing for diagnosis	Early (by 20 days)	113 (46.3)	131 (53.7)	244 (100)	<b>0.005</b>
	Late (>20 days)	40 (67.8)	19 (32.2)	59 (100)	
	(Missing)	74 (38.7)	117 (61.3)	191 (100)	

Bold indicated significance value ( $P < 0.05$ ).

Abbreviations: AL, anastomotic leak; AL A/B, type A and B ALs, according to the International Study Group of Rectal Cancer grading; AL C, type C according to the International Study Group of Rectal Cancer grading.

could not confirm this bond [23,24]. Still, there are many controversial papers regarding the role of neoadjuvant radiotherapy on AL incidence. In the early 1970s, Schrock et al. [25] documented a substantial increase in AL after radiotherapy. Recently, Arezzo et al. [1] separately analysed the effect of short- and long-course radiotherapy on AL, only showing a significant association with short-course treatment; however, the Dutch TME trial, which randomly allocated patients with RC in preoperative radiotherapy or in upfront surgery, concluded that the AL rate was not different between the two groups [26]. Unfortunately, due to the high number of missing values concerning neoadjuvant treatment and tumour response grade, any relationships between these factors and the risk of AL are not supported by sufficient evidence in this study.

An additionally identified independent risk factor for AL is tumour distance from the anal verge, consistent with literature evidence. In the 1990s, Rullier et al. reported a 6.5-fold increased risk in anastomoses located <5 cm from the anal verge; similarly, Vignali et al. documented a 7-fold increased leak rate risk after low rectal stapling [27,28].

In the last few decades, more patients with low- and mid-RC have undergone sphincter-saving procedures due to the advent of

circular stapling devices. Recently, a Cochrane review comparing stapling and handsewing in colorectal anastomosis concluded that ‘the evidence found was insufficient to demonstrate any superiority of stapled over handsewn techniques in colorectal anastomosis surgery, regardless of the level of anastomosis’ [29]. This observation is in line with the results of our retrospective study; indeed, a higher number of grade C leakages were reported after stapled anastomoses and the open approach resulted in a protective independent factor for AL in this study.

The present study does not show significant differences in AL rates among centres with different case volumes, despite the wide range reported (2.4%–24%). Several authors have stated that surgical experience directly affects leak rate, and that high case volume facilities achieve better postoperative outcomes [30,31]. In contrast, no significant differences in AL rates between high and low case volume centres have been reported. Sørensen et al. documented an even lower incidence of AL after resections performed by surgeons in training compared with skilled colleagues, as training starts with easier cases [32]. Likewise, in the present study, surgeons from referral centres were mostly faced with more complex cases, compared with surgeons from low case volume facilities (Table S2).

**TABLE 6** Anastomotic leak characteristics

TABLE 7 Multivariable analysis

Variable analysed		OR	95% CI	P value
BMI		1.02	0.99–1.05	0.182
Sex (vs. female)	Male	1.55	1.27–1.88	<0.001
Weight loss	Yes	1.26	0.91–1.75	0.165
cT3–T4 (vs. cT0–1–2)	Yes	1.17	0.92–1.48	0.194
Location (vs. low)	Middle	0.87	0.69–1.09	0.218
	High	0.68	0.52–0.87	0.003
Approach (vs. open)	MIS not converted	1.26	1.02–1.56	0.030
	MIS converted	1.53	1.02–2.28	0.039
Number of cartridges (vs. 1)	>1	1.26	1.00–1.59	0.055
Operative time (vs. <3 h)	3 h 00–4 h 59	1.18	0.91–1.54	0.210
	5 h 00+	1.54	1.15–2.04	0.003
Combined multiorgan resection	Yes	1.36	1.07–1.73	0.011

Abbreviations: BMI, body mass index; cT, clinical T stage according to the 8th edition of the TNM classification; MIS, minimally invasive surgery; Weight loss, loss of 10% or more of body weight over the last 6 months.

To date, even though the minimally invasive approach for RC is quickly spreading worldwide, the non-inferiority of laparoscopy compared with open surgery with respect to postoperative complications and oncological outcomes is still debated [33–37]. In the present study, the minimally invasive approach was significantly related to AL occurrence. Nevertheless, this study enrolled patients over a long time period (2000–2016). In the early 2000s, many surgeons were still at the beginning of their learning curves; the available devices were archaic, and techniques were not well standardized.

The duration of the procedure, combined multiorgan resections, and number of stapling cartridges  $\geq 2$  significantly influenced AL appearance. These intra-operative risk factors often characterize a challenging surgery for locally advanced diseases, or an otherwise poor-quality surgery performed by unskilled surgeons. Several authors showed that multiple applications of linear stapler cartridges increased the leak risk due to the unduly long stapling line, with an oblique angle in the lower location [38,39]. Unfortunately, it is commonly believed that several linear staplers are required in male patients with a low tumour and narrow pelvis. Indeed, in 2009 Kim et al. stated that 'a diverting ileostomy is mandatory in patients with middle and lower RC where multiple linear staplers were used' [38].

Consistent with data previously reported in the literature [40,41], further analyses in this study documented that the use of pelvic drainage was not protective against the incidence of AL, nor for avoiding consequent reoperation.

Based on the results from this large sample sized study, we generated a specific score to predict the risk of AL at the end of surgery, in time to decide whether to create a diverting stoma. Despite risk prediction not providing a tangible mode of prevention, the indication to construct a stoma can significantly reduce the dehiscence severity, avoid consequent reoperations, and reduce related morbidity and mortality. In 1983, Graffner et al. demonstrated that AL after restorative surgery for RC may appear in a high percentage of patients who had undergone a protective colostomy [42]. Consistent with

this report and data from the literature, our findings showed that a protective stoma did not reduce AL rate significantly; however, leak grade, reoperation rate and related 30-day mortality were significantly lowered. Nonetheless, while stoma creation could counteract dehiscence severity, it may cause patient discomfort and clinical problems, have a major effect on overall healthcare costs and may even become permanent in some cases. Considering the high rates of defunctioning stomas reported during rectal surgery, a warning from Austria suggests a benchmark of 10% or less for protective stomas, to limit the overall costs to €12 000 per patient treated [43].

Nevertheless, we believe that surgeons should consider these independent risk factors during restorative surgery for RC to eventually create a diverting stoma, and strictly follow the patient's postoperative course. Finally, surgeons could take advantage of the RALAR score (available online at <http://www.marianotomatis.it/RALARscore>) which can be used in operating rooms at the end of primary resections to determine the leak risk with more precision, as well as to decide whether to create a protective stoma.

This study has several limitations due to its retrospective design and relatively long accrual period. Several issues had important missing data, with a consequent lack of details. Moreover, this long accrual interval is characterized by many changes concerning perioperative treatment, surgical technique, new devices for minimally invasive approaches, and conservative management of postoperative complications. Notwithstanding, the RALAR study represents a large sample of Italian referral centres (the largest ever published) with expertise in RC treatment and can thus serve as an important benchmark for further trials.

## CONCLUSIONS

Anastomotic leak after restorative RC surgery is a fearsome complication with considerable morbidity and related mortality also in

large volume referral centres. Although the construction of a protective -ostomy does not significantly reduce the risk of leak, its severity, need for reoperation and related mortality seem significantly decreased. Surgeons should therefore properly recognize the pre-operative and intra-operative risk factors related to AL and with the help of a specific nomogram and risk score (RALAR score) they could immediately identify high-risk patients who may benefit from the construction of a protective stoma.

## ACKNOWLEDGEMENT

Open Access Funding provided by Università degli Studi di Torino within the CRUI-CARE Agreement. [Correction added on 26 May 2022, after first online publication : CRUI Funding statement has been added.]

## CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

## AUTHOR CONTRIBUTIONS

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## IRB STATEMENT

The study was approved by the Ethical Committee 'Comitato Etico Interaziendale AOU San Luigi Gonzaga di Orbassano, AASSLL TO3-TO4-TO' under study number 15525.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## REFERENCES

- Arezzo A, Migliore M, Chiaro P, Arolfo S, Filippini C, Di Cuonzo D, et al. The REAL (REctal Anastomotic Leak) score for prediction of anastomotic leak after rectal cancer surgery. *Tech Coloproctol.* 2019;23:649–63. <https://doi.org/10.1007/s10151-019-02028-4>
- Rahbari NN, Weitz J, Hohenberger W, Heald RJ, Moran B, Ulrich A, et al. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. *Surgery.* 2010;147:339–51. <https://doi.org/10.1016/j.surg.2009.10.012>
- Bruce J, Krukowski ZH, Al-Khairy G, Russell EM, Park KGM. Systematic review of the definition and measurement of anastomotic leak after gastrointestinal surgery. *Br J Surg.* 2001;88:1157–68. <https://doi.org/10.1046/j.0007-1323.2001.01829.x>
- Asteria CR, Gagliardi G, Pucciarelli S, Romano G, Infantino A, La Torre F, et al. Anastomotic leaks after anterior resection for mid and low rectal cancer: survey of the Italian Society of Colorectal Surgery. *Tech Coloproctol.* 2008;12:103–10. <https://doi.org/10.1007/s10151-008-0407-9>
- Hyman N, Manchester TL, Osler T, Burns B, Cataldo PA. Anastomotic leaks after intestinal anastomosis: it's later than you think. *Ann Surg.* 2007;245:254–8. <https://doi.org/10.1097/01.sla.0000225083.27182.85>
- Arezzo A, Verra M, Reddavid R, Cravero F, Bonino MA, Morino M. Efficacy of the over-the-scope clip (OTSC) for treatment of colorectal postsurgical leaks and fistulas. *Surg Endosc.* 2012;26(11):3330–3. <https://doi.org/10.1007/s00464-012-2340-2>
- van Koperen PJ, van Berge Henegouwen MI, Rosman C, Bakker CM, Heres P, Slors JFM, et al. The Dutch multicenter experience of the endo-sponge treatment for anastomotic leakage after colorectal surgery. *Surg Endosc.* 2009;23:1379–83. <https://doi.org/10.1007/s00464-008-0186-4>
- Challine A, Lefèvre JH, Creavin B, Benoit O, Chafai N, Debove C, et al. Can a local drainage salvage a failed colorectal or coloanal anastomosis? A prospective cohort of 54 patients. *Dis Colon Rectum.* 2020;63:93–100. <https://doi.org/10.1097/DCR.0000000000001516>
- Phitayakorn R, Delaney CP, Reynolds HL, Champagne BJ, Heriot AG, Neary P, et al. Standardized algorithms for management of anastomotic leaks and related abdominal and pelvic abscesses after colorectal surgery. *World J Surg.* 2008;32:1147–56. <https://doi.org/10.1007/s00268-008-9468-1>
- Nachiappan S, Faiz O. Anastomotic leak increases distant recurrence and long-term mortality after curative resection for colonic cancer. *Ann Surg.* 2015;262:e111. <https://doi.org/10.1097/SLA.0000000000000741>

11. Krarup PM, Nordholm-Carstensen A, Jorgensen LN, Harling H. Anastomotic leak increases distant recurrence and long-term mortality after curative resection for colonic cancer: a nationwide cohort study. *Ann Surg*. 2014;259:930–8. <https://doi.org/10.1097/SLA.0b013e3182a6f2fc>
12. Platell C, Barwood N, Dorfmann G, Makin G. The incidence of anastomotic leaks in patients undergoing colorectal surgery. *Color Dis*. 2007;9:71–9. <https://doi.org/10.1111/j.1463-1318.2006.01002.x>
13. Kingham TP, Pachter HL. Colonic anastomotic leak: risk factors, diagnosis, and treatment. *J Am Coll Surg*. 2009;208:269–78. <https://doi.org/10.1016/j.jamcollsurg.2008.10.015>
14. Hoshino N, Hida K, Sakai Y, Osada S, Idani H, Sato T, et al. Nomogram for predicting anastomotic leakage after low anterior resection for rectal cancer. *Int J Colorectal Dis*. 2018;33:411–8. <https://doi.org/10.1007/s00384-018-2970-5>
15. Sylla P, Rattner DW, Delgado S, Lacy AM. NOTES transanal rectal cancer resection using transanal endoscopic microsurgery and laparoscopic assistance. *Surg Endosc*. 2010;24:1205–10. <https://doi.org/10.1007/s00464-010-0965-6>
16. Reddavid R, Puca L, Osella G, Potenza E, Degiuli M. A comment on 'The REAL (REctal Anastomotic Leak) score for prediction of anastomotic leak after rectal cancer surgery' by Arezzo A et al. *Tech Coloproctol*. 2021;25(2):245–6. <https://doi.org/10.1007/s10151-020-02351-1>
17. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*. 2008;61(4):344–9. <https://doi.org/10.1016/j.jclinepi.2007.11.008>
18. Brierley JD, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumours. 8th ed. Union Int Cancer Control; 2017. <https://doi.org/10.1002/ejoc.201200111>
19. Mandard A-M, Dalibard F, Mandard J-C, Marnay J, Henry-Amar M, Petiot J-F, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. *Cancer*. 1994;73:2680–6. [https://doi.org/10.1002/1097-0142\(19940601\)73:11<2680:AID-CNCR2820731105>3.0.CO;2-C](https://doi.org/10.1002/1097-0142(19940601)73:11<2680:AID-CNCR2820731105>3.0.CO;2-C)
20. Wang L, Gu J. Risk factors for symptomatic anastomotic leakage after low anterior resection for rectal cancer with 30 Gy/10 f/2 w preoperative radiotherapy. *World J Surg*. 2010;34:1080–5. <https://doi.org/10.1007/s00268-010-0449-9>
21. Barnajian M, Pettet D, Kazi E, Foppa C, Bergamaschi R. Quality of total mesorectal excision and depth of circumferential resection margin in rectal cancer: a matched comparison of the first 20 robotic cases. *Color Dis*. 2014;16:603–9. <https://doi.org/10.1111/codi.12634>
22. Kwag SJ, Kim JG, Kang WK, Lee JK, Oh ST. The nutritional risk is an independent factor for postoperative morbidity in surgery for colorectal cancer. *Ann Surg Treat Res*. 2014;86:206–11. <https://doi.org/10.4174/ast.2014.86.4.206>
23. Park JS, Choi G-S, Kim SH, Kim HR, Kim NK, Lee KY, et al. Multicenter analysis of risk factors for anastomotic leakage after laparoscopic rectal cancer excision: the Korean laparoscopic colorectal surgery study group. *Ann Surg*. 2013;257:665–71. <https://doi.org/10.1097/SLA.0b013e31827b8ed9>
24. Warschkow R, Steffen T, Thierbach J, Bruckner T, Lange J, Tarantino I. Risk factors for anastomotic leakage after rectal cancer resection and reconstruction with colectostomy. A retrospective study with bootstrap analysis. *Ann Surg Oncol*. 2011;18:2772–82. <https://doi.org/10.1245/s10434-011-1696-1>
25. Schrock TR, Deveney CW, Dunphy JE. Factor contributing to leakage of colonic anastomoses. *Ann Surg*. 1973;177:513–8. <https://doi.org/10.1097/0000658-197305000-00002>
26. Marijnen CA, Kapiteijn E, van de Velde CJ, Martijn H, Steup WH, Wiggers T, et al. Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: report of a multicenter randomized trial. *J Clin Oncol*. 2002;20:817–25. <https://doi.org/10.1200/jco.2002.20.3.817>
27. Rullier E, Laurent C, Garrelon JL, Michel P, Saric J, Parneix M. Risk factors for anastomotic leakage after resection of rectal cancer. *Br J Surg*. 1998;85:355–8. <https://doi.org/10.1046/j.1365-2168.1998.00615.x>
28. Vignali A, Fazio VW, Lavery IC, Milsom JW, Church JM, Hull TL, et al. Factors associated with the occurrence of leaks in stapled rectal anastomoses: a review of 1,014 patients. *J Am Coll Surg*. 1997;185:105–13. [https://doi.org/10.1016/S1072-7515\(97\)00018-5](https://doi.org/10.1016/S1072-7515(97)00018-5)
29. Neutzling CB, Lustosa SA, Proenca IM, da Silva EM, Matos D. Stapled versus handsewn methods for colorectal anastomosis surgery. *Cochrane Database Syst Rev*. 2012. <https://doi.org/10.1002/14651858.cd003144.pub2>
30. Martling A, Cedermark B, Johansson H, Rutqvist LE, Holm T. The surgeon as a prognostic factor after the introduction of total mesorectal excision in the treatment of rectal cancer. *Br J Surg*. 2002;89:1008–13. <https://doi.org/10.1046/j.1365-2168.2002.02151.x>
31. Smith JAE, King PM, Lane RHS, Thompson MR. Evidence of the effect of 'specialization' on the management, surgical outcome and survival from colorectal cancer in Wessex. *Br J Surg*. 2003;90:583–92. <https://doi.org/10.1002/bjs.4085>
32. Sørensen LT, Jørgensen T, Kirkeby LT, Skovdal J, Vennits B, Wille-Jørgensen P. Smoking and alcohol abuse are major risk factors for anastomotic leakage in colorectal surgery. *Br J Surg*. 1999;86:927–31. <https://doi.org/10.1046/j.1365-2168.1999.01165.x>
33. Bonjer HJ, Deijen CL, Abis GA, Cuesta MA, van der Pas MHGM, de Lange-de Klerk ESM, et al. A randomized trial of laparoscopic versus open surgery for rectal cancer. *N Engl J Med*. 2015;372:1324–32. <https://doi.org/10.1056/nejmoa1414882>
34. Stevenson ARL, Solomon MJ, Lumley JW, Hewett P, Clouston AD, Gebiski VJ, et al. Effect of laparoscopic-assisted resection vs open resection on pathological outcomes in rectal cancer: the ALaCaRT randomized clinical trial. *JAMA - J Am Med Assoc*. 2015;314:1356–63. <https://doi.org/10.1001/jama.2015.12009>
35. Fleshman J, Branda ME, Sargent DJ, Boller AM, George VV, Abbas MA, et al. Disease-free survival and local recurrence for laparoscopic resection compared with open resection of stage II to III rectal cancer: follow-up results of the ACOSOG Z6051 randomized controlled trial. *Ann Surg*. 2019;269:589–95. <https://doi.org/10.1097/SLA.0000000000003002>
36. Fleshman J, Branda M, Sargent DJ, Boller AM, George V, Abbas M, et al. Effect of laparoscopic-assisted resection vs open resection of stage II or III rectal cancer on pathologic outcomes. The ACOSOG Z6051 randomized clinical trial. *JAMA - J Am Med Assoc*. 2015;314:1346–55. <https://doi.org/10.1001/jama.2015.10529>
37. Jeong S-Y, Park JW, Nam BH, Kim S, Kang S-B, Lim S-B, et al. Open versus laparoscopic surgery for mid-rectal or low-rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): survival outcomes of an open-label, non-inferiority, randomised controlled trial. *Lancet Oncol*. 2014;15:767–74. [https://doi.org/10.1016/S1470-2045\(14\)70205-0](https://doi.org/10.1016/S1470-2045(14)70205-0)
38. Kim JS, Cho SY, Min BS, Kim NK. Risk factors for anastomotic leakage after laparoscopic intracorporeal colorectal anastomosis with a double stapling technique. *J Am Coll Surg*. 2009;209:694–701. <https://doi.org/10.1016/j.jamcollsurg.2009.09.021>
39. Ito M, Sugito M, Kobayashi A, Nishizawa Y, Tsunoda Y, Saito N. Relationship between multiple numbers of stapler firings during rectal division and anastomotic leakage after laparoscopic rectal resection. *Int J Colorectal Dis*. 2008;23:703–7. <https://doi.org/10.1007/s00384-008-0470-8>
40. Denost Q, Rouanet P, Faucheron J-L, Panis Y, Meunier B, Cotte E, et al. To drain or not to drain infraperitoneal anastomosis after rectal excision for cancer. *Ann Surg*. 2017;265:474–80. <https://doi.org/10.1097/SLA.0000000000001991>



41. Menahem B, Vallois A, Alves A, Lubrano J. Prophylactic pelvic drainage after rectal resection with extraperitoneal anastomosis: is it worthwhile? A meta-analysis of randomized controlled trials. *Int J Colorectal Dis.* 2017;32:1531–8. <https://doi.org/10.1007/s00384-017-2891-8>
42. Graffner H, Fredlund P, Olsson SÅ, Oscarson J, Petersson BG. Protective colostomy in low anterior resection of the rectum using the EEA stapling instrument—a randomized study. *Dis Colon Rectum.* 1983;26:87–90. <https://doi.org/10.1007/BF02562579>
43. Koperna T, Heald RJ. Cost-effectiveness of defunctioning stomas in low anterior resections for rectal cancer: a call for benchmarking. *Arch Surg.* 2003;138:1334–9. <https://doi.org/10.1001/archsurg.138.12.1334>

## SUPPORTING INFORMATION

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**How to cite this article:** Degiuli M, Elmore U, De Luca R, De Nardi P, Tomatis M, Biondi A, et al; and collaborators from the Italian Society of Surgical Oncology Colorectal Cancer Network Collaborative Group. Risk factors for anastomotic leakage after anterior resection for rectal cancer (RALAR study): A nationwide retrospective study of the Italian Society of Surgical Oncology Colorectal Cancer Network Collaborative Group. *Colorectal Dis.* 2022;24:264–276. <https://doi.org/10.1111/codi.15997>

## APPENDIX 1

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