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

Maurizio Degiuli1 | Ugo Elmore2 | Raffaele De Luca3 | Paola De Nardi2 | Mariano Tomatis4 | Alberto Biondi5 | Roberto Persiani5 | Leonardo Solaini6 | Gianluca Rizzo7 | Domenico Soriero8 | Desiree Cianflocca9 | Marco Milone10 | Giulia Turri11 | Daniela Rega12 | Paolo Delrio12 | Corrado Pedrazzani11 | Giovanni D. De Palma10 | Felice Borghi9 | Stefano Scabini8 | Claudio Coco13 | Davide Cavaliere6 | Michele Simone3 | Riccardo Rosati14 | Rossella Reddavid1 | and collaborators from the Italian Society of Surgical Oncology Colorectal Cancer Network Collaborative Group†

1Division of Surgical Oncology and Digestive Surgery, Department of Oncology, San Luigi University Hospital, University of Turin, Turin, Italy
2Division of Gastrointestinal Surgery, San Raffaele Hospital, Milan, Italy
3Division of Surgical Oncology, IRCCS Istituto Tumori ‘G. Paolo II’, Bari, Italy
4Department of Oncology, University of Turin, Turin, Italy
5Fondazione Policlinico Gemelli—IRCCS, AREA di Chirurgia Addominale, Rome, Italy
6General and Oncologic Surgery, Morgagni-Pierantoni Hospital, Ausl Romagna, Forlì, Italy
7Fondazione Policlinico Universitario A. Gemelli—IRCCS, Chirurgia Generale Presidio Columbus, Rome, Italy
8Surgical Oncology Surgery, IRCCS Policlinico San Martino, Genoa, Italy
9Department of Surgery, S. Croce e Carle Hospital, Cuneo, Italy
10Department of Clinical Medicine and Surgery, Department of Gastroenterology, Endocrinology and Endoscopic Surgery, University of Naples ‘Federico II’, Naples, Italy
11Division of General and Hepatobiliary Surgery, Department of Surgical Sciences, Dentistry, Gynaecology and Paediatrics, University of Verona, Verona, Italy
12Colorectal Surgical Oncology, Abdominal Oncology Department, Fondazione Giovanni Pascale IRCCS, Naples, Italy
13Fondazione Policlinico Universitario A. Gemelli—IRCCS, Chirurgia Generale Presidio Columbus, Università Cattolica del Sacro Cuore, Rome, Italy
14Division of Gastrointestinal Surgery, San Raffaele Hospital, Vita Salute University, Milan, Italy

Correspondence
Maurizio Degiuli, Division of Surgical Oncology and Digestive Surgery, Department of Oncology, San Luigi University Hospital, University of Turin, Regione Gonzole 10, 10040 Orbassano, Turin, Italy.
Email: maurizio.degiuli@unito.it

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.

†The members of the Italian Society of Surgical Oncology Colorectal Cancer Network Collaborative Group are listed in Appendix 1.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2021 The Authors. Colorectal Disease published by John Wiley & Sons Ltd on behalf of Association of Coloproctology of Great Britain and Ireland
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 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.

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.
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 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 intra-operative 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, ISGCR 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 ≥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
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 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) | <0.001 |
| 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) | 0.045 |
| 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.
| 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) |
| (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.
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.

### TABLE 3 Clinical staging and pathological data

|                          | No AL       | AL          | 95% CI      | Total | $P$  |
|--------------------------|-------------|-------------|-------------|-------|------|
| Tumour distance from the AV (cm) | Median (IQR) |             |             |       |      |
| Upper rectum             | 1482 (91.5) | 137 (8.5)   | 3.7-17.6    | 1619 (100) | 0.004 |
| 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) |      |
| (Missing)                | 227 (93.8)  | 15 (6.2)    |             | 242 (100)  |      |
| ($\gamma$pT stage)       |             |             |             |       |      |
| In situ                  | 85 (94.4)   | 5 (5.6)     | 9.7-12.2    | 90 (100)  | <0.001 |
| 0                        | 388 (91.5)  | 36 (8.5)    | 10.4-14.3   | 424 (100) |      |
| 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)   | 9.7-12.2    | 126 (100) |      |
| ($\gamma$pN stage)       |             |             |             |       |      |
| 0                        | 3100 (91.0) | 307 (9.0)   | 11-18.6     | 3407 (100) | <0.001 |
| 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)  |      |
| pM stage                 |             |             |             |       |      |
| 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) |      |
| R grade                  | 0            | 4279 (90.5) | 449 (9.5)   | 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)                | 342 (82.0)  | 75 (18.0)   |             | 417 (100) |      |
| Mandard TRG No.          | Median (IQR) | 3.0 (2.0-4.0) | 3.0 (2.0-4.0) | 3.0 (2.0-4.0) | 0.379 |
| (Missing)                | 3355 (89.8) | 382 (10.2)  |             | 3737 (100) |      |

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

Abbreviations: ($\gamma$pN, pathological N stage according to the 8th edition of the TNM classification after neoadjuvant treatment ($Y$) when administered; ($\gamma$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).
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
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

| AL characteristics                  | AL A/B     | AL C    | Total | \( P \)   |
|-------------------------------------|------------|---------|-------|-----------|
| Total                               | 227 (46.0) | 267 (54.0) | 494 (100) | 1.000     |
| Medical complication                |            |         |       |           |
| No                                  | 182 (46.3) | 211 (53.7) | 393 (100) |           |
| Yes                                 | 40 (46.0)  | 47 (54.0)  | 87 (100)  |           |
| (Missing)                           | 5 (35.7)   | 9 (64.3)   | 14 (100)  |           |
| Clavien–Dindo grade                 |            |         |       | <0.001    |
| I–II                                | 130 (96.3) | 5 (3.7)  | 135 (100) |           |
| III+                                | 93 (26.3)  | 261 (73.7) | 354 (100) |           |
| (Missing)                           | 4 (80.0)   | 1 (20.0)   | 5 (100)   |           |
| Protective ostomy                   |            |         |       | <0.001    |
| No                                  | 80 (32.5)  | 166 (67.5) | 246 (100) |           |
| 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                |            |         |       | <0.001    |
| No                                  | 161 (94.2) | 10 (5.8)   | 171 (100) |           |
| Yes                                 | 50 (16.4)  | 255 (83.6) | 305 (100) |           |
| (Missing)                           | 16 (88.9)  | 2 (11.1)   | 18 (100)  |           |
| 30-day mortality                    |            |         |       | 0.007     |
| No                                  | 225 (47.3) | 251 (52.7) | 476 (100) |           |
| Yes                                 | 1 (7.1)    | 13 (92.9)  | 14 (100)  |           |
| (Missing)                           | 1 (25.0)   | 3 (75.0)   | 4 (100)   |           |
| Timing for diagnosis                |            |         |       | 0.005     |
| Early (by 20 days)                  | 113 (46.3) | 131 (53.7) | 244 (100) |           |
| 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.
TABLE 7 Multivariable analysis

| Variable analysed                  | OR   | 95% CI     | P value |
|------------------------------------|------|------------|---------|
| BMI                                | 1.02 | 0.99–1.05  | 0.182   |
| Sex (vs. female)                   | 1.55 | 1.27–1.88  | <0.001  |
| Weight loss                        | 1.26 | 0.91–1.75  | 0.165   |
| cT3–T4 (vs. cT0–1–2)               | 1.17 | 0.92–1.48  | 0.194   |
| Location (vs. low)                 | 0.87 | 0.69–1.09  | 0.218   |
| 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   | 1.00–1.59  | 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       | 0.107–1.73 | 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 ≥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 Universita 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
Statement of contribution Steering group: Maurizio Degiuli, Rossella Reddavid. Writing Group: Maurizio Degiuli, Rossella Reddavid, Francesco Evola, Mariano Tomatis, Ugo Elmore, Raffaele De Luca, Paola De Nardi, Mariano Tomatis, Alberto Biondi, Roberto Persiani, Leonardo Solaini, Davide Cavaliere, Michele Simone, Riccardo Rosati, Gianluca Rizzo, Domenico Soriero, Desiree Cianfocca, Marco Milone, Giulia Turri, Michela Mineccia, Francesca Pecchini, Gaetano Gallo, Daniela Rega, Paola Incollingo, Ugo Elmore, Raffaele De Luca, Paola De Nardi, Mariano Tomatis, collaborators Felice Borghi, Stefano Scabini, Claudio Coco, Domenico D’Ugo.

CONFLICT OF INTEREST
The authors have no conflicts of interest to declare.

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

REFERENCES
1. Arezzo A, Migliore M, Chiaro P, Arolo F, 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
2. 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
3. Bruce J, Krukowsk ZH, Al-Khairly 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
4. 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/10.1016/j.surg.2010.10.017
5. 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
6. Arezzo A, Verra M, Reddavid R, Cravero F, Bonino MA, Morino M. Efficacy of the over-the-scope clip (OTSC) for treatment of colorectal post-surgical leaks and fistulas. Surg Endosc. 2012;26(11):3330–3. https://doi.org/10.1007/s00464-012-2340-2
7. van Koperen PJ, van Berge Henegouwen MI, Bakker CM, Slors JFM, et al. The REAL (REctal Anastomotic Leak) score for prediction 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
8. Challine A, Lefèvre JH, Creavin B, Benoit O, Chafai N, Delancy R, 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/10.1016/j.dcr.2019.11.008
9. 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
10. Nachiappan S, Faiz O. Anastomotic leak increases distant recurrence and long-term mortality after curative resection for colon cancer. Ann Surg. 2015;262:e111. https://doi.org/10.1097/SLA.0000000000007474
11. Krarup PM, Nordholm-Carstensen A, Jorgensen LN, Harling H. 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
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. Multicenter analysis of risk factors for anastomotic leakage after 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.
19. Mandard A-M, Dalibard J-C, Marnay J, Henry-Amar P, Mandard J-C, Marnay J, 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
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, Petett D, Mandard J-C, Marnay J, Henry-Amar M, Petiot J-F, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinico-pathologic correlations. Cancer. 1994;73:2680-6. https://doi.org/10.1002/1097-0142(19940601)73:11<2680::AID-CNCR2 8207311055>3.0.CO;2-C
22. 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
23. Park JS, Choi GS, Kim SH, Kim HR, Kim NK, Lee KY, et al. Multicenter analysis of risk factors for anastomotic leakage after laparoscopic rectal cancer resection: the Korean laparoscopic colorectal surgery study group. Ann Surg. 2013;257:665-71. https://doi.org/10.1097/SLA.0b013e318278ed9
24. Warschik R, Steffen T, Thierbach J, Bruckner T, Lange J, Tarantino I. Risk factors for anastomotic leakage after rectal cancer resection and reconstruction with colorectal reservoir. A retrospective study with bootstrap analysis. Ann Surg Oncol. 2011;18:2772-82. https://doi.org/10.1245/s10434-011-1696-1
25. Schroock TR, Deveney CW, Duphly JE. Factor contributing to leakage of colonic anastomoses. Ann Surg. 1973;177:513-8. https://doi.org/10.1097/00000658-197305000-00002
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 N, 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
29. Neutzling CB, Lustosa SA, Proenca IM, da Silva EM, Matos D. Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in the treatment of rectal cancer. Int J Colorectal Dis. 2008;23:411-8. https://doi.org/10.1007/s00384-008-0470-8
30. 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, Pettersson 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

Additional supporting information may be found in the online version of the article at the publisher’s website.

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 anastomatic 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

COLLABORATORS FROM THE ITALIAN SOCIETY OF SURGICAL ONCOLOGY—COLORECTAL CANCER NETWORK COLLABORATIVE GROUP (ALL NAMES TO BE PUBMED CITABLE TOGETHER WITH NAMES IN HEADLINE AUTHORSHIP)

Francesco Evola, MD, University of Turin, Department of Oncology, Division of Surgical Oncology and Digestive Surgery, San Luigi University Hospital, Orbassano (Turin) Italy. Michela Mineccia, MD, Department of General and Oncological Surgery, ‘Umberto I’ Mauriziano Hospital, Turin, Italy. Francesca Pecchini, MD, Unità Operativa di chirurgia generale, d’urgenza e nuove tecnologie, OCSAE, Azienda Ospedaliero Universitaria di Modena, Italy. Gaetano Gallo, MD, Department of Medical and Surgical Sciences, University of Catanzaro, Catanzaro, Italy. Paola Incollingo, MD, General Surgery Unit, San Leonardo Hospital, ASL-NA3sud, Castellamare di Stabia-Naples, Italy. Fabio Maiello, MD, Department of Surgery—General Surgery Unit, Hospital of Biella, Biella, Italy. Andrea Barberis, MD, Unit of General and Hepatobiliary Surgery, E.O. Ospedali Galliera, Genoa, Italy. Monica Ortenzi, MD, Clinica Chirurgica Universita’ Politecnica delle Marche, Ospedali Riuniti Ancona, Italy. Vittoria Bellato, MD, Minimally Invasive and Gastrointestinal Surgery Unit, Università e Policlinico Tor Vergata, Rome, Italy. Caterina Foppa, MD, Humanitas Clinical and Research Center, Via Alessandro Manzoni, 56, 20089, Rozzano, Milan, Italy; Humanitas University, Department of Biomedical Science, Pieve Emanuele-Milan, Italy. Vincenzo Adamo, MD, General Surgery, Ospedale Michele e Pietro Ferrero, Verduno, Cuneo, Italy. Cristina Bombardini, MD, AOI Ferrara, Department of Surgical Morphology and Experimental Medicine, Ferrara, Italy. Alessandro Giuliani, MD, Department of Surgery, Misericordia Hospital, Grosseto, Italy. Francesca Cravero, MD, Department of Surgery, General Surgery Unit, Santo Spirito Hospital, Casale Monferrato, AL, Italy. Marco Amisano, MD, Department of Surgery, General Surgery Unit, Santo Spirito Hospital, Casale Monferrato, AL, Italy. Pietro Paolo Bianchi, MD, Department of Surgery, Misericordia Hospital, Grosseto, Italy. Gabriele Anania, MD, AOI Ferrara, Department of Surgical Morphology and Experimental Medicine, Ferrara, Italy. Marco Calgaro, MD, General Surgery, Ospedale Michele e Pietro Ferrero, Verduno, Cuneo, Italy. Antonino Spinelli, MD, PhD, FASCRS, Humanitas Clinical and Research Center, Via Alessandro Manzoni, 56, 20089, Rozzano, Milan, Italy; Humanitas University, Department of Biomedical Science, Pieve Emanuele-Milan, Italy. Giuseppe SSica, MD, Minimally Invasive and Gastrointestinal Surgery Unit, Università e Policlinico Tor Vergata, Rome, Italy. Marito Guerrieri, MD, Clinica Chirurgica Universita’ Politecnica delle Marche, Ospedali Riuniti Ancona, Italy. Marco Filauro, MD, Unit of General and Hepatobiliary Surgery, ‘Umberto I’ Mauriziano Hospital, Turin, Italy. Domenico D’Ugo, MD, Fondazione Policlinico Gemelli—IRCCS, AREA di Chirurgia Addominale, Rome, Italy.