Validation of the International Study Group of Rectal Cancer definition and severity grading of anastomotic leakage

Yakup Kulu, MD,[a] Alexis Ulrich, MD,[a] Thomas Bruckner, PhD,[b] Pietro Contin, MD,[a] Thilo Welsch, MD,[a] Nuh N. Rahbari, MD,[a] Markus W. Büchler, MD,[a] *and* **Jürgen Weitz, MD,[a]**
Heidelberg, Germany

Background. *The International Study Group of Rectal Cancer (ISREC) has proposed a generally applicable definition and severity grading of (AL) after sphincter-preserving resection of the rectum. This work has been carried out to test for validity.*
Methods. *A total of 746 patients who were identified from a prospective rectal cancer database underwent sphincter-preserving anterior resection of the rectum between October 2001 and January 2011. The incidence and severity of AL was determined using the criteria established by the ISREC. Patients with AL were categorized according to the ISREC scheme. The clinical outcomes were analyzed and compared between the groups.*
Results. *The overall AL rate was 7.5% (56/746). The 56 patients with AL were distributed among the different groups as follows: Grade A, 16%; grade B, 23%; and grade C, 61%. Compared with the grade A patients, grades B and C patients had significantly elevated serum C-reactive protein levels (*$P < .01$*). None of the grade A patients were transferred to the intensive care unit (ICU). Their further hospital stay was uneventful. The length of stay in the ICU was significantly longer for grade C patients compared with grade B patients (*$P < .001$*). The median hospital stay of grade C patients was significantly longer than that of grades A and B patients (*$P < .001$*).*
Conclusion. *The definition and severity grading of AL after anterior resection of the rectum proposed by the ISREC provides a simple, easily applicable, and valid classification. Using this classification system may facilitate comparison of results from different studies on AL after sphincter-preserving rectal surgery. (Surgery 2013;153:753-61.)*

From the Department of General, Visceral and Transplantation Surgery,[a] and the Institute for Medical Biometry and Informatics,[b] University of Heidelberg, Heidelberg, Germany

In the last 2 decades, management of patients with adenocarcinoma of the rectum has improved substantially. Surgery builds the basis of the therapy of rectal cancer.[1] Important developments such as total mesorectal excision,[2] new stapling devices,[3-5] and acceptance of less extensive distal margins[6] have provided the tools and the evidence to preserve the sphincter even in very low tumors and to restore intestinal continuity. Consequently, the restoration of intestinal continuity after sphincter saving rectal surgery, with or without formation of a neorectal reservoir, involves the formation of an anastomosis. A great deal has been published about the risk factors for anastomotic leak.[7-12] The leakage rates found in the literature vary considerably and are reported to range between 3% and 23%.[13] The occurrence of anastomotic leakage (AL) after sphincter-saving rectal cancer surgery is a major complication, which may have substantial adverse effects on the short- and long-term outcomes for the individual. It is of utmost importance to identify measures to minimize the risk of AL. However, owing to the various definitions of AL, the data available are difficult to interpret and compare. The same is true for many of the complications that arise after hepatobiliary and pancreatic surgery. In recent years, major complications, such as pancreatic fistula,[14] postpancreatic hemorrhage,[15] delayed gastric emptying[16] after pancreatic resections, bile leakage after hepatobiliary and pancreatic surgery,[17] posthepatectomy hemorrhage,[18] and posthepatectomy liver failure[19] after liver surgery, have been proposed.

Accepted for publication February 5, 2013.

Reprint requests: Jürgen Weitz, MD, Department of Visceral, Thoracic and Vascular Surgery, University Hospital Carl Gustav Carus of the Technical University Dresden, Dresden, Germany. E-mail: uergen.weitz@uniklinikum-dresden.de.

0039-6060/$ - see front matter

© 2013 Mosby, Inc. All rights reserved.

http://dx.doi.org/10.1016/j.surg.2013.02.007

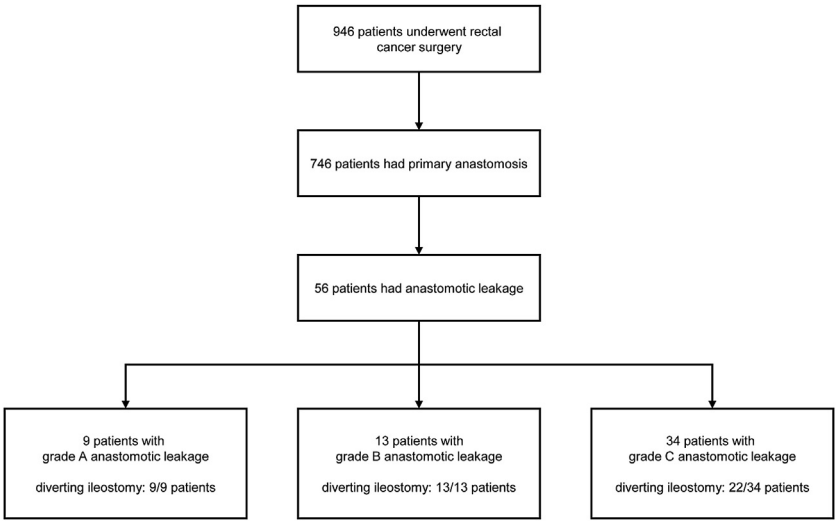

Fig. Flowchart summarizing patients with anastomotic leakage.

Some of these definitions have been tested and proved to be valid and applicable.[17,20-22]

The International Study Group of Rectal Cancer (ISREC) has addressed the lack of an objective and easily applicable definition of AL in rectal cancer surgery.[13] A review of the literature and critical evaluation of the 59 available definitions of AL has resulted in a consensus definition. According to that definition an anastomotic leak is defined as a communication between the intra- and extraluminal compartments resulting from a defect in the integrity of the intestinal wall at the anastomosis between the colon and rectum or the colon and anus. Furthermore, leakage originating from the suture or staple line of a neorectal reservoir, as well as a pelvic abscess in the proximity of the anastomosis is also considered to be AL. An abscess "in proximity" is defined as a pelvic abscess around the anastomotic site without an obvious fecal fistula. Depending on the impact of the AL on clinical management, 3 grades of leakage severity were defined and classified as grades A, B, and C.

The ISREC proposal for the definition and severity grading of AL after anterior resection of the rectum has not been validated in an independent patient cohort. We sought to test whether the proposed scheme to define and grade AL is suitable by analyzing our cohort of patients after sphincter-preserving anterior rectum resection.

PATIENTS AND METHODS

The cohort in this study comprises all 746 patients who underwent sphincter-preserving rectal cancer surgery and restoration of bowel continuity at our institution (Fig) between October 2001 and January 2011 ($n = 56$) who were diagnosed with AL. All patients had histologically proven adenocarcinoma of the rectum. Patient demographic, preoperative assessment and treatment, comorbidities, operative details, postoperative morbidity and mortality, histologic, and follow-up data were collected prospectively.

Neoadjuvant therapy. Based on the results of the preoperative assessment, patients underwent neoadjuvant therapy in locally advanced cases. The diagnostic workup included a physical examination with a digital rectal examination, laboratory tests including measurement of carcinoembryonic antigen levels, colonoscopy, endorectal ultrasonography, abdominal ultrasonography and/or a contrast computed tomography, and chest x-ray. The majority of patients with suspected nodal involvement and/or invasion of the mesorectum (T3 tumor) underwent neoadjuvant short-term radiotherapy with a total dose of 25 Gy (5 consecutive daily doses of 5 Gy). If the preoperative staging revealed a locally advanced stage T4 tumor, threatened circumferential margins, or tumors in close proximity to the sphincter (within approximately 2 cm above the dentate line), patients were considered for neoadjuvant chemoradiotherapy (CRT). The CRT regimen consisted of pelvic irradiation with 28 fractions of single doses of 1.8 Gy over 6 weeks (total dose, 50.4 Gy) combined with 5-fluorouracil–based chemotherapy (continuous infusion of 300 mg/m^2 within 24 hours) daily during each course of radiotherapy. Surgery after completion of short-term radiotherapy and CRT were

scheduled within 2 days and after 4–6 weeks, respectively.

Operative technique. Preoperative bowel preparation (except in patients with obstructing cancers) with a polyethylene glycol electrolyte solution was given 1 day before surgery. Patients were seen by the anesthesiologist to determine American Society of Anesthesiologists (ASA) score, which is based on a scale of 1–5 (1, normal healthy patient; 2, mild systemic disease; 3, severe systemic disease; 4, severe systemic disease that is a constant threat to life; and 5, a moribund patient not expected to survive without surgery). The enterostomal therapist was consulted to mark the site for the protective loop ileostomy. An open resection was performed for all patients. Patients were placed in a lithotomy position. Perioperative, prophylactic antibiotics were given at the induction of anesthesia. After laparotomy through a midline incision, the left colon was mobilized up to the middle colic artery. The pelvic nerve plexuses were identified and preserved during dissection and the inferior mesenteric artery was ligated close to the aorta. The inferior mesenteric vein was divided at the inferior border of the pancreas. Depending on the localization of the tumor, a partial or total mesorectal excision was undertaken. Bowel continuity was restored by transanal double stapling anastomosis. The anvil of the circular stapler (Covidien, Mansfield, MA) of appropriate size was placed at the distal cut end of the descending colon and anastomosed to the stapled rectal end. After completion, the anastomosis was tested by transanal air insufflation. Drains were routinely placed during surgery. A transverse coloplasty pouch (TCP) or colon J pouch was created as a neorectal reservoir for total mesorectal excision with anastomosis within 2–3 cm from the dentate line was performed. TCP was the preferred mode of neorectal reservoir formation. A diverting stoma was routinely constructed in this group of patients. Patients with tumors in the upper third of the rectum underwent partial mesorectal excision and, in general, did not require a protective ileostomy and pouch formation.

Postoperative management. Serum CRP levels and white blood counts (WBC) were recorded routinely before the operation and on postoperatively every other day until the peak level was reached, and was continued thereafter depending on the postoperative course of the patient. An adequate diagnostic workup was initiated based on the present general or specific clinical signs suggestive of an anastomotic leak. Whereas abdominal or pelvic pain, abdominal distention, fever, and leukocytosis were considered general indicators, turbid/purulent discharge from the drains, laparotomy incision, vagina, or rectum were specific symptoms resulting from AL. If an anastomotic leak was suspected, computed tomography with rectal contrast enema was undertaken. Additional investigations, such as digital rectal examination and endoscopy, were performed if necessary. The severity of the symptoms was decisive in treating the patient either conservatively, with percutaneous drainage, transanal revision, or relaparotomy.

Definitions. Total hospital stay was defined as the period of time from admission until discharge from the hospital. Intensive care unit (ICU) transfer and stay were defined as transfer to the ICU and the duration of treatment there after deterioration of the clinical condition except for routine postoperative admission. Mortality was defined as in-hospital death owing to any cause.

The incidence of other complications than AL and pelvic abscess were also listed and compared across all leakage grades. Wound infection was defined as any evidence of infection (erythema, purulent discharge, tenderness) requiring antibiotic treatment and/or opening of the wound. Postoperative hemorrhage was defined as bleeding in the first 6 hours postoperatively resulting in a need for transfusion and/or operative intervention. Urinary retention was defined as the inability to urinate resulting in a need for transurethral catheterization or suprapubic cystostomy. A fascial dehiscence was defined as an opening along the surgical suture within the fascia of the abdominal wall requiring reoperation. Pneumonia was defined as an inflammatory condition of the lung confirmed by the presence of a new infiltrate on chest x-ray, elevated body temperature (>38°C), and WBC or positive sputum cultures requiring intravenous antibiotic treatment. Myocardial infarction was diagnosed by serum troponin T elevation and/or ST elevation and/or pathologic Q waves on electrocardiogram.

Serum C-reactive protein (CRP) levels and WBC were recorded across all leakage grades. In patients with grades B and C AL, the CRP and WBC levels were documented on the day the leakage was diagnosed. A comparison was made between the highest CRP and WBC serum level during the postoperative course of patients with grade A AL.

Statistical analyses. The nature of this study is explorative; no sample size estimation is possible. Empirical distribution of continuous data was presented as the median and range and the possible differences between groups were tested by Kruskal–Wallis test. Categorical data were

expressed as absolute and relative frequencies and compared using the $\chi 2$ test. SAS software (Release 9.1, SAS Institute, Inc, Cary, NC) was used for analysis.

RESULTS

Between October 2001 and January 2011, 746 patients with an adenocarcinoma of the rectum underwent sphincter-preserving anterior resection with simultaneous reconstruction of the intestinal continuity in our department. AL was identified in 56 patients (7.5%). The analysis has been conducted on these 56 patients. According to the definition and severity grading of the ISREC, 9 patients met the criteria for grade A (16%), 13 for grade B (23%), and 34 for grade C AL (61%). Three patients with a grade C AL were managed by posterior rectotomy. For this operation, the patient is in prone position and a midline incision is made extending from the lower sacrum to the margin of the external anal sphincter. In all 3 cases, a lavage of the pelvis was performed and a drainage was placed.

Table I outlines the characteristics of all the patients. The median ages of grades A, B, and C patients were 61 (range, 57–78), 62 (range, 34–81), and 66 (range, 44–80) years of age, respectively. However, the median age tended to be higher for grade C patients compared with grades A and B patients. The 3 groups were equally distributed according to gender. Although grades A and C patients displayed similar distributions according to the ASA score of the patients, grade B patients had a low ASA score less frequently. The majority of concomitant medical risk factors were smoking, diabetes, coronary heart disease, overweight, renal insufficiency, and chronic obstructive pulmonary disease. Short-term neoadjuvant radiotherapy was equally frequent across the 3 groups. Neoadjuvant CRT was received less frequently by grade C patients. There were more patients with tumors with a distance of >10 cm to the anal verge in grade C patients than in grades A and B patients. More patients with grade B and C AL had UICC stages III and IV disease compared with patients with grade A AL.

Operative and perioperative outcomes. The operative and perioperative results for all AL grades are summarized in Table II. The duration of hospital stay increased as did the severity of the leakage and was 13 days (range, 9–21) for grade A patients, 16 days (range, 12–65) for grade B patients, and 33.5 days (range, 16–85) for grade C patients ($P < .001$). None of the patients with grade A AL were transferred to the ICU and only 1 grade B patient was transferred to the ICU. Patients with grade C AL usually developed fecal or purulent drain contents leading to peritonitis, fever, and increased laboratory parameters of infection requiring transfer to the ICU in 18 out of 34 patients (53%; $P < .001$) resulting in a median ICU stay of 3 days (range, 0–70; $P < .001$). Grades A, B, and C patients were managed with percutaneous abscess drainage placement in 0%, 92%, and 38% of cases ($P < .001$). In line with the definition, relaparotomy was only carried out in patients with grade C AL (100%).

The preferred mode for neorectal reservoir reconstruction was TCP of the 46 patients, 40 (71%) underwent either transverse coloplasty (n = 36 [90%]), colonic J-pouch (n = 3 [7.5%]), or side-to-end anastomosis (n = 1 [2.5%]). The frequency of pouch formation was higher in grades A and B patients compared with grade C patients. In 1 out of the 40 patients (2.5%) with pouch formation, the AL was identified at the staple line of the TCP. This patient had grade C leakage.

Two patients died in the postoperative course. Both patients had grade C anastomotic leak and died of multiorgan failure caused by sepsis 15 and 47 days after the initial operations. Medical complications such as pneumonia and myocardial infarction and operative complications, except for AL and pelvic abscess (eg, wound infection), were more common among grades B and C compared with grade A patients.

Serum CRP and WBC. We compared the highest CRP and serum leukocyte values during the postoperative course of grade A patients with the CRP and serum leucocyte values of grades B and C patients determined just before the diagnosis of AL (Table II). The median serum leucocyte value of the patients with grade A AL was 9/nL (range, 4–15) and not elevated. In contrast, most patients with grade B AL had leukocytosis (median, 14; range, 4–32). Some of the grade C patients (18%) had leukopenia as a result of sepsis; therefore, the serum leucocytes values in grade C patients ranged between 1 and 26 (median, 9). The CRP values of the grades B and C patients were significantly higher than those of the grade A patients (grade B, 190 mg/L [range, 50–380]; grade C, 209 mg/L [range, 12–517]; grade A, 104 mg/L [range, 34–233]; $P = .01$).

In 53% of the patients with grade C leakage, the CRP values of 200 mg/mL were exceeded at the time of diagnosis of the AL, which is a measure of massive inflammatory reaction. In 23% of grade B and 21% of grade C patients, even CRP values of 300 mg/mL were exceeded. In contrast, the serum CRP and WBC elevation in group A patients was moderate (Table III).

Table I. Patient characteristics

	Grade, n *(%) or median (range)*			
	A	*B*	*C*	P
n	9	13	34	
Age (yrs)	61 (57–78)	62 (34–81)	66 (44–80)	.42
Gender				.77
Male	8 (89)	10 (77)	27 (79)	
Female	1 (11)	3 (23)	7 (21)	
ASA score				.21
1 and 2	7 (78)	6 (46)	24 (71)	
3 and 4	2 (22)	7 (54)	10 (29)	
Medical risk factors				.86
Smoker	1 (11)	3 (23)	4 (12)	.59
Diabetes	1 (11)	0	5 (15)	.35
Coronary heart disease	1 (11)	1 (8)	2 (6)	.86
Body mass index >27 kg/m^2	5 (56)	2 (15)	14 (41)	.12
Renal insufficiency	0	0	2 (6)	NA
COPD	1 (11)	2 (15)	2 (6)	.57
Neoadjuvant therapy				
RT	3 (33)	5 (38)	11 (32)	.92
CRT	3 (33)	3 (23)	3 (9)	.15
Tumor distance from anal verge (cm)				.45
<5	4 (44)	8 (62)	13 (38)	
5–10	4 (44)	4 (31)	11 (32)	
>10	1 (11)	1 (7)	10 (29)	
Resection margins				.18
0	9 (100)	11 (85)	33 (97)	
1	0	2 (15)	1 (3)	
2	0	0	0	
UICC				.35
0	2 (22)	0	2 (6)	
1	1 (11)	4 (31)	9 (24)	
2	4 (44)	2 (15)	7 (21)	
3	2 (22)	5 (38)	14 (41)	
4	0	4 (7)	2 (6)	

ASA, American Society of Anesthesiologists; *CJP*, colon J pouch; *COPD*, chronic obstructive pulmonary disease; *CRT*, chemoradiotherapy; *RT*, short-term radiotherapy; *TCP*, transverse coloplasty pouch; *UICC*, Union for International Cancer Control.

Subgroup analysis of patients with a diverting ileostomy at initial operation. The AL rate among patients after rectal cancer surgery with primary anastomosis and diverting ileostomy was 6.7% (44/654). The distribution between the groups was 20% (9/44), 30% (13/44), and 50% (22/44) for groups A, B, and C, respectively. The median serum CRP levels remained higher in grade C patients. However, the differences between the groups were not statistically significant (grade A, median 104 mg/L [range, 34–233]; grade B, median 190 mg/L [range, 50–380]; grade C, median 219 mg/L [range, 50–517]; $P = .07$). Owing to their clinical deterioration, 12 grade C patients were transferred to the ICU compared with 0 grade A patients and 1 grade B patient ($P = .002$). The ICU duration of stay for patients with grade C AL was up to 70 days (median, 3; $P = .008$). The median hospital stay of patients with grade C AL was significantly longer (grade A, median 13 days [range, 9–21]; grade B, median 16 days [range, 12–65]; grade C, median 36 days [range, 18–85]; $P < .00001$; Table IV).

DISCUSSION

Sufficient restoration of intestinal continuity after sphincter-preserving rectal cancer surgery has been considered one of the quality indicators of surgical performance.[23,24] AL has been associated with increased morbidity and mortality[25-28] in the perioperative period and with adverse impact on late functional results[29-31] and long-term outcomes.[32-34] Owing to the lack of a generally accepted definition of AL, the rates after anterior

Table II. Operative and perioperative outcomes

	Grade, n *(%) or median (range)*			
	A	*B*	*C*	P
n	9	13	34	
Hospital stay (d)	13 (9–21)	16 (12–65)	33,5 (16–85)	<.001
ICU transfer	0	1 (8)	18 (53)	<.001
ICU stay (d)	0	0 (0–7)	3 (0–70)	<.001
Pelvic abscess drainage	0	12 (92)	13 (38)	<.001
Relaparotomy	0	0	34 (100)	NA
Mortality	0	0	2 (6)	.51
Morbidity				
Surgical complications				
Wound infection	1 (11)	2 (16)	9 (27)	.51
Postoperative hemorrhage	0	1 (8)	1 (3)	NA
Urinary retention	1 (11)	3 (24)	1 (3)	.09
Fascial dehiscence	1 (11)	0	0	.55
Medical complications				.33
Pneumonia	0	0	7 (21)	.41
Myocardial infarction	0	1 (8)	1 (3)	NA
Operative time (min)	210 (140–420)	240 (140–420)	230 (120–420)	.44
Pouch				.36
Yes	7 (78)	11 (85)	22 (65)	
No	2 (22)	2 (15)	12 (35)	
Stoma formation				.01
Diverting stoma at initial operation	9 (100)	13 (100)	23 (68)	
Subsequent stoma formation	0	0	11 (32)	
CRP (mg/L), normal range, <5	104 (34–233)	190 (50–380)	209 (12–517)	.01
Leukocytes (/nL), normal range, 4–10	9 (4–15)	14 (4–32)	9 (1–26)	.01
Blood loss (mL)	800 (400–1,400)	900 (200–3,000)	500 (100–2,500)	.07
Transfusion of PRBCs				.83
Yes	2 (22)	2 (15)	8 (24)	
No	7 (78)	11 (85)	26 (76)	
Amount of PRBC transfusion (U)	0 (0–4)	0 (0–4)	0 (0–4)	NA

ICU, Intensive care unit; *PRBC*, packed red blood cells.

resection of the rectum varied between 3% and 23%. Existing studies were difficult to compare because of the inconsistency in patient selection, the differences in the treatments given, and the varying follow-up times. The different definitions of AL added to that difficulty.

Therefore, the ISREC published a definition and severity grading for AL after sphincter-preserving anterior resection of the rectum.[13] In reviewing the literature, the authors found 59 articles providing a definition of AL after anterior resection. Critical evaluation resulted in the identification of 11 definitions with a severity grading for AL after anterior resection. With respect to the terminology, the most frequently used term to describe the complication of failure of integrity of restored continuity was AL. According to the evaluation of these publications, the clinical symptoms associated with AL, the diagnostic workup to confirm the suspicion of AL and ultimately the diagnostic management was defined. According to its impact on clinical management, a severity grading of A, B, and C was proposed.

In this regard, our aim was to evaluate if the stratification of patients into the different groups based on the definition and grading of the ISREC was valid in our patient cohort. The grade A

Table III. Postoperative serum C-reactive protein (CRP) and white blood cell count after anastomotic leakage

	Grade, n *(%)*			
	A	*B*	*C*	P
N	9	13	34	
Leukopenia (<4/nL)	0	0	6 (18)	.08
Leukocytosis (>20/nL)	0	2 (15)	6 (18)	.54
CRP >200 mg/L	1 (11)	4 (31)	18 (53)	.07
CRP >300 mg/L	0	3 (23)	7 (21)	.31

Table IV. Subgroup analysis of patients with a diverting ileostomy at initial surgery

	Grade, n *(%) or median (range)*			
	A	*B*	*C*	P
n	9	13	22	
CRP (mg/L), normal range, <5	104 (34–233)	190 (50–380)	219 (50–517)	.07
ICU transfer, *n* (%)	0	1 (8)	12 (55)	.002
ICU stay (d)	0	0 (0–7)	3 (0–70)	.008
Hospital stay (d)	13 (9–21)	16 (12–65)	36 (18–85)	<.00001

CRP, C-reactive protein; *ICU,* intensive care unit.

patients in our cohort had an uneventful postoperative course. Of the group B patients, 92% had a radiologic drain placed in the pelvis and were treated with antibiotics less frequently. According to the ISREC definition, an anastomotic leak requiring relaparotomy is classified as grade C. Because grade B AL is defined as requiring active therapeutic intervention without operative reintervention, we counted 3 patients with a posterior rectotomy compared with the group of grade C patients. Patients with grade C leakage comprised more than half of all the leakage cases (61%). The asymptomatic group A occurred in only 16% of the cases and group B leakage in 23% of the cases. Because group A was asymptomatic for AL and diagnosis is usually made during a routine workup before stoma closure, it is reasonable to assume that the estimated number of undetected AL in grade A patients is higher.

According to the definition of the ISREC, an abscess in vicinity of the anastomotic site without an obvious fecal fistula was classified as an AL. Seven (12.5%) patients (1 grade A, 4 grade B, and 2 grade C) had such abscesses. No patient had an abscess which was not in proximity of the anastomosis. However, 16 patients (29%; 1 grade A, 4 grade B, and 11 grade C) with abscesses in proximity of the anastomotic site, had simultaneously an obvious fecal fistula.

In the present study, patients with grade A AL had a median hospital stay of 13 days. There was no additional treatment indicated. The clinical management of the patients was consistent with that of patients with the radiologic leakage described in the literature. The median hospital stay of patients with grade B AL was 16 days. Of the 13 patients (92%), 12 of those designated as grade B a pelvic drain was placed by interventional radiology. Compared with the patients with grades A and B AL, patients with grade C AL had a significantly longer hospital stay (median, 33.5 days). The indication for surgery was sepsis, necrosis of the colon, feculent content in the drains, and peritonitis. Clinical management of these patients required significantly more ICU transfers (53% of grade C patients vs 8% grade B and 0% grade A patients). As a consequence of septic complications, grade C patients displayed a higher frequency of medical and surgical complications, such as wound infection and pneumonia, compared with grades A or B patients. However, this difference did not attain significance. However, in the postoperative course, clinical management and hospital stay across the 3 groups were substantially different and they could be easily distinguished using the ISREC severity grading. The classifications available in the literature distinguish between radiologic and clinical leakage or between minor (no need for reoperation) and major leakage (need for reoperation).[26,35-37] If anastomotic leaks are classified by radiologic or clinical leaks, no differentiation can be made between clinical leaks that were managed with (ISREC grade C) or without (ISREC grade B) operative revision. Similarly, if anastomotic leaks are classified according to minor and major leaks, patients who were not initially diagnosed (ISREC grade A) were not included. Our analysis demonstrated that depending on the postoperative course, the ISREC grading facilitates a valid classification system enabling a reliable correlation between the anastomotic leak and the severity of its impact on the clinical course of the patient.

Evaluation of specific laboratory parameters, such as serum CRP and WBC, were not included in the grading system defined by the ISREC. However, Welsch et al[38] evaluated the CRP levels as an early predictor of infectious postoperative complications in rectal operations. The authors concluded that if wound infection, urinary tract infection, and pneumonia can be ruled out, an in-depth search for AL is necessary. Because the results of the laboratory tests were listed and evaluated as the typical clinical characteristics of patients with different severity grades of AL after anterior rectal resection, we examined them. The serum CRP level and WBC were collected on the day the diagnosis of AL in grades B or C patients

Table V. Diverting ileostomy at initial surgery and its impact on the incidence of anastomotic leakage rate

	Patients without initial stoma (n = *92)*	*Patients with initial stoma* (n = *654)*	P
Leakage rate (%)	13 (12/92)	6.7 (44/654)	.03
Grade A (%)	0 (0/92)	1.4 (9/654)	.26
Grade B (%)	0 (0/92)	2 (13/654)	.17
Grade C (%)	13 (12/92)	3.4 (22/654)	<.0001

Table VI. Subgroup analysis of patients without a diverting ileostomy at initial surgery

	Grade, n *(%) or median (range)*		
	A	*B*	*C*
n	0	0	12
CRP (mg/L), normal range, <5	—	—	176 (12–330)
ICU transfer, *n* (%)	—	—	6 (50)
ICU stay (d)	—	—	2 (0–42)
Hospital stay (d)	—	—	10 (29–68)

CRP, C-reactive protein; *ICU,* intensive care unit.

was made. The highest serum CRP level and WBC during the postoperative course of each grade A patient were collected for comparison. Our findings confirmed the typical clinical characteristic suggested by Rahbari et al (Table III). Owing to the severity of the infectious complication caused by AL, the laboratory values represent a relevant tool during clinical assessment. Patients with AL may not be graded using the laboratory values; however, our analysis demonstrates that changes are consistent with the severity grading of AL.

The subgroup analysis of patients who received a diverting ileostomy during initial surgery revealed that the presence of a stoma reduces the rate of patients with grade C AL (Table V). This finding is consistent with earlier published data[39] demonstrating that although stoma formation after rectal cancer surgery does not prevent septic complications completely, it does reduce the rate of septic complications. In our cohort, 92 patients were operated without a diverting ileostomy. It is important to point out that all of the 12 patients who developed an anastomotic leak were classified as grade C (Table VI). All of them needed a laparotomy and subsequently received a stoma. It is not within the scope of this publication to evaluate the relevance of a diverting ileostomy during rectal cancer surgery. However, it is obvious that the clinical course of patients with an anastomotic leak after being operated with a diverting ileostomy at initial surgery may not allow for the differentiation in severity grading. This is reflected by the less marked differences in serum CRP levels between the groups.

In this study, we analyzed our cohort of patients to assess the presence and severity grading of AL in patients undergoing sphincter-preserving anterior rectal resection according to the ISREC proposal. Evaluation of the clinical impact of AL led to accurate classification of grades A, B, and C anastomotic leaks. The scheme proved to be easily applicable and valid, at least in the setting of a high-volume center. With regard to the modern management of patients with AL, operative reintervention in the postoperative course is only indicated if a septic focus, which is not manageable with percutaneous drain placement, is to be cleared. These patients may present with peritonitis, sepsis and organ failure. Owing to their deteriorating clinical condition, the patients in this subpopulation require relaparotomy, which enables a clear differentiation between grades B and C. We conclude that the ISREC definition and severity grading of AL after anterior resection of the rectum provides a simple, easily applicable, and valid classification. Using this classification system may facilitate the comparison of results from different studies on AL after sphincter-preserving rectal cancer surgery.

REFERENCES

1. Weitz J, Koch M, Debus J, Hohler T, Galle PR, Buchler MW. Colorectal cancer. Lancet 2005;365:153-65.
2. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery–the clue to pelvic recurrence? Br J Surg 1982;69:613-6.
3. Goligher JC. Use of circular stapling gun with peranal insertion of anorectal purse-string suture for construction of very low colorectal or colo-anal anastomoses. Br J Surg 1979;66:501-4.

4. Griffen FD, Knight CD Sr, Knight CD Jr. Results of the double stapling procedure in pelvic surgery. World J Surg 1992; 16:866-71.
5. Kyzer S, Gordon PH. Experience with the use of the circular stapler in rectal surgery. Dis Colon Rectum 1992;35:696-706.
6. Ueno H, Mochizuki H, Hashiguchi Y, Ishikawa K, Fujimoto H, Shinto E, et al. Preoperative parameters expanding the indication of sphincter preserving surgery in patients with advanced low rectal cancer. Ann Surg 2004;239:34-42.
7. Eberl T, Jagoditsch M, Klingler A, Tschmelitsch J. Risk factors for anastomotic leakage after resection for rectal cancer. Am J Surg 2008;196:592-8.
8. Jung SH, Yu CS, Choi PW, Kim DD, Park IJ, Kim HC, et al. Risk factors and oncologic impact of anastomotic leakage after rectal cancer surgery. Dis Colon Rectum 2008;51:902-8.
9. Lee WS, Yun SH, Roh YN, Yun HR, Lee WY, Cho YB, et al. Risk factors and clinical outcome for anastomotic leakage after total mesorectal excision for rectal cancer. World J Surg 2008;32:1124-9.
10. Lyall A, McAdam TK, Townend J, Loudon MA. Factors affecting anastomotic complications following anterior resection in rectal cancer. Colorectal Dis 2007;9:801-7.
11. Matthiessen P, Hallbook O, Andersson M, Rutegard J, Sjodahl R. Risk factors for anastomotic leakage after anterior resection of the rectum. Colorectal Dis 2004;6:462-9.
12. Peeters KC, Tollenaar RA, Marijnen CA, Klein KE, Steup WH, Wiggers T, et al. Risk factors for anastomotic failure after total mesorectal excision of rectal cancer. Br J Surg 2005;92:211-6.
13. 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.
14. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 2005;138:8-13.
15. Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, et al. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery 2007;142:20-5.
16. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery 2007;142:761-8.
17. Koch M, Garden OJ, Padbury R, Rahbari NN, Adam R, Capussotti L, et al. Bile leakage after hepatobiliary and pancreatic surgery: a definition and grading of severity by the International Study Group of Liver Surgery. Surgery 2011;149:680-8.
18. Rahbari NN, Garden OJ, Padbury R, Maddern G, Koch M, Hugh TJ, et al. Post-hepatectomy haemorrhage: a definition and grading by the International Study Group of Liver Surgery (ISGLS). HPB (Oxford) 2011;13:528-35.
19. Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery 2011;149:713-24.
20. Pratt WB, Maithel SK, Vanounou T, Huang ZS, Callery MP, Vollmer CM Jr. Clinical and economic validation of the International Study Group of Pancreatic Fistula (ISGPF) classification scheme. Ann Surg 2007;245:443-51.
21. Welsch T, Borm M, Degrate L, Hinz U, Buchler MW, Wente MN. Evaluation of the International Study Group of Pancreatic Surgery definition of delayed gastric emptying after pancreatoduodenectomy in a high-volume centre. Br J Surg 2010;97:1043-50.
22. Welsch T, Eisele H, Zschabitz S, Hinz U, Buchler MW, Wente MN. Critical appraisal of the International Study Group of Pancreatic Surgery (ISGPS) consensus definition of postoperative hemorrhage after pancreatoduodenectomy. Langenbecks Arch Surg 2011;396:783-91.
23. Bittner R, Burghardt J, Gross E, Grundmann RT, Hermanek P, Isbert C, et al. [Quality indicators for diagnostic and therapy of rectal carcinoma]. Zentralbl Chir 2007;132:85-94.
24. Thompson GA, Cocks JR, Collopy BT, Cade RJ, Ewing HP, Rogerson JW, et al. Colorectal resection in Victoria: a comparison of hospital based and individual audit. Aust N Z J Surg 1996;66:520-4.
25. Chessin DB, Enker W, Cohen AM, Paty PB, Weiser MR, Saltz L, et al. Complications after preoperative combined modality therapy and radical resection of locally advanced rectal cancer: a 14-year experience from a specialty service. J Am Coll Surg 2005;200:876-82.
26. Eckmann C, Kujath P, Schiedeck TH, Shekarriz H, Bruch HP. Anastomotic leakage following low anterior resection: results of a standardized diagnostic and therapeutic approach. Int J Colorectal Dis 2004;19:128-33.
27. Khan AA, Wheeler JM, Cunningham C, George B, Kettlewell M, Mortensen NJ. The management and outcome of anastomotic leaks in colorectal surgery. Colorectal Dis 2008;10:587-92.
28. 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.
29. den Dulk M, Noter SL, Hendriks ER, Brouwers MA, van der Vlies CH, Oostenbroek RJ, et al. Improved diagnosis and treatment of anastomotic leakage after colorectal surgery. Eur J Surg Oncol 2009;35:420-6.
30. Hallbook O, Sjodahl R. Anastomotic leakage and functional outcome after anterior resection of the rectum. Br J Surg 1996;83:60-2.
31. Nesbakken A, Nygaard K, Lunde OC. Outcome and late functional results after anastomotic leakage following mesorectal excision for rectal cancer. Br J Surg 2001;88:400-4.
32. Law WL, Choi HK, Lee YM, Ho JW, Seto CL. Anastomotic leakage is associated with poor long-term outcome in patients after curative colorectal resection for malignancy. J Gastrointest Surg 2007;11:8-15.
33. McArdle CS, McMillan DC, Hole DJ. Impact of anastomotic leakage on long-term survival of patients undergoing curative resection for colorectal cancer. Br J Surg 2005;92:1150-4.
34. Walker KG, Bell SW, Rickard MJ, Mehanna D, Dent OF, Chapuis PH, et al. Anastomotic leakage is predictive of diminished survival after potentially curative resection for colorectal cancer. Ann Surg 2004;240:255-9.
35. Chambers WM, Mortensen NJ. Postoperative leakage and abscess formation after colorectal surgery. Best Pract Res Clin Gastroenterol 2004;18:865-80.
36. O'Grady G, Secker A. Colorectal cancer management in the provincial New Zealand setting of Nelson. Aust N Z J Surg 2007;77:1004-8.
37. Tytherleigh MG, Bokey L, Chapuis PH, Dent OF. Is a minor clinical anastomotic leak clinically significant after resection of colorectal cancer? J Am Coll Surg 2007;205:648-53.
38. Welsch T, Muller SA, Ulrich A, Kischlat A, Hinz U, Kienle P, et al. C-reactive protein as early predictor for infectious postoperative complications in rectal surgery. Int J Colorectal Dis 2007;22:1499-507.
39. Ulrich AB, Seiler C, Rahbari N, Weitz J, Buchler MW. Diverting stoma after low anterior resection: more arguments in favor. Dis Colon Rectum 2009;52:412-8.