

Late Anastomotic Leakage After Rectal Cancer Surgery: Incidence and Differential Risk Factors

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BACKGROUND: Anastomotic leakage is a major complication of rectal cancer surgery, contributing to increased morbidity, poorer oncologic outcomes, and permanent stoma formation. However, consensus on its diagnostic time frame and risk factors is lacking. Anastomotic leakage in the late postoperative period is usually underrecognized owing to inconsistent definitions and variable surveillance protocols.

OBJECTIVE: To investigate the serial incidence and risk factors for overall and late anastomotic leakage after curative-intent rectal cancer surgery.

DESIGN: Retrospective cohort study.

SETTINGS: Asan Medical Center, a tertiary referral center in Seoul, Korea.

PATIENTS: This study included 4472 patients who underwent rectal cancer resection with anastomosis between 2012 and 2020. Patients undergoing palliative or combined surgeries were excluded.

MAIN OUTCOME MEASURES: We analyzed the incidence and timing of anastomotic leakage and identified independent risk factors for overall and late anastomotic leakage using logistic regression.

RESULTS: The overall anastomotic leakage incidence was 3.2% (n = 145), with late anastomotic leakage comprising 48.3% (n = 70) of cases. Notably, 24.1% (n = 35) were diagnosed more than 1 year postoperatively. Of those with late anastomotic leakage, 78.6% (n = 56) had undergone diverting stoma formation. Independent risk factors for overall anastomotic leakage included younger age, male sex, low tumor location, and high inferior mesenteric artery ligation. Late anastomotic leakage was independently associated with neoadjuvant chemoradiotherapy (OR 3.573), robotic surgery (OR 4.734), and adjuvant chemotherapy (OR 3.420).

LIMITATIONS: The retrospective design and single-institution surveillance protocol may limit generalizability.

CONCLUSIONS: Late anastomotic leakage occurs at a rate comparable to early anastomotic leakage and presents with distinct risk factors. Extended surveillance and tailored management are warranted in high-risk patients. See **Video Abstract**.



FUGA ANASTOMÓTICA TARDÍA TRAS CIRUGÍA DE CÁNCER RECTAL: INCIDENCIA Y FACTORES DE RIESGO DIFERENCIALES

ANTECEDENTES: La fuga anastomótica es una complicación importante de la cirugía del cáncer rectal, que contribuye al aumento de la morbilidad, a peores resultados oncológicos y a la formación de un estoma permanente. Sin embargo, no existe consenso sobre el plazo para su diagnóstico y los factores de riesgo. La fuga anastomótica en el periodo posoperatorio tardío suele pasar desapercibida debido a la inconsistencia de las definiciones y a la variabilidad de los protocolos de vigilancia.

OBJETIVO: Investigar la incidencia seriada y los factores de riesgo de la fuga anastomótica general y tardía tras la cirugía de cáncer rectal con intención curativa.



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DISEÑO: Estudio de cohorte retrospectivo.

ENTORNO: Centro Médico Asan, un centro de referencia terciario en Seúl, Corea.

PACIENTES: Este estudio incluyó a 4472 pacientes que se sometieron a una resección de cáncer rectal con anastomosis entre 2012 y 2020. Se excluyó a los pacientes sometidos a cirugías paliativas o combinadas.

PRINCIPALES MEDIDAS DE RESULTADO: Analizamos la incidencia y el momento de la fuga anastomótica e identificamos los factores de riesgo independientes de fuga anastomótica general y tardía mediante regresión logística.

RESULTADOS: La incidencia general de fuga anastomótica fue del 3,2 % (n = 145), y la fuga anastomótica tardía representó el 48,3 % (n = 70) de los casos. Cabe destacar que el 24,1 % (n = 35) se diagnosticó más de un año después de la operación. De los que presentaron fuga anastomótica tardía, el 78,6 % (n = 56) se había sometido a una formación de estoma de derivación. Los factores de riesgo independientes para la fuga anastomótica general incluyeron la edad más joven, el sexo masculino, la ubicación baja del tumor y la ligadura de la arteria mesentérica inferior alta. La fuga anastomótica tardía se asoció de forma independiente con la quimiorradioterapia neoadyuvante (odds ratio 3,573), la cirugía robótica (odds ratio 4,734) y la quimioterapia adyuvante (odds ratio 3,420).

LIMITACIONES: El diseño retrospectivo y el protocolo de vigilancia de una sola institución pueden limitar la generalización.

CONCLUSIONES: La fuga anastomótica tardía se produce a una tasa comparable a la fuga anastomótica temprana y presenta factores de riesgo distintos. Se justifica una vigilancia prolongada y un tratamiento personalizado en pacientes de alto riesgo. (*AI-generated translation*)

KEY WORDS: Anastomotic leak; Postoperative complications; Rectal neoplasms; Surgical stomas.

Despite advancements in surgical techniques and instrumentation within the era of minimally invasive surgery, anastomotic leakage (AL) remains a common complication in rectal cancer surgery. AL occurrence is associated with increased mortality and morbidity, higher reoperation rates, increased health care costs, and a high possibility of permanent stoma formation.^{1,2} Moreover, studies have revealed the adverse impact of AL on oncologic outcomes, including reduced survival rates and increased recurrence.³⁻⁵ Therefore, identifying the risk factors and clinical characteristics of AL in the preoperative and perioperative periods is essential to guide preventive strategies.

The incidence of AL after rectal cancer surgery varies significantly, spanning 3% to 20%, reflecting differences in surgical techniques and the lack of a consistent definition and standardized observation period.^{1,6} The International Study Group of Rectal Cancer has provided a standardized definition, describing AL as a communication between the internal and external intestinal spaces owing to anastomotic defects, and classified AL severity into 3 grades.⁷ AL occurs in the early postoperative phase and during the delayed period, with delayed AL representing a distinct clinical entity that differs from early AL.⁸⁻¹⁰ Despite inconsistent classification of early and late leaks, several studies have classified AL temporally as early (≤ 30 days postoperatively) and late (> 30 days postoperatively).^{8,10} Late AL frequently presents with different clinical features, such as chronic sinus or fistula formation, and is typically managed by stoma reconstruction after stoma reversal, often resulting in prolonged stoma dependence.^{8,10,11} Although early leaks are generally managed with temporary diversion, late leaks typically require a more durable, prolonged diversion to prevent fecal contamination of the anastomotic site.⁸ Despite growing recognition of late AL, consensus on its optimal diagnostic timeframe is lacking, with most studies predominantly focusing on the prevention of early AL.¹

Various factors influencing early AL development have been revealed, including male sex, a narrow bony pelvis, obesity, lower anastomosis location, and preoperative radiotherapy.¹² Late AL reportedly occurs at different anastomotic sites compared with early AL and is relatively unaffected by intraoperative factors such as operative time and blood loss.¹³ Similarly, late AL has been associated with preoperative radiotherapy and postoperative factors such as adjuvant therapy, changes in microcirculation and microbiota, and stoma status.^{8,10,11} However, evidence regarding the specific risk factors and epidemiological characteristics of late AL remains limited. Furthermore, determining its true incidence and clinical manifestations is challenging, as many cases are diagnosed incidentally through subclinical findings on contrast studies or radiologic imaging.⁹

This study aimed to investigate the serial incidence of AL after rectal cancer surgery and identify the risk factors associated with overall and late AL.

MATERIALS AND METHODS

Patients and Variables

We conducted a retrospective review of patients who underwent curative-intent rectal cancer surgery with anastomosis between January 2012 and December 2020 at Asan Medical Center, Seoul, South Korea. Patients who underwent surgery for rectal cancer, defined as tumors within 15 cm of the anal verge (AV), visualized using endoscopy or MRI, were included. Only

procedures involving anastomosis, such as anterior, low anterior, and ultralow anterior resection (ultraLAR), were considered. Surgeries without anastomosis, including Hartmann's procedure, transanal local excision, and end-enterostomy formation, were excluded. Patients who underwent palliative surgery and combined operation for synchronous malignancies or invasion in other organs were also excluded. Of 4472 patients who underwent curative rectal cancer resection, 223 (5.0%) were lost to follow-up. Most were referred to regional centers for adjuvant chemotherapy and postoperative surveillance, whereas a small number were lost to follow-up for unknown reasons (Fig. 1).

This study was approved by the Institutional Review Board of Asan Medical Center (IRB No. 2025-0881). The requirement for informed consent was waived because of the retrospective nature of the study.

Definition of AL

AL was defined as a disruption of the anastomotic site or the presence of a fluid collection or abscess adjacent to the anastomosis. The clinical manifestations of AL vary depending on its onset and severity. We assessed the degree of AL and classified its severity according to the International Study Group of Rectal Cancer definition: grade A (asymptomatic, requiring no active intervention), grade B (requiring active intervention without re-laparotomy, such as antibiotics, percutaneous drainage, or diversion), and grade C (requiring re-laparotomy with anastomotic revision or take-down).

In early AL cases, follow-up imaging was performed in patients who exhibited clinical signs suggestive of leakage. Abdominopelvic CT was performed in cases where patients presented with sustained inflammatory

markers (fever, leukocytosis, or elevated C-reactive protein) beyond postoperative day 3, new-onset abdominal or pelvic pain, or changes in the color of intra-abdominal drain output.¹⁴ AL was diagnosed on the basis of imaging findings of fluid collections around the anastomosis site, usually accompanied by evidence of extraluminal air, peritonitis, or increased free air (Fig. 2A). In some cases, despite the presence of AL, patients presented with peritonitis without evident fluid collection or extraluminal air. Therefore, correlating radiologic findings with clinical symptoms—such as abdominal pain, changes in drain output, high fever, or signs of sepsis—was essential for accurate diagnosis. In patients who underwent immediate reoperation without prior imaging owing to severe clinical signs, intraoperative findings such as gross contamination or direct visualization of a defect at the anastomosis site were used to confirm leakage. In cases where the patient's condition was clinically stable and the leakage was suspected to be minor or sealed off, nonoperative management and serial clinical and radiologic follow-up were adopted.

Late AL was defined as leakage occurring beyond 30 days after surgery, presenting as generalized or localized peritonitis (with or without a perianastomotic abscess), fistula formation, or a chronic sinus tract associated with an anastomotic defect. Asymptomatic cases were occasionally identified incidentally during routine oncologic surveillance. In contrast-enhanced abdominopelvic CT, AL manifested as extraluminal air or fluid collections adjacent to the anastomotic site, usually accompanied by fistula tract formation, or a perianastomotic abscess (Fig. 2B). In the chronic phase, AL often presented as a persistent fistulous tract or sinus with less prominent fluid collection or extraluminal air compared to acute-phase

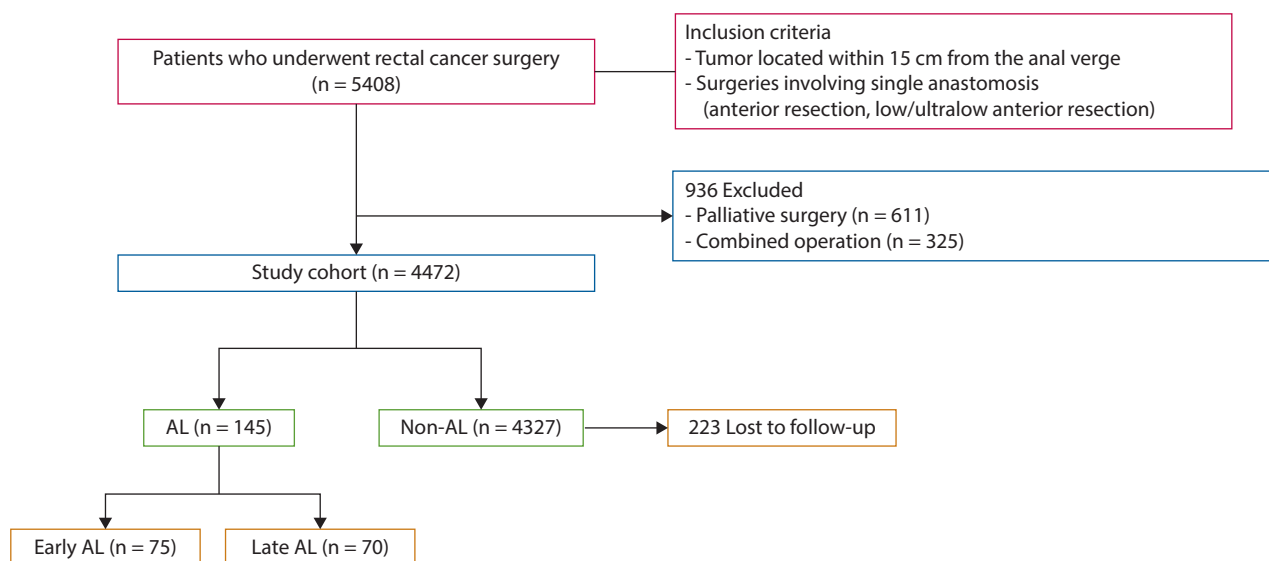


FIGURE 1. Consort diagram. AL = anastomotic leakage.

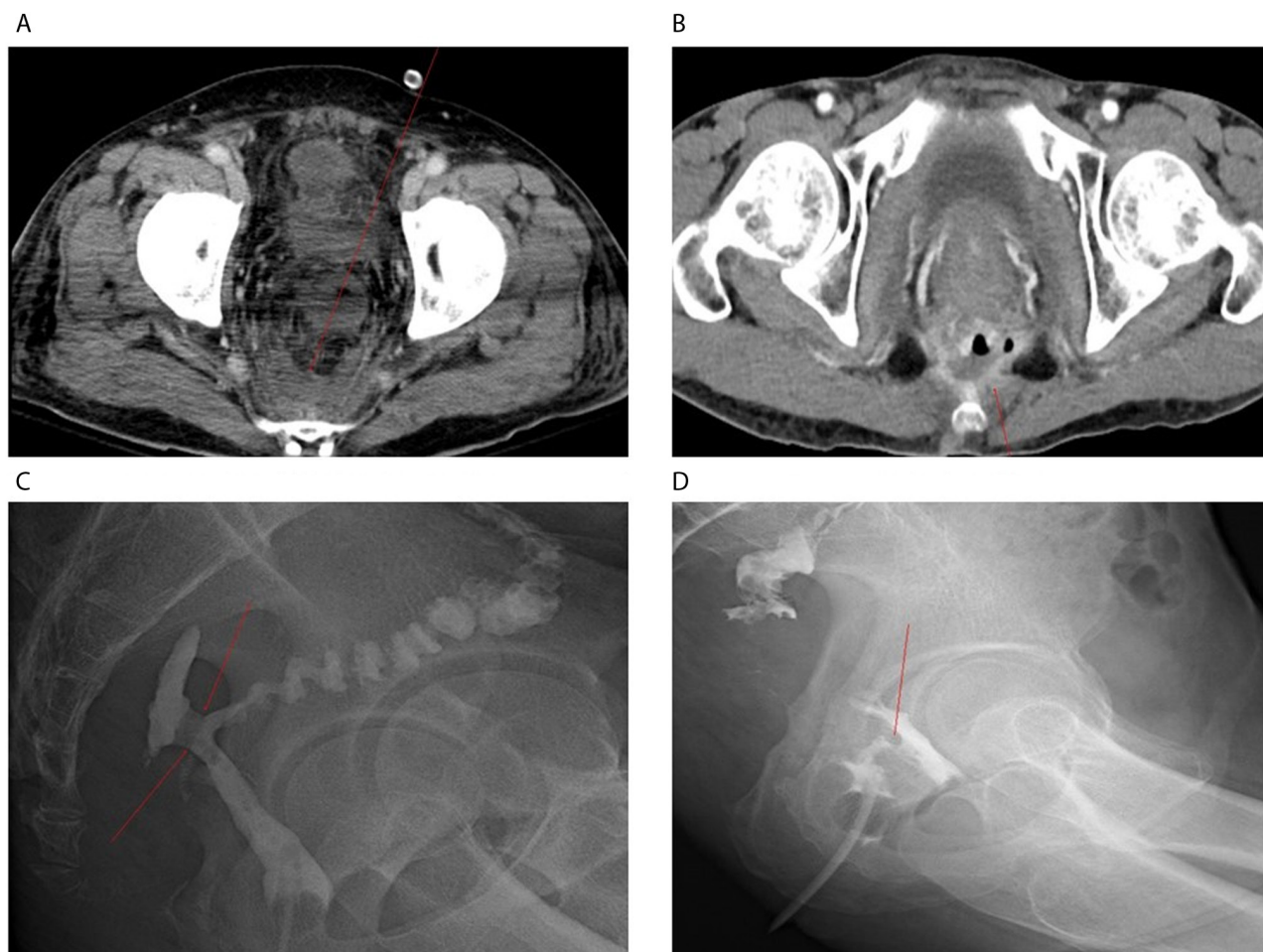


FIGURE 2. Radiologic imaging of early and late anastomotic leakage. Early anastomotic leakage (A & B). Inflammatory changes and a presacral fluid collection (axial CT scan) (A). A localized fluid collection and extraluminal air pockets around the anastomosis (axial CT scan) (B). Late anastomotic leakage (C & D). A persistent sinus tract originating from the anastomotic site (water soluble contrast study) (C). Water-soluble contrast study revealing fistulous spillage (extravasation) of contrast material from the rectum into the surrounding pelvic space (D).

leakage. On water-soluble contrast enema, leakage was defined as contrast extravasation from the bowel lumen into the peritoneal cavity, pelvic cavity, retroperitoneum, or a sinus tract (Fig. 2C). Fistulous communication to adjacent structures, such as the skin, bladder, or vagina, was also considered diagnostic (Fig. 2D).

AL cases were classified by timing into early (≤ 30 days postoperatively) and late (> 30 days postoperatively). In addition, time to leakage was further stratified into 5 intervals: ≤ 5 days, 6 to 30 days, 31 to 90 days, 91 days to 1 year, and > 1 year postoperatively. Clinically, this period represents the immediate postoperative recovery phase, during which acute complications, such as early AL, typically occur. It also corresponds to the period when patients are generally evaluated for adjuvant therapy, making it a relevant threshold for clinical decision-making. We further subdivided leakage into ≤ 5 days and 6 to 30 days to distinguish events occurring during inpatient versus outpatient status. In our institution, patients are typically discharged around postoperative day 5; therefore, this cutoff is clinically

meaningful, as the timing influences both the promptness of detection and the immediacy of management. For the late-onset phase, we used 90-day and 1-year postoperative cutoffs. The 90-day cutoff was chosen because it aligns with the typical timing of stoma reversal in patients who underwent diversion and adjuvant chemotherapy. The 1-year cutoff was selected to coincide with the standard timing of the routine abdominopelvic CT and first surveillance colonoscopy, during which additional asymptomatic leaks may be identified by direct intraluminal examination, even in patients who have previously undergone stoma reversal.

Treatment and Surveillance

Throughout the study period, treatment strategies for rectal cancer at our institution followed a consistent, standardized protocol. Patients with clinically advanced mid-to-low rectal cancer (cT3–4 or N+) generally received neoadjuvant chemoradiotherapy (nCRT) consisting of long-course radiotherapy (50–50.4 Gy in 25–28 fractions), followed by radical resection 6 to 8 weeks after completion. Concurrent

chemotherapy during nCRT was administered with either 5-fluorouracil/leucovorin or capecitabine, the latter being the preferred regimen. Adjuvant chemotherapy was routinely recommended for all medically fit patients who underwent nCRT, most commonly FOLFOX (folinic acid, fluorouracil, and oxaliplatin) for pathologic stage II and III (ypStage II–III) disease and capecitabine monotherapy for others. nCRT was not uniformly required for all cases of clinically advanced mid-to-low rectal cancer. When an R0 resection appeared achievable, the decision between upfront surgery and nCRT was individualized on the basis of patient comorbidities and socioeconomic circumstances. For upper rectal cancers, upfront surgery was the standard approach, and nCRT was considered only in cases where tumor downstaging was necessary. In patients undergoing upfront surgery, adjuvant chemotherapy was indicated for patients with high-risk stage II and all patients with stage III disease. Total neoadjuvant therapy and neoadjuvant chemotherapy were not used during this period, as these treatment modalities were not yet approved or reimbursed under the national health insurance system. Consequently, there were no substantial changes in the therapeutic paradigm for rectal cancer throughout the study period.

In our institution, 6 dedicated colorectal surgeons with high surgical proficiency consistently used standardized techniques. Radical resection was performed according to the principles of tumor-specific mesorectal excision, and the double stapling technique was routinely used for stapled anastomosis. To assess anastomotic integrity, intraoperative leak testing was routinely performed, primarily with the air-leak test.

The primary surgical approach at our institution was minimally invasive, such as laparoscopic (most common) or robotic. Robotic surgery was introduced during the early phase of the study period (2012–2020) and was preferentially performed for very low rectal tumors to enable precise dissection within the narrow pelvic cavity—so-called technically demanding cases that inherently had a higher risk of AL. This selective application was partly driven by reimbursement policies; because national health insurance did not cover robotic surgery, its use was generally reserved for complex cases where its theoretical benefits were thought to justify the additional financial burden on the patient. In our center, all robotic rectal surgeries were performed by a consistent group of 6 experienced colorectal surgeons who had previously overcome the learning curve for both laparoscopic and robotic total mesorectal excision before the study period. Open surgery was only performed in cases of severe adhesion, cancer obstruction, huge size of cancer, or severe cancer invasion to an adjacent organ. Regarding the use of lateral pelvic lymph node dissection (LPND), most surgeons at our institution considered LPND in patients whose maximum short-axis of the lateral pelvic node was >7 mm after nCRT or who had malignant clinical features

such as being larger, round, or speculated in shape; having mixed signals; or having increased FDG uptake.

Patients were followed up at regular intervals of 3 to 12 months for approximately 5 years postoperatively. Abdominopelvic CT scans were performed every 6–12 months as part of the routine follow-up. Colonoscopic evaluation was conducted within 1 year of surgery and subsequently every 2 to 3 years. In patients with a diverting stoma, reversal was generally performed 3 to 6 months after surgery. For those who received adjuvant chemotherapy, stoma reversal was deferred until completion of chemotherapy. A water-soluble enema was routinely performed before stoma reversal to evaluate for subclinical AL. When radiologic findings suggested possible leakage, further management, ranging from close observation to surgical or nonsurgical intervention, was determined on the basis of defect severity and extent.

Statistical Analysis

Clinicopathological variables were compared between patients with and without AL and between early and late AL groups using Pearson's χ^2 test, Fisher exact test, or Student *t* test, as appropriate. Multivariable logistic regression models were specified a priori based on both clinical relevance and univariate screening, in which variables with a *p* value of <0.1 in the univariate analysis were included to identify independent predictors of overall and late AL. A 2-tailed *p* value of <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, NY), and R, version 4.2.2 (<http://www.r-project.org>).

RESULTS

Clinicopathological Features of Rectal Cancer: AL vs Non-AL Group

Among the 4472 patients included in the analysis, 145 (3.2%) developed AL, whereas 4327 (96.8%) were classified as non-AL. The AL group comprised significantly younger and more male patients than the non-AL group; however, the absolute difference in mean age was small (57.8 ± 11.5 vs 61.2 ± 11.2 years). nCRT was more frequently performed in the AL group (41.4% vs 27.8%, *p* = 0.001). Tumors in the AL group were significantly closer to the AV, and ultraLAR and robotic surgery were performed more frequently. High ligation of the inferior mesenteric artery (IMA), LPND, and stoma formation were significantly more common in the AL group. No significant differences were observed between the groups regarding the anastomotic technique (stapled vs handsewn) or the pathologic T stage (Table 1).

Incidence and Timing of AL

Among patients who developed AL after curative-intent rectal cancer surgery, the leakage timing varied

TABLE 1. Clinical characteristics of patients in AL and non-AL groups

Variable	AL (N = 145)	Non-AL (N = 4327)	p
Age, y	57.8 ± 11.5	61.2 ± 11.2	0.001
Sex			0.010
Male	108 (74.5)	2721 (62.9)	
Female	37 (25.5)	1606 (37.1)	
BMI	23.8 ± 3.7	23.8 ± 3.1	0.864
Neoadjuvant CRT	60 (41.4)	1202 (27.8)	0.001
Tumor location (from AV), cm	5.8 ± 3.0	7.3 ± 3.4	<0.001
Location group			0.007
≤5 cm	68 (46.9)	1374 (31.8)	
>5 cm	74 (51.7)	2539 (58.7)	
Type of surgery			0.001
AR	0 (0)	230 (5.3)	
LAR	71 (49.0)	2426 (56.1)	
UltraLAR	74 (51.0)	1659 (38.3)	
Approach			<0.001
Open	34 (23.4)	1086 (25.1)	
Laparoscopic	55 (37.9)	2025 (46.8)	
Robotic	56 (38.6)	1092 (25.2)	
IMA ligation level			<0.001
Low	22 (15.2)	874 (20.2)	
High	123 (84.8)	2795 (62.3)	
Anastomosis detail			0.798
Stapler	133 (91.7)	4012 (93.0)	
Hand sewing	12 (8.3)	266 (6.2)	
ISR	16 (11.0)	316 (7.3)	0.127
LPND	11 (7.6)	127 (3.0)	0.003
Stoma formation	66 (45.5)	1550 (35.8)	0.021
DRM, cm	2.1 ± 1.9	2.5 ± 1.9	0.025
Positive CRM	32 (22.1)	969 (22.4)	0.980
T stage			0.111
0,1	25 (17.2)	1007 (23.3)	
2	29 (20.0)	918 (21.2)	
3	84 (57.9)	2148 (49.6)	
4	7 (4.8)	225 (5.2)	
N stage			0.120
0	84 (57.9)	2794 (64.6)	
1	42 (29.0)	1088 (25.1)	
2	19 (12.1)	430 (9.9)	
Adjuvant chemotherapy	91 (62.8)	2585 (59.7)	0.520

Data presented as mean ± SD or n (%).

AR = anterior resection; AV = anal verge; CRM = circumferential resection margin; CRT = chemoradiation therapy; DRM = distal resection margin; IMA = inferior mesenteric artery; IQR = interquartile range; ISR = intersphincteric resection; LAR = low anterior resection; LPND = lateral pelvic lymph node dissection.

significantly. Of these patients, 26.2% (n = 38) experienced leakage within 5 days postoperatively, and 25.5% (n = 37) experienced leakage between 6 and 30 days. Leakage developed in 4.1% of patients (n = 6) between 31 and 90 days, and 20.0% (n = 29) experienced leakage between 91 days and 1 year. Notably, 24.1% (n = 35) of leakages were diagnosed beyond 1 year postoperatively (Fig. 3).

Clinicopathological Features of Rectal Cancer: Early vs Late AL Groups

Among the 145 patients with postoperative AL, 75 (51.7%) were classified into the early AL group and 70 (48.3%) into the late AL group. The late AL group showed no differences in age or sex compared with the early AL

group. However, the late AL group comprised a significantly higher proportion of patients who received nCRT. Patients in the late AL group were more likely to have low-lying tumors, and ultraLAR was more frequently performed. Furthermore, robotic surgery and LPND were significantly more common in the late AL group, with temporary stoma and adjuvant chemotherapy frequently administered (Table 2).

Among the 70 patients who developed late AL, 15 (21.4%) did not have a diverting stoma created during the initial surgery. A total of 11 patients (15.7%) underwent diversion but developed leakage before stoma reversal. The remaining 44 patients (62.9%) had a diverting stoma at initial surgery and experienced leakage after stoma reversal.

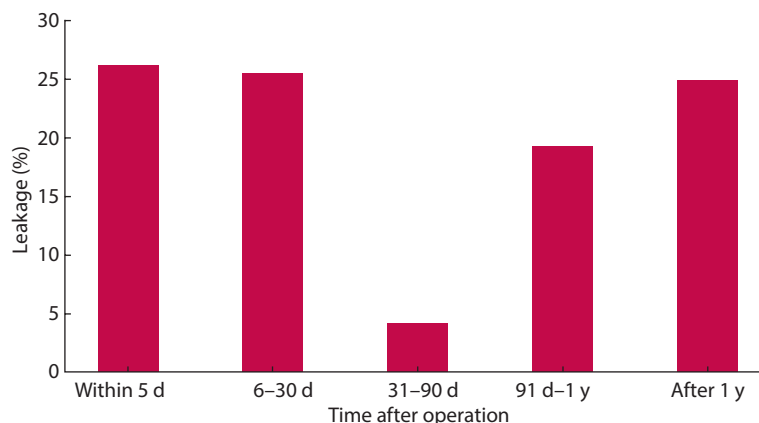


FIGURE 3. Incidence of anastomotic leakage according to time after operation.

TABLE 2. Clinical characteristics of patients in the early and late AL groups

Variable	Early AL (N = 75)	Late AL (N = 70)	p
Age, y	59.4 ± 11.2	56.1 ± 11.6	0.086
Sex			0.233
Male	59 (78.7)	48 (68.6)	
Female	16 (21.3)	22 (31.0)	
BMI	24.0 ± 3.6	23.5 ± 3.9	0.408
Neoadjuvant CRT	14 (18.7)	46 (65.7)	<0.001
Tumor location (from AV), cm	7.2 ± 2.9	4.4 ± 2.3	<0.001
Location group			<0.001
≤5 cm	22 (29.3)	49 (69.0)	
>5 cm	53 (70.7)	22 (31.0)	
Type of surgery			<0.001
LAR	54 (72.0)	17 (23.9)	
UltraLAR	21 (28.0)	53 (75.7)	
Approach			0.001
Open	20 (26.7)	14 (20.0)	
Laparoscopic	37 (49.3)	18 (25.7)	
Robotic	18 (24.0)	38 (54.3)	
IMA ligation level			0.072
Low	7 (9.3)	15 (21.4)	
High	68 (90.7)	55 (78.6)	
Anastomosis detail			0.291
Stapler	71 (94.7)	61 (87.1)	
Hand sewing	4 (5.3)	8 (11.2)	
ISR	4 (5.3)	12 (16.9)	0.045
LPND	2 (2.6)	9 (12.6)	0.045
Stoma formation	11 (14.7)	55 (78.6)	<0.001
DRM, cm	2.6 ± 1.8	1.7 ± 1.8	0.004
Positive CRM	18 (24.0)	14 (20.0)	0.997
T stage			0.201
0 or 1	10 (13.3)	15 (21.4)	
2	15 (20.0)	14 (20.0)	
3	44 (58.7)	40 (57.1)	
4	6 (8.0)	1 (1.6)	
N stage			0.210
0	48 (64.0)	36 (51.4)	
1	17 (22.7)	25 (35.7)	
2	10 (13.3)	9 (12.7)	
Adjuvant chemotherapy	36 (48.0)	55 (78.6)	<0.001

Data presented as mean ± SD or n (%).

AL = anastomotic leakage; AR = anterior resection; AV = anal verge; CRM = circumferential resection margin; CRT = chemoradiation therapy; DRM = distal resection margin; IMA = inferior mesenteric artery; IQR = interquartile range; ISR = intersphincteric resection; LAR = low anterior resection; LPND = lateral pelvic lymph node dissection.

Although 35.8% of patients (1550/4327) underwent diversion in the non-AL group, the diversion rate of the late AL group was high at 78.6% (55/70; see Supplemental Fig. 1 at <https://links.lww.com/DCR/C593>).

Distinct Clinical Characteristics and Management of Late AL

A total of 64 patients experienced AL beyond 90 days postoperatively. Among them, 47% of patients (30/64) were diagnosed through either the emergency room ($n = 18$) or outpatient clinic ($n = 12$) after presenting with clinical symptoms such as abdominal pain, fever, anal pain, anal discharge, vaginal fecal discharge, or fecaluria. Approximately half of these symptomatic patients demonstrated fistulous communication with adjacent organs, including rectovaginal, rectovesical, or rectourethral fistulas. The remaining 53% (34/64) were diagnosed radiographically during routine oncologic surveillance within the 5-year follow-up period. Radiologic findings consistent with AL included extraluminal contrast leakage on water-soluble enema, air-containing fluid collections, or anastomotic dehiscence on abdominopelvic CT. Among these 34 patients, 8 were diagnosed by water-soluble contrast enema performed before stoma reversal, which demonstrated extraluminal contrast leakage.

Thirty-six were diagnosed with AL >1 year postoperatively. Of these, 80% of patients (29/36) developed leakage after stoma reversal, indicating that prior water-soluble contrast enema studies had been negative for leakage. The remaining 7 patients had prior imaging reports showing small presacral fluid collections, which were

initially interpreted as physiologic postoperative findings. The median interval between the last leak-negative imaging and the first leak-positive study was 6 months (range, 5–11 months). All patients had undergone at least 1 imaging evaluation before the 1-year mark. In most cases of leakage beyond 1 year, initial findings were either no abnormal findings or only equivocal perianastomotic fluid collections without associated symptoms, making early detection difficult. However, when subsequent imaging demonstrated clear evidence of extraluminal air or anastomotic dehiscence, or when patients developed new or worsening symptoms, these patients were classified as having late-onset ALs.

Consequently, the management strategy for late-onset AL differed from that for early-onset cases. Although early leaks were typically managed with temporary ileostomy diversion, late-onset leaks required a more durable, prolonged diversion. Preventing fecal passage through the anastomotic site was essential. In our institution, end colostomy was most commonly performed as a definitive and safe diversion method for late-onset leakage. By closing the distal limb of the colostomy, fecal flow through the anastomosis was completely blocked. However, the stoma reversal rate was notably lower compared with early-onset leakage. Only 20.3% of patients (15/74) with late AL and 17.0% of those with leakage occurring beyond 90 days underwent stoma reversal after confirmation of complete anastomotic healing. Moreover, in selected cases where clinical signs of leakage did not improve after stoma formation, revision of the anastomosis was considered as an additional surgical option (see Supplemental Fig. 1 at <https://links.lww.com/DCR/C593>).

TABLE 3. Factors associated with anastomotic leakage

Variable	Univariate OR (95% CI)	<i>p</i>	Multivariate OR (95% CI)	<i>p</i>
Age	0.974 (0.960–0.988)	<0.001	0.980 (0.963–0.993)	0.003
Sex		0.008		0.002
Male	1.662 (1.142–2.419)		1.823 (1.241–2.677)	
Female	Reference		Reference	
Neoadjuvant CRT	1.832 (1.308–2.567)	<0.001	1.373 (0.888–2.124)	0.164
Tumor location	1.146 (1.084–1.209)	<0.001	1.197 (1.110–1.292)	<0.001
Pathologic T stage		0.079		0.008
0 or 1	Reference		Reference	
2	1.272 (0.740–2.189)		1.192 (0.687–2.069)	
3	1.575 (1.002–2.477)		1.836 (1.152–2.927)	
4	1.253 (0.535–2.933)		2.087 (0.863–5.047)	
Approach		0.026		0.087
Open	Reference		Reference	
Laparoscopic	0.868 (0.562–1.339)		1.283 (0.793–2.079)	
Robotic	1.638 (1.061–2.529)		1.555 (0.981–2.463)	
IMA ligation		0.011		0.024
Low	Reference		Reference	
High	1.813 (1.145–2.872)		1.890 (1.184–3.018)	
LPND	2.715 (1.432–5.146)	0.002	1.477 (0.755–2.891)	0.259
Stoma formation	1.497 (1.073–2.088)	0.018	1.939 (1.228–3.059)	0.004

AR = anterior resection; CRT = chemoradiation therapy; IMA = inferior mesenteric artery; LAR = low anterior resection; LPND = lateral pelvic lymph node dissection.

Factors Associated With the Occurrence of Leakage After Rectal Cancer Surgery

The multivariate model for overall AL was adjusted for age, sex, nCRT, tumor location, pathologic T stage, surgical approach, high IMA ligation, LPND, and stoma formation. Younger age and male sex were independently associated with increased leakage risk. Lower tumor location (closer proximity to the AV; OR 1.197; 95% CI, 1.110–1.292; $p = <0.001$), pathologic T3 stage (OR 1.836; 95% CI, 1.152–2.927; $p = 0.008$), high IMA ligation (OR 1.890; 95% CI, 1.184–3.018; $p = 0.024$), and stoma formation (OR 1.939; 95% CI, 1.228–3.059; $p = 0.004$) were significantly associated with leakage (Table 3).

Subsequently, the model for late AL was adjusted for age, sex, nCRT, pathologic T stage, surgical approach, adjuvant chemotherapy, and stoma formation. Factors associated with late leak occurrence were evaluated. nCRT was significantly associated with an increased risk (OR 3.331; 95% CI, 1.023–10.844; $p = 0.046$). Robotic surgery, compared with the open approach, was associated with a higher risk of late AL (OR 5.211; 95% CI, 1.174–23.129; $p = 0.014$), as was adjuvant chemotherapy administration (OR 6.710; 95% CI, 1.927–23.368; $p = 0.003$) and stoma formation (OR 19.406; 95% CI, 5.077–74.173; $p < 0.001$; Table 4).

DISCUSSION

In our study, we demonstrated that 48.3% of AL occurred beyond the early postoperative period, with 24.1% diagnosed beyond 1 year postoperatively. These findings emphasize that late AL is not a rare phenomenon, as its incidence is similar to that of early AL. Moreover, different risk factors for late AL suggest a distinct clinical

entity between early and late AL. Although previous studies have compared early and late AL, our study used a large, single-center cohort with a standardized surveillance protocol to provide a more accurate estimate of the true incidence and temporal distribution of late leakage.¹⁵ The present study highlights the clinical significance of meticulous surveillance and tailored management for AL after rectal cancer surgery, even beyond the late postoperative period. By delineating these detailed clinical and procedural aspects, our study fills a gap in the literature by offering a comprehensive understanding of the epidemiologic and management differences between early and late AL.

The overall incidence of AL in our cohort was 3.2%, which is consistent with the lower end of the range reported in previous studies, reflecting variability in patient selection, surgical technique, leakage definition, and surveillance duration.⁷ Late AL detection remains inconsistent across studies, partly owing to variable follow-up protocols. Some investigators consider only events within 30 days postoperatively, underestimating the true incidence.¹⁶ In contrast, a recent study involving longer surveillance has reported late leak rates of approximately 18%, highlighting its clinical relevance.¹¹ Regarding the clinical significance of late AL, some authors have stated that late AL may have limited oncologic implications; however, others have underscored its association with local recurrence, prolonged morbidity, and delayed initiation of adjuvant therapy.^{17–19} Discrepancies in the reported manifestations of late AL may be attributed to the lack of standardized definitions and structured long-term surveillance. Moreover, late AL diagnosis is often challenging owing to its nonspecific clinical features, leading to incidental detection and underassessment.

TABLE 4. Factors associated with late anastomotic leakage

Variable	Univariate OR (95% CI)	<i>p</i>	Multivariate OR (95% CI)	<i>p</i>
Age	0.975 (0.946–1.004)	0.088	1.043 (0.986–1.103)	0.144
Sex		0.169		0.217
Male	1.691 (0.802–3.574)		2.280 (0.616–8.448)	
Female	Reference		Reference	
Neoadjuvant CRT	8.351 (3.897–17.096)	<0.001	3.331 (1.023–10.844)	0.046
Tumor location	1.716 (1.303–2.261)	<0.001	1.015 (0.788–1.308)	0.908
Pathologic T stage		0.170		0.141
0 or 1	Reference		Reference	
2	0.622 (0.210–1.847)		0.272 (0.050–1.559)	
3	0.611 (0.242–1.507)		1.836 (1.152–2.927)	
4	0.113 (0.012–1.073)		2.087 (0.863–5.047)	
Approach		0.014		0.014
Open	Reference		Reference	
Laparoscopic	0.695 (0.287–1.684)		0.963 (0.260–3.565)	
Robotic	3.016 (1.246–7.298)		5.211 (1.174–23.129)	
LPND	5.385 (1.121–25.871)	0.036	4.589 (0.505–41.686)	0.176
Adjuvant chemotherapy	3.972 (1.917–8.233)	<0.001	6.710 (1.927–23.368)	0.003
Stoma formation	21.333 (9.051–50.285)	<0.001	19.406 (5.077–74.173)	<0.001

CRT = chemoradiation therapy; IMA = inferior mesenteric artery; LAR = low anterior resection; LPND = lateral pelvic lymph node dissection.

At our institution, postoperative surveillance included routine serial imaging, specifically colonoscopy, abdominopelvic CT, or water-soluble contrast enema, with an acceptable follow-up loss rate of 5%. In patients who underwent stoma formation, water-soluble enema was routinely administered to identify AL before stoma reversal, with postoperative surveillance maintained after stoma reversal. This protocol enabled us to identify asymptomatic or minimally symptomatic cases, enhancing the reliability of our retrospective detection of late AL. Consequently, we revealed a comprehensive distribution of leakage onset, even beyond 1 year postoperatively. This temporal pattern highlights the need for extended surveillance beyond the conventional 30-day postoperative window, particularly in high-risk patients. Furthermore, in our institution, the definitive management strategy demonstrated that late AL was commonly treated with permanent end colostomy, whereas early AL was typically managed with temporary ileostomy formation. Consequently, late AL imposes a greater long-term stoma-related burden on patients, both functionally and psychologically. A high index of suspicion is essential for colorectal surgeons to ensure timely diagnosis and management of late AL. Although routine long-term imaging follow-up enables timely detection of clinically meaningful late anastomotic leaks, it should be balanced against the risk of overdiagnosis and guided by careful clinical judgment.

The well-known risk factors for overall AL were male sex and lower tumor location, findings consistent with our study. In our cohort, younger age emerged as a risk factor for AL, which contrasts with previous study findings suggesting that older patients are more susceptible owing to reduced tissue perfusion, multiple comorbidities, and impaired wound healing capacity.^{6,19} This discrepancy may be a result of the tendency to use relatively more aggressive surgical strategies in younger patients with the same disease.^{20,21} Pathologic T stage, especially the T3 stage, was identified as a significant factor for overall AL, reflecting the increased technical complexity and anastomotic stress in more invasive tumors. The reason why T4 stage did not reach statistical significance would be attributed to the smaller number of T4 cases; most low rectal T4 tumors had received preoperative chemoradiotherapy, resulting in underrepresentation in the final pathology and a possible selection bias toward technically resectable cases. High IMA ligation was associated with increased risk of overall AL, possibly owing to compromised colonic perfusion, although previous studies have reported conflicting results.^{22–24} These contrasting findings may result from variations in collateral circulation, patient comorbidities, and intraoperative assessment techniques such as indocyanine green angiography. In our institution, indocyanine green angiography was not used during the enrolled period, which would affect the association between high IMA ligation and the occurrence of AL. Although nCRT is a well-established risk factor for AL in general, it was not a risk factor for overall AL in our study.

Among 1262 patients who underwent nCRT, 986 (78.1%) had a diverting stoma created at the time of surgery. Given the standardized treatment protocol for nCRT patients, the higher incidence of late leakage in this group may be partly explained by the routine use of diversion, which may lead to potential detection bias related to the presence of a diverting stoma and the low incidence of overall AL.

The identification of specific risk factors for late AL remains an area of ongoing debate. In our study, age, sex, pathologic T stage, IMA ligation, and lower tumor location, which were related factors for overall AL, were not risk factors for late AL. This suggests that distinctive factors beyond intraoperative or demographic factors affect the occurrence of late AL. In our study, nCRT was a significant independent risk factor for late AL, impairing anastomotic healing owing to radiation-induced fibrosis and ischemia. Despite the differences in radiation dosage, surgical timing, and tumor response, recent evidence consistently supports nCRT as a relevant factor in late AL.^{8,11} Furthermore, robotic surgery and adjuvant chemotherapy administration emerged as significant predictors of late AL in our analysis. One plausible explanation for the observed association between robotic surgery and late AL is that robotic approaches are preferentially used for very low rectal tumors, which necessitate a higher rate of diverting stoma creation. We interpreted the observed association between robotic surgery and late AL as reflecting a selection bias related to operative complexity associated with patient and tumor characteristics rather than surgeon bias or an intrinsic risk attributable to the robotic approach itself. The decision to perform a diverting stoma was made intraoperatively based on the surgeon's judgment of the generally perceived risk of AL, particularly in patients with a low rectal tumor, narrow pelvis, irradiated pelvis, or low perfused and poor tissue condition. The higher rate of stoma formation in the AL group may in part reflect surgeon bias rather than a direct causal relationship. Evidence supporting the effect of adjuvant chemotherapy on the overall incidence of AL after rectal cancer surgery is limited. Studies have proposed that chemotherapy-induced immunosuppression, mucosal fragility, and delayed wound healing may contribute to the disruption of anastomotic integrity.^{25–27} The relationship between adjuvant chemotherapy and late AL remains unclear and warrants further investigation. Furthermore, total neoadjuvant therapy has increasingly replaced postoperative adjuvant chemotherapy in many centers, particularly in the United States. Future studies are needed to determine whether the timing and modality of systemic therapy influence the incidence and clinical presentation of late AL under current treatment protocols.

The role of a diverting stoma in AL prevention remains controversial. Recent studies indicate that although a protective stoma may not prevent AL, it can reduce the clinical severity of leakage when it occurs.^{28–30} Reactivation of AL after stoma closure is not uncommon, with reported incidences ranging from 2% to 16% among patients

undergoing stoma reversal.³⁰ In our cohort, 62.9% of late AL cases developed after stoma reversal, whereas 15.7% occurred during the stoma period. These findings suggest that a diverting stoma does not prevent late AL but may delay its clinical presentation. Subclinical anastomotic defects may remain undetected until fecal stream restoration.^{29,31} Diagnostic studies aimed at identifying subclinical AL in patients with a diverting stoma are currently lacking. This diagnostic limitation may delay the recognition and appropriate management of late AL, potentially causing chronic pelvic sepsis. Implementing surveillance protocols during the stoma period, particularly in high-risk patients, may facilitate earlier detection of asymptomatic leakage and improve clinical outcomes.

This study had some limitations. First, its retrospective design inherently introduces potential biases, including selection bias and inconsistencies in clinical documentation. Second, although our institutional protocol for serial imaging enhances the detection of late AL, the generalizability of our findings may be limited to centers with similar surveillance intensity. Moreover, some late AL may represent subclinical anastomotic defects that existed earlier but were not radiographically apparent until later imaging. Although our operational definition of late leakage is clinically appropriate, it may include both truly delayed leaks and those that were subclinical during the early postoperative period. Third, the low overall incidence of AL, despite our large sample size, may limit the statistical power for certain subgroup analyses. Finally, oncologic outcomes were not systematically evaluated in this study, which limits our ability to determine the long-term oncologic implications of the observed findings. Future prospective studies with long-term follow-up are warranted to clarify the oncologic implications of this management strategy in this patient population. Despite the limitation, this study has several strengths. It is one of the few large-scale investigations to delineate the serial incidence and distinct risk factors for late AL after rectal cancer surgery. The use of a standardized institutional surveillance protocol, including serial imaging postoperatively and after stoma reversal, allowed for the reliable identification of late AL, including clinically subtle cases.

This study delineated the serial incidence and distinct risk factors associated with overall and late AL, offering novel insights into their different clinical profiles. These findings underscore the significance of prolonged monitoring and tailored management strategies for patients at high risk for AL, particularly late AL. Such approaches may improve surgical safety and oncologic outcomes after rectal cancer surgery.

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