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Review of Risk Factors for Anastomotic Leakage in Colorectal Surgery

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Rezumat

Factori de risc pentru fistula anastomotică în chirurgia colo-rectală

Fistula anastomotică după chirurgia colorectală este o complicație severă care duce la creșterea morbidității și mortalității. Multiple studii au identificat ca factori de risc pentru fistulă sexul masculin, obezitatea, utilizarea preoperatorie de steroizi sau anti-inflamatorii nesteroidiene, durata prelungită a operației, experiența chirurgicală și transfuzia de sânge preoperator. Chirurgia laparoscopică nu este inferioară față de abordul deschis în ceea ce privește rata de fistulă anastomotică. Au fost efectuate studii privind excizia totală de mezorect laparoscopică și scorul ASA, distanța tumorii de orificiul anal au fost identificate ca factori predictivi pentru creșterea timpului operator și complicații postoperatorii după excizia totală de mezorect laparoscopică. Există dovezi solide că radiochimioterapia preoperatorie pentru cancer rectal crește riscul de fistulă anastomotică. Pregătirea preoperatorie mecanică nu reduce incidența fistulelor postoperatorii. Utilizarea stomelor de protecție nu reduce rata fistulelor, dar atenuează consecințele clinice ale acesteia.

Cuvinte cheie: fistulă anastomotică, chirurgie colorectală, factori de risc, cancer colorectal

Abstract

Anastomotic leakage after colorectal surgery is a serious complication leading to increased morbidity and mortality. Multiple studies have found as risk factors for anastomotic leakage: male gender, obesity, preoperative steroid and non-steroidal anti-inflammatory drug use, longer duration of operation, surgical experience and preoperative blood transfusion. The laparoscopic approach is not inferior to open surgery in terms of rate of anastomotic fistula. Several studies have also shown the ASA score and tumor distance from the anal verge as predictors for increased operative time and morbidity after laparoscopic total mesorectal excision. There is strong evidence that preoperative radiochemotherapy for rectal cancer increases the risk for anastomotic leakage. The preoperative bowel preparation does not reduce the incidence of postoperative leaks. The use of diversion stoma has not been shown to reduce leak rate, but mitigates the clinical effects of fistula.

Key words: anastomotic leakage, anastomotic fistula, colorectal surgery, risk factors, colorectal cancer

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Introduction

Anastomotic fistula after colorectal surgery represents a major and potentially life-threatening postoperative compli-

cation. The incidence rate has been reported to be as high as 1% to 19% (1-5). Furthermore, postoperative mortality associated with anastomotic complications ranges from 6% to 22% (2, 3, 5, 6) and accounts for approximately one third of all deaths following colorectal surgery (7).

There is still significant heterogeneity between surgeons in what they define as anastomotic leakage. In a systematic review of gastrointestinal anastomotic leakage 49 papers were found with 29 different definitions (8). In 2010, specific guidelines on the definition of an anastomotic leak with a grading system of severity following rectal surgery were published by the International Study Group of Rectal Cancer (9). According to this paper, anastomotic leakage should be defined as a defect of the intestinal wall at the anastomotic site (including suture and staple lines of neorectal reservoirs) leading to a communication between the intra- and extraluminal compartments.

Clinical risk assessment for anastomotic leakage by the operating surgeon has a low predictive value and underestimates leakage risk (10). There has been a recent trend to create more (nonfunctional) stomas to counteract the problem of anastomotic leakage. The clinical decision about whether to perform a colonic anastomosis or a stoma remains difficult. However, unnecessary stoma can also induce morbidity and discomfort and increase healthcare costs (11). In addition, continuity is never restored in many patients. To provide an objective assessment of the risk of anastomotic failure and to evaluate the necessity for diverting ileostomy or non-restorative surgery, several leakage scores were developed (12-14).

Despite the fact that many studies have identified risk factors for anastomotic leakage, to date, it is not possible to perfectly predict the occurrence of fistula in an individual patient. Judging by the plethora of risk factors identified in the literature, anastomotic leakage has multiple overlapping etiologies and these factors can be divided into two categories: local factors and general factors.

Local factors

The single most significant risk factor for leakage is distance of the anastomosis from the anal verge (15-18). The lower the anastomosis (particularly below 6 cm) the higher is the risk of fistula. Risks appear similar and related to height whether suturing or mechanical stapling is employed, although there is an apparent trend towards reduced leakage in the stapled low anastomosis (19). Lopez-Kostner et al. showed in a study of 819 patients with rectal or sigmoid cancers, that the leak rate was 0.14% when the anastomosis was above 15 cm, 5.4% when it was 10-15 cm from the anal verge and 8.4% when it was below 10 cm from the anal verge (20). Rullier et al. have shown an overall leak rate of 13% in a study of 272 consecutive anterior resections and the leak rate was 6.5 times higher in anastomoses located < 5 cm from the anal verge (2). Similarly, Vignali et al. reported in a review of 1014 patients with stapled rectal anastomoses, a leak rate of 7.7% after low rectal stapling (< 7 cm of the anal verge) compared with 1% for high stapling (21).

In a meta-analysis of 13 randomized controlled trials assessing hand-sewn and stapled colon and rectal anastomoses, MacRae and McLeod found no difference in leak rate between the groups (22). In a recent Cochrane review of 9 trials involving 1233 patients, there was insufficient evidence to demonstrate any superiority of stapled over the handsewn techniques in colorectal anastomoses in terms of postoperative fistula (23).

Surgical experience, especially in colorectal surgery, has been claimed by many investigators to have impact over the leakage rate (24, 25). In this regard, some studies have shown that high-volume surgeons and specialized colorectal surgeons have a lower incidence of complications than non-specialists and low-volume surgeons (26, 27). However, there are other authors who disagree with this statement. A study by Sorensen et al. showed that the incidence of fistula was lower for surgeons in training compared with senior colleagues, one explanation being that these surgeons tend to operate on less complicated cases (28). Other authors found no statistical difference between the consultant, supervised and independent trainees in terms of anastomotic leakage rate, local recurrence rate and 30-day mortality rate (29).

Mechanical bowel preparation (MBP) before elective colorectal surgery has been the standard for over a century. MBP was employed to clear the bowel lumen of faeces and to decrease bacterial load in the bowel before the construction of colocolic anastomosis, theoretically reducing the rates of infectious postoperative complications, such as anastomotic dehiscence. However, bowel preparation has not been shown to influence anastomotic leak rates and there has been a recent trend away from this practice (30-33). Despite this evidence, a survey of colorectal surgeons in the United States published in 2003 revealed that 99% of the surgeons surveyed used MBP before surgery (34). In 2006, a multinational audit of 1082 patients from 295 hospitals in Europe and the United States revealed that 86%-97% of patients received preoperative MBP (35). In a review by Eskicioglu et al., it was concluded that there is good evidence supporting the omission of MBP in the preoperative management of patients undergoing elective right-sided and left-sided colorectal surgical resections (36). However, for patients undergoing low anterior resection with or without diverting stomas, there is insufficient evidence to support or refute the omission of MBP in the preoperative management of these patients.

Several studies confirmed that laparoscopic colorectal surgery improved early postoperative outcomes in terms of reduced intraoperative blood loss, postoperative pain, ileus and hospital stay (37-39). However, anastomotic leakage is also a major issue in patients with colorectal cancer undergoing this approach. Despite the fact that laparoscopic surgery for rectal cancer has technical difficulties (the difficulty of the pelvic approach, lack of tactile sense, inadequate cutting angle after transection), there are several studies that compared it with open surgery and showed non-inferior results in terms of oncologic safety and anastomotic leakage rate (40-44). Although many comparison studies of laparoscopic versus open surgery for rectal cancer have been reported (see *Table 1*), no statistical

Table 1. List of clinical trials comparing open versus laparoscopic approach comparing the risk of anastomotic fistula

First author, year (reference)	Type of study	Pathology	Open surgery AL	Laparoscopic surgery AL
Maartense, 2004 (40)	RCT/ unicentric	UC and FAP	1/30 (3.3%)	3/30 (10%)
Laurent, 2009 (46)	RS/ unicentric	Rectal cancer	15/233 (6.4%)	12/238 (5%)
Kang, 2010 (47)	RCT/ multicenter	Rectal cancer	0/170	2/170 (1.2%)
Liu, 2010(42)	RCT/ unicentric	Rectal cancer	3/85 (3.5%)	2/96 (2%)
Orenstein, 2011 (43)	RS/unicentric	Benign and malign colonic disease	9/323 (2.8%)	1/66 (1.5%)
Martijn, 2013 (48)	RCT/ multicenter	Rectal cancer	25/240 (10%)	58/461(13%)
Bonjer, 2015 (49)	RCT/ multicenter	Colon cancer	10/545 (2%)	15/535 (3%)
Kim, 2015 (44)	RS/ unicentric	Rectal cancer	32/550 (5.8%)	77/1154 (6.7%)

AL – anastomotic leakage, FAP - familial adenomatous polyposis, RCT - randomized controlled trial, RS - retrospective study, UC- ulcerative colitis

difference in terms of anastomotic leakage has been shown. Patterns of anastomotic leakage after laparoscopic surgery for rectal cancer may differ from those after open surgery (44).

Kim et al. evaluated the risk factors for anastomotic leakage in 270 patients with distal sigmoid colon and rectal cancer that underwent laparoscopic intracorporeal colorectal anastomosis with a double stapling technique. They found a rate of anastomotic leakage of 6.3%. Tumor location (middle or lower rectal cancer), operation time (> 200 min), number of stapler firings (> 2), and diameter of the circular stapler (> 31 mm) were significant risk factors for anastomotic leakage. The number of stapler firings increased significantly increased leakage in men ($p = 0.023$), in patients with a tumor at a lower level ($p = 0.034$), and in those with longer operation times ($p < 0.001$) (45).

A prospective multicenter study of more than 1000 patients undergoing laparoscopic colorectal procedures found an overall leakage rate of 4.25% (colon 2.9% and rectum 12.7%) and 30-day mortality rate of 1.57% (16). They showed that the laparoscopic approach to colorectal surgery was not associated with a higher risk of anastomotic leaks than open surgery. The leakage rates after rectal resections nevertheless were high, especially for the lower rectum (< 10 cm, anastomotic leakage rate of 24.1%), indicating the difficulties of this procedure. Therefore, anterior rectal resections can be recommended only for very experienced laparoscopic colorectal surgeons, eventually in combination with a diversion ileostomy or colostomy. A multicenter study performed in the United States found that laparoscopic surgery was associated with a shorter hospital stay, lower hospital costs, and potentially lower mortality compared with open surgery in patients with diverticulitis and colorectal cancer (50). Laparoscopy was associated with lower rates of all postoperative complications and was independently associated with lower anastomotic leak rates compared with open surgery (9.42% vs 13.47%).

The use of robotic approach is an exciting development in colorectal surgery. Robotic surgery could potentially address many of the limitations of the conventional laparoscopic technique. A review of robotic colorectal surgery concluded that robotic surgery is both safe and feasible, but has no clear advantages over laparoscopic colorectal surgery in terms of early postoperative outcomes or complications profile (51). It has shorter learning curve, a lower conversion rate, but

increased operative time and cost (51). There is also a trend towards better results in anastomotic leak rates in colorectal robotic surgery, but data from individual studies are contradictory. There are studies that found a lower rate of anastomotic leakage in the robotic group with no statistical difference (52-54) and studies with a higher rate of anastomotic leakage in robotic versus laparoscopic surgery (8.6% vs. 2.9%) with no statistical difference (55). Cost is one of the main concerns regarding robotic colorectal surgery. For example one study reported a cost three times higher for robotic surgery compared with cost for conventional laparoscopic surgery (56).

Proximal fecal diversion by ileostomy or colostomy, while not abolishing leakage, diminishes its effects and may prevent serious consequences (6, 57). The routine use of a protective stoma remains controversial, mostly due to a lack of adequate control studies. Despite this debate, most would agree that selective defunctioning stoma is optimal if prediction of leakage were possible. In reality, accurate prediction of leakage is difficult although one may identify certain individuals who are at increased risk. Thus, factors influencing leak rates should be evaluated and when risks are high or when dehiscence has occurred, fecal diversion can avert a life-threatening situation. Law et al. found in a prospective study in 196 patients with rectal cancer from 3 to 12 cm from the anal verge treated by anterior resection with TME, that a diverting stoma and male gender were the only significant factors affecting anastomotic leakage (58). Buchs et al. showed in a prospective monocentric study that three risk factors are involved in anastomotic dehiscence: ASA score ≥ 3 , prolonged operative time (> 3 hours) and rectal location of the disease. They concluded that these factors should be considered in perioperative decision-making regarding defunctioning stoma formation (3).

However one study using data from the Dutch Surgical Colorectal Audit found no statistical difference for the anastomotic leakage rate between patients with and without a defunctioning stoma (6.4% versus 7.5%) (59). At the same time one must consider complications associated with surgery for closing diverting stoma: necrosis or stenosis of the anastomosis, abscess or peristomal cellulitis. Williams et al. reported a 25% morbidity and 2% mortality in a study of patients with low rectal anastomosis and diverting ileostomy, when closing the stoma (60).

Clinical significance of prophylactic drainage in colorectal

surgery has been arguable for years concerning its role in prevention and detection of anastomotic leak. In colorectal surgery, drains are expected to prevent hematoma, fluid collection, or abscess formation, to act as an indicator of postoperative complication, or to minimize the severity of complication-related symptoms. Routine drainage has not been supported by meta-analyses and it failed to demonstrate any benefit in reducing anastomotic leak rate, minimizing symptoms or severity of related complications, or serving as a warning function (61-63). Moreover, some reports even showed that drain itself is an independent risk factor of anastomosis (17). However, other studies showed that pelvic drainage was significantly associated with a lower anastomotic leakage rate after rectal cancer surgery (64, 65).

There are multiple reports showing an association between pre-operative radiotherapy and/or chemotherapy and incidence of anastomotic leakage (see Table 2). Schrock et al. have observed that fistulae after radiotherapy in patients with colorectal anastomosis have tripled (66). There was a decrease in the sero-muscular blood flow at 4 weeks after irradiation, a change that persisted for 4 months after treatment, regardless of the type of colorectal anastomosis, manual or mechanical. Using a dose of 50-60 cGy, intestinal anastomosis can be performed at 2 weeks after irradiation, with a normal healing pattern. If digestive anastomosis is performed with one irradiated intestinal segment, a normal healing of the anastomosis can be achieved if it was made at least one week after exposure (67). In case of digestive anastomosis with one intestinal segment irradiated, the irradiation dose can be increased to 80 cGy without affecting resistance anastomosis. Conversely, increasing the dose where both intestinal segments of the anastomosis are irradiated one can expect a decrease of anastomotic resistance (68).

Kobayashi et al. found a leakage rate of 6.3% and pre-operative radiotherapy as independent risk factor for the development of anastomotic dehiscence (69). However, in the Dutch study which randomized 1861 patients to either preoperative short course radiotherapy combined with TME,

or TME alone, the authors found no significant difference in anastomotic dehiscence with a leak rate of 12% in patients who had TME alone compared with 11% in those who had radiotherapy and surgery (70). It is likely that long-course radiotherapy and chemo-radiotherapy may increase the risk of leakage. Although radiotherapy is considered to be a risk factor for anastomotic leakage, clinicians should not omit the use of neoadjuvant therapy in the treatment of rectal cancer due to improved rates of local control, overall survival and sphincter preservation (69). Intraoperative or immediately postoperative radiotherapy administration does not influence the healing of colonic anastomoses (71).

The use of intraperitoneal Cisplatin has a negative effect on anastomotic healing in the first week after surgery (72). Methotrexate administered intraperitoneally both intra- and immediate postoperative decreases resistance of digestive anastomoses, which is why its administration is not recommended (73). Hyperthermic intraoperative intraperitoneal chemotherapy with Doxorubicin or Cisplatin and Mitomycin C has been shown to increase the risk of digestive fistula (74, 75). In contrast, the use of intraperitoneal Adriamycin or 5-fluorouracil is not dangerous for intestinal anastomoses (73, 76). Post-operative chemotherapy including Bevacizumab can lead to delayed colorectal anastomotic complications including spontaneous dehiscence or colo-cutaneous fistula from the anastomosis. The risk is increased for patients with low anastomosis and preoperative irradiation for rectal location (77-79).

General factors

Anastomotic leakage after lower gastrointestinal anastomosis was reported to be more common for men, probably due to differences in pelvic anatomy. Rullier et al. have analyzed variables associated with anastomotic leakage in 272 consecutive anterior resections and showed that fistula was 2.7 times higher in men compared to women (2). Law et al. reported in their study gender as a risk factor for anastomotic leakage after low anterior resection with TME (58). Lipska et al. also showed

Table 2. Comparative results concerning the impact of neoadjuvant therapy on anastomotic leakage for rectal cancer treatment

First author, year of publication (reference)	Doeksen A., 2007(80)	Vermaas M., 2007(81)	Wang L., 2010(82)	Maas H., 2013(83)
Number of centers	unicentric	multicenter	unicentric	multicenter
Type of study	retrospective	prospective	retrospective	retrospective
Number of patients	104	521	217	642
Tumor location	all rectal cancers	all rectal cancers	mid-low rectal cancer	all rectal cancers
Preoperative RxT + surgery	39	364	217	346
Surgery alone	65	157	None	296
Diverting stoma	31	156	64	-
Incidence of anastomotic leakage	<ul style="list-style-type: none"> • 39% in RxT group + surgery group • 19% in surgery alone group 	10.3%	11.5%	<ul style="list-style-type: none"> • 16% in RxT + surgery group • 10% in surgery alone group
Risk factors for anastomotic leakage		<ul style="list-style-type: none"> - end-to-end anastomosis - time of surgery (between 4 and 8 days after the end of RxT) 	<ul style="list-style-type: none"> - male gender - level of anastomosis ≤ 4 cm - no defunctioning stoma - blood loss >200 ml. 	

RxT - radiotherapy

in a study of 541 patients that men are at a higher risk. The rate of anastomotic leakage increases in men with previous abdominal surgery, rectal cancer ≤ 12 cm from the anal verge or prolonged operating time. The risk of anastomotic leakage increased when two or more risk factors were present (84). However, several other authors showed that gender was not a risk factor for anastomotic dehiscence in colorectal surgery (85-88).

Malnutrition can coexist with many other factors that influence the healing process of the anastomosis. One study concluded that only severe degrees of malnutrition are associated with significant effects on colonic anastomoses and wound infection (89). At the same time, in patients with digestive fistulae, malnutrition worsens the prognosis of the leakage. Malnutrition exerts an adverse effect on tissue healing by affecting processes such as collagen synthesis or synthesis of sulfated mucopolysaccharides or affecting fibroblast proliferation. Some authors have observed a relationship between preoperative serum albumin level and the occurrence of anastomotic fistulas. Golub et al. reported an incidence of 6.9% of fistula in patients with albumin level less than 3 mg/dL, while for the level of serum albumin higher, the incidence of fistulae was only 2.8% (90). Several authors reported a preoperative serum albumin level less than 3.5 g/dl to be a significant risk factor for anastomotic leaks (88, 91-93). Other authors found that a level of serum proteins under 6g/dl is an independent risk factor for anastomotic leakage (85, 94).

The role of anemia in healing anastomoses remains controversial. Some authors have shown that in anemic patients there is an increased incidence of colonic anastomoses and abdominal wound dehiscence (94, 95). Zaharie et al. have shown that low levels of serum hemoglobin < 9.9 mg/dL is an independent factor for anastomotic fistula (85). Other authors found no effect of preoperative anemia on the incidence of fistulas (90). It is possible, however, that other factors associated with anemia in surgical patients are responsible for producing anastomosis dehiscence. Thus, anemia might play a role in anastomotic healing when combined with other factors such as malnutrition, type of surgery or hypovolemia with production of tissue hypoxia.

Recent studies have suggested a negative role of blood transfusions in the outcome of patients with cancer (86, 87, 96, 97). Blood transfusions lead to depression of the immune system increasing the risk of postoperative infectious complications and the incidence of anastomotic fistulas. Tadros et al. showed that blood transfusions increase the incidence of anastomotic abscess and poor healing of anastomoses (98). A multivariate analysis of factors associated with intestinal anastomotic fistulae showed that the incidence of digestive fistulas is significantly higher in transfused patients (14.3%) compared with patients untransfused (2.9%), independent of blood loss, hypotension or preoperative hemoglobin (90). Boccola et al. also found that postoperative blood transfusion is an independent predictive factor for anastomotic leakage (17).

In accordance with most authors, the ASA score ≥ 3 was strongly correlated with an increased risk for anastomotic leak (99-102). Buchs et al. showed that for every unit increase in the

ASA score, there is a 2.5 times increased risk of leak (3). Bakker et al. confirmed high ASA grade as independent risk factor for anastomotic leak (59). Another risk factor for anastomotic dehiscence is represented by medical comorbidities (pulmonary, cardiac, renal)(84, 86, 103), reflected in the high Charlson score (59).

Prolonged operating time has frequently been identified as a risk factor in univariate (3, 21, 86, 93) but more rarely in multivariate analysis (3, 101, 104). Prolonged operation time reflects intraoperative difficulties, particularly, when working low in the pelvis or in the presence of adhesions from previous operations, previous radiotherapy, bleeding, obesity or less experienced surgical team. Laparoscopic resections in colorectal diseases request a longer operation time to be performed (42-44, 48).

Emergency surgery is also considered a risk factor for both anastomotic leakage (59, 99, 105-107) and postoperative mortality (59, 99, 105, 108, 109). Poor general condition and nutritional status is associated with a higher risk of morbidity and mortality in these patients (109, 110). The presence of peritonitis and/or bowel obstruction increase the risk of anastomotic leakage. Anastomosis is not completely contraindicated in emergency colorectal surgery (101, 111). Use of a temporary proximal stoma is a safe option for feasibility of anastomosis in presence of peritonitis (112-114).

Chronic steroid therapy was significantly associated with leaks (90, 93, 104, 115). In a study by Slieker et al., the incidence of anastomotic leakage was significantly higher in patients treated with long-term corticosteroids (50% leak) and in patients taking corticosteroids perioperatively (19% leak) (116). A systematic review showed an anastomotic leakage rate of 6.77% in the corticosteroid group and 3.26% in the non-corticosteroid group (117). Gorissen found that use of non-steroidal anti-inflammatory drugs (NSAIDs) leads to an increase in anastomotic leakage rate (118). In a meta-analysis, Burton et al., found no statistically significant difference in incidence of anastomotic dehiscence in patients using perioperative non-steroidal anti-inflammatory drugs (119).

Conclusions

Anastomotic leakage remains a major issue of colorectal surgery, leading to significant morbidity, increased healthcare costs, and even death. Despite numerous studies on this topic, it is still difficult to accurately predict anastomotic leakage. Surgeons should be aware of high-risk patients who may develop this complication. A good understanding of risk factors could potentially reduce the incidence of anastomotic leak and allow appropriate selection of patients for diverting stomas; otherwise to avert the fistula the Hartmann procedure remains the only option.

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