72601_Auto_Edited.docx

The impact of anastomotic leakage on long-term prognosis after colorectal cancer surgery

Impact of anastomotic dehiscences on long-term prognosis in patients operated on for colon and rectal cancer

Valeria Tonini, Manuel Zanni

Abstract

Colorectal cancer is one of the most common malignancies in the world. Despite significant improvements in surgical technique, postoperative complications still occur in a fair percentage of patients undergoing colorectal surgery. The most feared complication is anastomotic leakage. It negatively affects short-term prognosis, with increased post-operative morbidity and mortality, higher hospitalization time and costs. Moreover it may require further surgery with the creation of a permanent or temporary stoma. While there is no doubt about the negative impact of anastomotic dehiscence on the short-term prognosis of patients operated on for colorectal cancer, still under discussion is its impact on the long-term prognosis. Some Authors have described an association between leakage and reduced overall survival, disease-free survival, and increased recurrence, while other Authors have found no real impact of dehiscence on long term prognosis. The purpose of this paper is to review all the literature about the impact of anastomotic dehiscence on long-term prognosis after colorectal cancer surgery. The main risk factors of leakage and early detection markers are also summarized.

Key Words: anastomotic lekeage; colorectal surgery; colon cancer; rectal cancer; long term prognosis; long term survival

Tonini V, Zanni M. The impact of anastomotic leakage on long-term prognosis after colorectal cancer surgery. *World J Gastrointest Surg* 2023; In press

Core Tip: The purpose of this review is to describe the impact of anastomotic dehiscences on long-term outcomes in patients operated for colon and rectal cancer.

INTRODUCTION

Definition, incidence and classification

Anastomotic leakage (AL) is a major cause of postoperative morbidity and mortality after colorectal cancer (CRC) surgery. AL is a defect of the intestinal wall integrity at the colorectal or colo-anal anastomosis site (including suture and staple lines of neorectal reservoirs) leading to a communication between the intra- and extraluminal compartments [1]. However, there are several definitions of AL in literature and most studies define it using clinical signs (pain, fever, tachycardia, peritonitis, purulent or fecal drainage), radiographic findings (fluid and/or gas-containing collections), and/or intraoperative features (peritoneal effusion and ruptured anastomosis) [1,2]. The use of different definitions in clinical studies can partly explain the considerable variations in AL reported rates. The incidence of AL reported in different studies is highly variable (2-19%) and certainly influenced first of all by the surgeon's experience and the emergency or elective surgical setting. It is also influenced by the site of the anastomosis: it is lowest for ileocolic anastomoses (1-3%) and highest for coloanal anastomoses (10-20%) [3-5].

AL has been divided into "early" and "late" depending on whether AL is diagnosed within or after 30 days after surgery [6]. In general, early AL manifests with severe peritonitis and it is mainly related to a technical error in performing the anastomosis, usually due to malvascularization of the intestinal stumps or tension at the anastomotic

site [7]. In contrast, late AL is often associated with long-standing pelvic abscess [8] and is due to preexisting conditions in patients, such as local sepsis, poor nutrition, immunosuppression, morbid obesity, and radiation exposure [9].

Anastomotic leakage is also classified according to severity into grade A, B and C. Grade A is represented by AL that does not require active therapeutic intervention, grade B by AL that requires active therapeutic intervention but manageable without re-laparotomy, and grade C by AL that requires re-laparotomy [1].

Risk factors

Several risk factors for anastomotic dehiscence following colorectal surgery have been identified over the years. They can be classified for convenience into preoperative, intraoperative, and postoperative [10]. Preoperative risk factors commonly reported in the literature include male sex [7], obesity [11], tobacco habit, alcohol consumption, an ASA score of 3 or higher [6], and prolonged corticosteroid intake [12]. Tumor location, size and stage must be considered among the risk factors. Akiyoshi *et al* [13] reported that tumor localization in the rectum, rather than the colon, was independently predictive of AL development on multivariate analysis.

The AL rate was 10 times higher (20.6% *vs* 2.3%) when the anastomotic region was located within 5 cm of the anal verge [14]. Low anterior resection (LAR) involves surgery in an anatomically confined space and when tumor size and/or stage increases, intrapelvic manipulation becomes limited and rectal dissection more challenging. In a series of 154 patients with rectal carcinoma, tumor size ≥5 cm in diameter was associated with a 4-fold increased risk of leakage [15]. Zhu *et al* [16] found that tumors greater than 3 cm in diameter, as well as TNM stage, were independently associated with leakage.

Intraoperative risk factors include: the surgeon experience (and hospital size) [7], the number of linear stapler firings [7], left colic artery ligation [17], emergency surgery (patients with peritonitis and/or bowel obstruction are at higher risk of postoperative

adverse events) [18], operative time [19] and blood loss during surgery. Intra-operatively, it is also important to ensure good vascularization of the anastomosed bowel segments. Indocyanine green (ICG) fluorescence angiography may help in this evaluation. In a recent meta-analysis, an incidence of anastomotic dehiscence was observed in 3.8% of cases in the ICG group and 7.8% in the control group in which indocyanine green was not used [20].

Postoperative risk factors are anemia, hypoalbuminemia, and late initiation of enteral nutrition [21].

Early detection and markers

Early detection of AL is crucial to treat patients limiting negative effects. Baeza-Murcia *et al* [22] analyzed the accuracy of C-reactive protein (CRP) and procalcitonin (PCT) for early detection of AL and have found that CRP is more accurate than PCT on both postoperative day (POD) 3 and 5. According to this study CRP measured on postoperative day 5 is the most useful test for early diagnosis of AL and that values above 9.1 mg/dL are indicative of anastomotic dehiscence.

In a recent meta-analysis by Yeung *et al* (23) a CRP cutoff level of 14.8 mg/dL at POD 3 had a sensitivity and specificity of 95%, while CRP cut-off levels of 12.3 mg/dL at day 4, 11.5 mg/dL at day 5, 10.5 mg/dL at day 6, and 9.6 mg/dL at day 7 had a sensitivity and specificity of 100% for anastomotic dehiscence. According to García-Granero *et al* [24] and El Zaher *et al* [25], PCT is also a very good predictor of anastomotic dehiscence, particularly from POD 5 or higher. The predictive power of PCT may also be enhanced in combination with CRP or WBC, or both (AUC 0.92, 0.92, 0.93, respectively) [25]. A recent meta-analysis by Xu *et al* [26] shows that PCT at POD3 has potential clinical value in the early diagnosis of AL and has better diagnostic accuracy in patients undergoing laparoscopic surgery. Cut-off values are recommended in the range of 0.7-1.3 ng/mL to ensure accurate diagnosis and safe discharge. However, PCT is a valid predictor only for patients with major clinical losses confirmed by radiology and presenting with severe clinical signs and symptoms that require a

change in therapeutic management and in most cases a reintervention. Cousin *et al* [27] conducted a meta-analysis and concluded that PCT does not add value to CRP in the diagnosis of AL.

It can be said that CRP and PCT at postoperative day 5 have a high negative predictive value, which would allow early and safe discharge. Tavernier *et al* [28] considered 5 criteria for safe early discharge after laparoscopic colorectal surgery: a CRP level of less than 15 mg/dL, absence of fever during the entire hospital stay (temperature <38°C), return of bowel function (flatus with or without stool), adequate pain control with oral analgesics (pain less than 5 out of 10 on a 10-point visual analog scale) and tolerance of a solid diet. The negative predictive value in ruling out an anastomotic leak was 98.4% for all 5 criteria combined. The false-negative rate was 13.3%.

Relationship between AL and short-term prognosis

AL affects the outcome of surgery, worsening the short-term outcomes and increasing the time and cost of hospitalization [29,30]. The mortality related was reported to be between 0.8% and 27% [31]. Mortality was higher after leak from a colonic anastomosis than after leak from a rectal anastomosis (43.8% vs. 7.1%) [31]. Bertelsen *et al* found in a multicenter study a 4-fold increase in 30-day mortality in patients with AL [32]. According to a Cochrane review, AL is associated with a perioperative mortality rate of 2% to 24% and high morbidity, with the risk of a definitive ostomy exceeding 25% [33]. Warps *et al* [34] found an overall AL rate of 4.8%, ranging from 4.0% (right hemicolectomy) to 15.4% (subtotal colectomy). AL was predominantly managed with reintervention, ranging from 81.2% of cases after transversectomy to 92.4% after sigmoid resection. After reintervention, the highest mortality rates were observed for transversectomy (15.4%) and right hemicolectomy (14.4%) and the lowest for sigmoid resection (5.6%) and subtotal colectomy (5.9%). The ICU admission rate was 62.6% overall (range 56.7-69.2%) and the stoma rate ranged from 65.5% (right hemicolectomy) to 93.0% (sigmoid resection).

Relationship between AL and long -term prognosis

While the short-term consequences of AL are well known, its impact on long-term prognosis in CRC patients is still debated.

In the literature, the first authors to concern themselves with outcomes related to anastomotic dehiscence after resective surgery for colorectal cancer were Phillips *et al* [35] and Sauven *et al* [36]. In both cases, the parameter evaluated was local recurrence (LR). In the first study, AL did not appear among the significant risk factors for recurrence, while in the second, anastomotic dehiscence was associated with an increased rate of LR. In the same years, Amato *et al* [37] evaluated the association between CRC and AL by focusing exclusively on patients with rectal tumors operated with an anterior resection. In this study, AL did not influence the recurrence rate.

In 1991, Akyol *et al* [38] performed a study on patients operated for left colon or rectal cancer and demonstrated an important influence of AL on recurrence and cancer-specific survival (CSS) at 24 mo. The independence of the impact of dehiscence on outcomes from tumor stage was highlighted. This was the first study that analyzed local and distant recurrence separately and used multivariate Cox regression.

Two years later, a study published by Fujita *et al* [39] showed the impact of AL on LR and disease-free survival (DFS). DFS is significantly lower in the AL group for patients with Duke stage A and B cancers but not for C and D. The importance of this work also lies in the separate evaluation of subjects with colon and rectal cancer.

Petersen *et al* [40] studied the influence of leakage on LR, CSS, overall survival (OS) and postoperative mortality. AL influence only LR and CSS, confirming the previous findings of Akyol *et al* (14). Branagan *et al* [41] reached similar conclusions in 2005. Further studies [42-44] showed a correlation between AL and higher 30-day mortality, lower OS and CSS.

Law *et al* [45] in 2007 found a significant association between AL and 5-year cancer-specific survival, 30-day mortality and recurrence (local and systemic).

According to the study by Eberhardt *et al* [46], AL does not change the risk of recurrence and mortality for colon cancer, whereas it does for rectal cancer. The article also offers an assessment of OS, CSS, LR and overall recurrence for each stage, as well as an analysis of these outcomes at both 1 and 5 years after surgery.

According to Marrà *et al* [47], AL significantly reduces overall survival without affecting the risk of recurrence, while other studies [48-58] have found an impact of leakage on OS, recurrence, and DFS. However, Katoh *et al* [50] evaluated only patients with stage II CRC and Breugom *et al* [54] only patients with stage I-III colon cancer. To be precise, Park *et al* [56] in 2016 found an effect of AL on OS and DFS only for patients with rectal cancer. Nachiappan *et al* [52] found a reduction in OS in patients with AL who required reoperation compared with subjects without AL. Ramphal *et al* [58] demonstrated that local recurrence develops with the same frequency in symptomatic and asymptomatic dehiscence.

Krarup *et al* [59-60] identified in patients with AL an increase in DR and in mortality. However, there was no significant association with local recurrence. Nordholm-Carstensen *et al* [61] and Ng *et al* [62] evaluated the impact of AL in patients with stage IV CRC. The 3-year survival rate is affected by dehiscence for both colon (18.7% *vs* 44.6%) and rectum (53.7% *vs* 73.3%).

The first meta-analysis on this topic was performed by Mirnezami [63] on 22 studies. It reported an association between AL and local recurrence, distant recurrence (DR) and cancer-specific mortality.

The subsequent meta-analysis by Ha *et al* [64] evaluated 34 studies and divided the results into two categories. In the first group rectal anastomosis data were analyzed, and AL was associated with increased LR and reduced OS, CSS, and DFS. There were no significant effect on distant recurrence. In the second group colic anastomoses were analyzed and AL was associated with reduced OS and DFS and there was no correlation with local or distant recurrence.

The studies by Sammour *et al* [65] and Goto *et al* [66] also analyzed CSS. They showed a significant reduction in 5-year OS for patients with AL, without finding differences in

LR, CSS and postoperative mortality (in rectal carcinoma, leakage affects only the latter). The second one documented instead a reduction in OS (80. 8% *vs* 90.3%) and CSS (89.6% *vs* 95.1), an increase in local recurrence and no correlation with distant recurrence.

A subsequent meta-analysis conducted in 2020 by Mohamed *et al* [67] demonstrated a lack of significant effect of AL on recurrences, however it reduced OS, DFS and CSS.

Recent articles on this topic were written by Stormark *et al* [68] and Kryzauskas *et al* [69]. The former concluded that leakage only after surgery for stage III CRC is able to reduce survival, whereas the latter demonstrated that AL impaired disease-free and overall survival in patients undergoing sigmoid and rectal surgery.

Regarding rectal cancer alone, the first data of the new millennium showed an increase in LR and a decrease in CSS [70,71]. Subsequent studies can be divided into 3 categories. In the first group, there are studies that supported the absence of an impact of AL on cancer outcomes such as OS, CSS, DFS, LR and DR [72-79]. The second group covers studies defining AL as an independent prognostic factor for reduced OS, CSS, DFS and increased recurrence [80-83]. In the third group, we can place studies [84-88] midway between the first two categories, as the study of Noh *et al* [88], demonstrating that AL is associated with increased LR and reduced DFS, whereas its relationship with OS and distant recurrence is not significant. These findings were confirmed in a recent study by Peltrini *et al* [89].

To the above groups, we must also add studies evaluating also perioperative mortality. Ptok *et al* [90] and Hain *et al* [91] found an impact of dehiscence on 30-day mortality, DFS, and LR, whereas Eriksen *et al* [92] and Bertelsen *et al* [32] found an increase in 30-day mortality, but without a significant increase in LR. Bertelsen also noted the lack of reduction in OS and impact on distant recurrence [32].

Lim *et al* [93] in 2015 classified ALs into 3 categories based on the consequences: I) generalized peritonitis; II) localized peritonitis with or without abscess; III) fistula. Oncologic outcomes were evaluated separately for each type and reduced OS and LRFS

(local recurrence-free survival) were identified. According to Bostrom *et al* [94], leaks only impact OS if they require intervention.

In 2022, Dulskas *et al* [95] evaluated AL in patients undergoing right colectomy for CRC and concluded that AL is a factor that negatively affects long term prognosis. In contrast, a Dutch retrospective study found that disease recurrence is not associated with AL after CRC resection [96].

Koedam *et al* [97], analyzing data from the COLOR and COLOR II studies, show that ALs after rectal cancer surgery are associated with an increased rate of LR and a decreased DFS at 5-year follow-up. DR and OS are not significantly affected. Regarding colon cancer surgery, no significant effect of AL on long-term oncologic outcomes was observed, presumably because of a relatively low leakage rate. Strengths of this study include the randomized, multicenter design of the two included studies [98,99] and uniform study protocol for perioperative care and follow-up to limit practice variability. All studies on this topic are summarized in **Table 1**.

CONCLUSION

AL appears to be an independent risk factor influencing long-term oncologic outcomes after rectal cancer surgery. On the other hand, regarding colon cancer, the results are still extremely heterogeneous and unclear. Further studies on patients undergoing resection for colorectal cancer are needed to confirm the oncological impact of AL. Based on these data, we would recommend more frequent follow-up for patients with AL after CRC cancer surgery.

72601_Auto_Edited.docx

ORIGINALITY REPORT

21%
SIMILARITY INDEX

PRIMARY SOURCES

1	www.researchgate.net Internet	132 words —	4%
2	link.springer.com Internet	99 words —	3%
3	pdfs.semanticscholar.org Internet	98 words —	3%
4	www.ncbi.nlm.nih.gov Internet	53 words —	2%
5	Thomas W. A. Koedam, Boukje T. Bootsma, Charlotte L. Deijen, Tim van de Brug et al. "Oncological Outcomes After Anastomotic Leakage After Surgery for Colon or Rectal Cancer", Annals of Surgery, 2022 Crossref	50 words —	2%
6	jamanetwork.com Internet	45 words —	2%
7	Freddy Penninckx. "Anastomotic leakage: a disaster or a challenge with an impact on survival after rectal cancer surgery? : Editorial", Colorectal Disease, 03/2011 Crossref	32 words —	1%
8	Antonio Sciuto, Giovanni Merola, Giovanni D De Palma, Maurizio Sodo, Felice Pirozzi, Umberto M	20 words —	1%

Bracale, Umberto Bracale. "Predictive factors for anastomotic leakage after laparoscopic colorectal surgery", World Journal of Gastroenterology, 2018
Crossref

9   Ingvar Sverrisson, Folke Folkvaljon, Abbas Chabok, Pär Stattin, Kenneth Smedh, Maziar Nikberg. "Anastomotic leakage after anterior resection in patients with rectal cancer previously irradiated for prostate cancer", European Journal of Surgical Oncology, 2018   20 words — 1%
Crossref

10   Maria Michela Chiarello, Pietro Fransvea, Maria Cariati, Neill James Adams, Valentina Bianchi, Giuseppe Brisinda. "Anastomotic leakage in colorectal cancer surgery", Surgical Oncology, 2022   17 words — 1%
Crossref

11   epdf.pub   15 words — 1%
Internet

12   www.researchsquare.com   13 words — < 1%
Internet

13   Gi Won Ha, Jong Hun Kim, Min Ro Lee. "Oncologic Impact of Anastomotic Leakage Following Colorectal Cancer Surgery: A Systematic Review and Meta-Analysis", Annals of Surgical Oncology, 2017   12 words — < 1%
Crossref

14   Seok-Byung Lim, Chang Sik Yu, Chan Wook Kim, Yong Sik Yoon, In Ja Park, Jin Cheon Kim. "The types of anastomotic leakage that develop following anterior resection for rectal cancer demonstrate distinct characteristics and oncologic outcomes", International Journal of Colorectal Disease, 2015   12 words — < 1%
Crossref