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Preoperative, intraoperative and postoperative risk factors for anastomotic leakage after laparoscopic low anterior resection with double stapling technique anastomosis

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Abstract

Anastomotic leakage (AL) is one of the most devastating complications after rectal cancer surgery. The double stapling technique (DST) has greatly facilitated intestinal reconstruction especially for anastomosis after low anterior resection (LAR). Risk factor analyses for AL after open LAR have been widely reported. However, a few studies have analyzed the risk factors for AL after laparoscopic LAR. Laparoscopic rectal surgery provides an excellent operative field in a narrow pelvic space, and enables total mesorectal excision (TME) surgery and preservation of the autonomic nervous system with greater precision. However, rectal transection using a laparoscopic linear stapler is relatively difficult compared with open surgery because of the width and limited performance of the linear stapler. Moreover, laparoscopic LAR exhibits a different postoperative course compared with open LAR, which suggests that the risk factors for AL after laparoscopic LAR may also differ from those after open LAR. In this review, we will discuss the risk factors for AL after laparoscopic LAR.

Keywords: Risk factor; Anastomotic leakage; Laparoscopic low anterior resection; Rectal cancer, Double stapling technique anastomosis

Core tip:

Recently, many studies have reported that laparoscopic rectal surgery is becoming popular and exhibits favorable outcomes compared with open surgery. However, the AL rate after laparoscopic LAR is yet about 10 %, and AL remains a huge challenge despite many surgical and technological advances. Here we review the current litarature published with respect to the risk factors for AL after laparoscopic LAR.

INTRODUCTION

Laparoscopic surgery for colon cancer was introduced in the 1990s, and has shown promising results. Laparoscopic low anterior resection (LAR) for rectal cancer is technically more difficult than laparoscopic colectomy because of the difficulties related to a narrow pelvic space. A higher incidence of positive circumferential margins after laparoscopic LAR was reported in an initial randomized controlled trial (RCT)[1], but an increasing number of studies have shown that laparoscopic surgery for rectal cancer provides surgical safety and oncological outcomes equivalent to open surgery[2-6]. Recent large-scale RCTs such as COLOR II[7] and COREAN[8] have reported favorable outcomes for laparoscopic surgery compared with open surgery for rectal cancer.

The double stapling technique (DST) has greatly facilitated intestinal reconstruction, especially for anastomosis after LAR. Anastomotic leakage (AL) is one of the most devastating complications after rectal cancer surgery. AL impairs not only short-term outcomes (morbidity, mortality, length of hospital stay, and financial cost) but also long-term oncological outcomes (survival and local recurrence)[9-11]. Therefore, it is important to identify the patients who are at high risk of AL for improving overall outcomes. Despite technical improvements and instrumental developments, recent studies have reported that the AL rate ranges from 3% to 19%[9,12-15]; the most commonly reported rate is approximately 10-13% from recent large population databases in the USA[12] and Japan[15]. AL after rectal resection is influenced by many factors including not only surgical factors but also medical factors related to the systemic conditions in patients.

Several risk factors, including age, sex, intraoperative bleeding, obesity, preoperative chemoradiotherapy, protective diverting stoma, pelvic drainage, tumor size, tumor location and the level of anastomosis have been reported to be risk factors for AL after open LAR[16-21]. In contrast, only a few studies have examined risk factors for AL after laparoscopic LAR[22-31] (Table 1). In addition, the rates of protective diverting stoma, preoperative chemoradiotherapy (CRT), and TME in each study were not consistent, which might produce different results. Several studies reported that laparoscopic surgery and open surgery for rectal cancer did not differ in terms of the AL rate[1,2,4]. Laparoscopic rectal surgery provides an excellent operative field in a narrow pelvic space, and enables the preservation of autonomic nerves more precisely. However, rectal transection using a laparoscopic linear stapler is relatively difficult when compared with open surgery because of the width and limited performance of the linear stapler. The devices and techniques used for laparoscopic LAR are different from those used for open LAR. Moreover, laparoscopic LAR exhibits a different postoperative course compared with open LAR, including less blood loss, faster recovery of peristalsis, faster initiation of oral intake, and shorter hospital stay. Notably, multicenter, prospective and cohort studies using propensity score matching analysis have reported that risk factors for AL after laparoscopic or robotic LAR are different from those after open LAR[30,31]. Factors related to technical difficulty such as male sex, previous abdominal surgery, lower location of tumor and the use of more than 2 cartridges for rectal transection were found to be significant only in laparoscopic or robotic LAR groups[31].

In this review, we will discuss the risk factors for AL after laparoscopic LAR. Risk factors are categorized into 1) preoperative, 2) intraoperative, and 3) postoperative factors. The identification of high-risk patients has great clinical relevance and ultimately improves patient outcomes. Although more prospective studies are needed, this review provides major insight into identifying important risk factors for AL after laparoscopic LAR.

1. PREOPERATIVE RISK FACTORS

Male Gender

Males have a narrow pelvis, which makes rectal dissection and anastomosis more difficult and more prone to surgical complications. In fact, male gender has been reported as an increased risk factor for AL after open LAR[16,17,19-21] as well as laparoscopic LAR[28,30,31]. The influence of androgen-related differences in the intestinal microcirculation may be involved[32].

Body mass index (BMI)

Some studies have shown that obesity measured by body mass index (BMI) can increase the risk of AL[33-35]. Yamamoto *et al*[27] reported that BMI was independently predictive for AL after laparoscopic LAR. In place of BMI, waist circumference and waist/hip ratio may predict the risk of AL[36]. In addition, measuring visceral fat area may be more sensitive than BMI in predicting AL after laparoscopic surgery[37].

Preoperative radiotherapy (RT) / chemoradiotherapy (CRT)

Preoperative radiotherapy (RT) with or without concomitant chemotherapy is generally recommended for patients with locally advanced rectal cancer followed by total mesorectal excision (TME) surgery. It is accepted that these therapeutic modalities can reduce the local recurrence rate[38-40]. Although effective in targeting cancer cells, RT has a wide array of detrimental effects on intestinal tissue and wound healing and has long been believed to be a risk factor for AL. There are many retrospective studies that have reported the relationship between preoperative RT and AL[20,21,28]. However, prospective trials and cohort studies have shown contradictory results. The MRC CR07 RCT[41] reported that there was no difference in AL between preoperative RT and selective postoperative CRT. A Dutch TME trial[42] reported that there was no significant difference in AL rates (TME plus preoperative RT vs TME alone). A recent report using propensity score matching analysis have also reported that preoperative CRT does not increase the risk of AL after LAR[43]. Most surgeons perform a temporary protective diverting stoma to minimize the consequences of AL in patients who have received preoperative CRT or RT.

Preoperative chemotherapy

Preoperative chemotherapy is a well-known risk factor for AL[13]; however, the mechanism underlying this association is poorly understood. Recent use of antiangiogenic agents also increases the risk of AL. The first studies examining bevacizumab (Avastin), a humanized anti-vascular endothelial growth factor antibody, reported several patients with bowel perforation[44,45]. The mechanism of this perforation is proposed to be arterial microthromboembolic disease leading to bowel ischemia. The same mechanism can cause AL. Bevacizumab has a half-life of 20 days, and the manufacturer recommends stopping its treatment at least 4 weeks before surgery.

Antibiotics

A meta-analysis of eight RCTs reported that combining preoperative intestinal decontamination with oral antibiotics and perioperative intravenous antibiotics reduced postoperative infection including AL, compared with use of intravenous antibiotics alone[46]. Notably, a recent RCT showed that intravenous plus oral antibiotics (cefmetazole, kanamycin and metronidazole) significantly reduced the risk of surgical site infection compared with intravenous antibiotics alone (7.3% vs. 12.8%, $P = 0.028$), while no significant difference was seen in the rate of AL[47]. Further studies are required to elucidate the effect of preoperative oral antibiotics on AL.

Medications

Although it is assumed that impaired healing with corticosteroid use would affect the AL rate, it is difficult to find an absolute correlation. Prolonged use of corticosteroids can be a risk factor for AL, particularly when combined with other immunosuppressive drugs[48-50]. A recent systematic review reported that the AL rate after lower gastrointestinal surgery was 6.8% in the corticosteroid group compared with 3.3% in the non-corticosteroid group, although the duration and dose of corticosteroid treatment were heterogeneous[51]. A meta-analysis with six RCTs reported that perioperative use of nonsteroidal anti-inflammatory drugs (NSAIDs) had no statistically significant effect on the AL rate[52]. However, non-selective NSAIDs and non-selective cyclooxygenase (COX) 2 inhibitors were reported to be associated with a higher AL rate[53]. Therefore, NSAIDs should be used with caution in the postoperative period. In general, the postoperative pain after laparoscopic surgery is less than that after open surgery, which may result in the decreased usage of NSAIDs and decreased rate of AL in laparoscopic surgery.

Other factors, such as smoking and alcohol, have also been reported to be risk factors for AL after LAR[31,54-57]. The effect of smoking might be secondary to ischemia caused by smoking-related microvascular disease. Large quantities of alcohol consumption might be a surrogate for poor nutritional status.

2. INTRAOPERATIVE RISK FACTORS

Level of anastomosis

It is widely accepted that the risk of AL increases with more distal anastomosis. Although it is well accepted that a low anastomosis has a higher incidence of AL, the mechanism remains unknown. It is hypothesized that the height of the anastomosis or the tumor location can reflect technical difficulties of LAR, resulting in local tissue trauma, increased tension, or poor blood supply. A number of studies reported that lower anastomosis level is an important risk factor for AL after open LAR[16-21] as well as laparoscopic LAR[23-26,28,31].

Surgical technique and multiple stapler firings

Surgical technique has a substantial impact on postoperative complications including AL. In laparoscopic LAR, optimal port placement is important to reduce the number of linear stapler firings for rectal transection in a narrow pelvis. The use of multiple staplers (e.g. ≥3 cartridges) for rectal transection is a major cause of AL after laparoscopic LAR[22,23,26,28,29,31]. When the number of stapler cartridges increases, there is a concern that an increased number of stapler firings can lead to small defects between the staple lines and, in turn, cause AL. Therefore, laparoscopic surgeons need to make efforts to reduce the number of linear stapler firings to two or less. Several different techniques have been proposed to reduce AL. Ito *et al*[22] reported that vertical rectal transection through an additional suprapubic site was useful for avoiding multiple stapler firings and decreasing the AL rate. Kuroyanagi *et al*[58] reported that rectal transection was performed using two cartridges in most cases, with coordinated operator-assistant movement, and that removal of the crossing point of staple lines was important to delete the potential source of AL. In a clinical setting, we previously analyzed whether the remnant crossing point could increase the AL rate, and found that it was not significantly associated with AL[29]. Therefore, we assume that surgeons do not need to persist in removal of the crossing point, especially when the crossing point is placed near the edge of the rectal stump and so removal of the crossing point is technically difficult.

It is notable that intracorporeal[59] or transanal[60] reinforcing sutures could effectively reduce AL after LAR, but the results of these studies are not conclusive. DST is inevitably associated with bilateral intersecting staple lines at the rectal stump, so-called dog ears. The dog ears are the weak spots associated with potential AL[61]. Recently, a combined laparoscopic LAR and eversion technique without dog ear formation was reported to be useful to reduce AL for mid and distal rectal cancer[62].

Precompression before stapler firings

We previously reported that a sufficient amount of precompression time before stapler firings resulted in reduced intestinal wall thickness and proper staple formation in animal models[63-65]. In addition, we recently reported that precompression before stapler firings and tumor size (≥ 5.0 cm) were associated with AL after laparoscopic LAR in a clinical setting, and that precompression before stapler firing tended to reduce the AL occurring in the early postoperative period[29]. Precompression time before stapler firings and proper cartridge selection according to the wall thickness are critical to achieve secure staple formation.

Diameter of circular stapler

Kim *et al*[23] reported the association between a larger diameter circular stapler and increased rates of AL. They speculated that a larger diameter circular stapler made the distal rectum more distended. A distended rectum with thinned rectal wall may cause inadequate blood supply to the anastomosis site. We previously analyzed whether the diameter of a circular stapler could affect the AL rate, and found that it was not significantly associated with AL[29]. Further studies are required to elucidate the effect of diameter of a circular stapler.

Tumor characteristics

Tumor size is a well-known risk factor for AL after laparoscopic LAR[13,29,30]. A bulky tumor could adversely affect the ease of rectal transection and anastomosis in the limited pelvic space. Some studies demonstrated that tumor size greater than 5 cm was independently predictive of AL[13,29]. Advanced stage is also a risk factor for AL after laparoscopic LAR[28].

Blood supply

Despite the multifactorial etiology of AL, insufficient perfusion and technical factors are considered to play a substantial role in the development of AL[9,66-68]. For this reason, surgeons often assess intestinal perfusion by several clinical checks, such as the color of the bowel wall, palpable pulsation, and bleeding from marginal arteries. These checks are subjective and based on the surgeon’s experience, and may well lead to misinterpretations even by experienced surgeons[69]. In recent years, near-infrared (NIR) fluorescence technology with indocyanine green (ICG) has been the most promising method that provides a real-time assessment of intestinal perfusion[70-74]. The first study to use fluorescence imaging for colorectal surgery was published by Kudszus *et al*[70]. They reported that fluorescence imaging resulted in a proximal change of the initially planned transection line in 13.9% (28/201), and that intraoperative fluorescence imaging reduced AL by 4% compared with a control group (7.5% vs. 3.5%). These data have been confirmed by Jafari *et al*[71] during robotic-assisted laparoscopic rectal surgery. Moreover, a multi-institutional prospective study, PILLAR-II, recently reported that fluorescence imaging changed surgical plans in 8% (11/139), and that the AL rate was 1.4% (2/139) in laparoscopic left-sided/anterior resection[73]. In addition, Sterwinter *et al*[75] evaluated the intraluminal aspect of the anastomosis transanally after DST construction using a transanal NIR imaging system. The assessment of rectal stump perfusion by transanal ICG imaging can be a promising method, although further studies are needed to correlate this technique to the clinical outcome. However, another recent another report stated that the intraoperative fluorescence imaging does not reduce the AL rate in colorectal surgery from a case-matched retrospective study with the use of historical control subjects[76]. Because of the limited number of patients and the likely multifactorial nature of AL, it is hard to draw robust conclusions concerning the beneficial effect of fluorescence imaging on the AL rate.

The concept of high ligation of the inferior mesenteric artery to achieve optimal oncological results suppresses the vascular supply from the left colic artery, and vascularization of the proximal colon is dependent on marginal vessels from the middle colic artery. The preservation of the left colonic artery in laparoscopic LAR was reported to be associated with lower risk of AL[77]. With the progressive increase in the aging population, vascular disease can also be a factor contributing to insufficient blood supply, even in the case of low ligation.

Blood loss

Blood loss greater than 100 ml and blood transfusion are independent risk factors for AL[28-30,78,79], but it is unclear whether this is a specific manifestation due to blood loss or whether blood loss is a surrogate for poor operative technique or challenging surgery.

Operation time

Although operation time is well known to be one of the risk factors for AL after laparoscopic LAR[23-25,28,29,31], the experienced skill of the surgeon is also thought to act as a confounding variable. In patients with severe obesity, narrow pelvis, bulky tumor, and in cases with adverse intraoperative events, the operation time is prolonged. When the operation time is long, bacterial exposure and tissue damage can increase, which may cause inflammation and ultimately increase AL.

Anastomotic tension

Many surgeons assume that sufficient mobilization of the splenic flexure is necessary to lower anastomotic tension, especially when the anastomotic site is very low. Minimal anastomotic tension is thought to be one of the requirements of proper surgical technique; yet, this concept remains largely hypothetical. To our knowledge, there have been no experimental studies investigating the role of tension during an intestinal anastomosis. Lack of data likely stems from the difficulty in designing studies that investigate anastomotic tension in a clinical setting.

3. POSTOPERATIVE RISK FACTORS

Diverting stoma (DS)

Fecal diversion is one of the most widely used methods to prevent AL. However, there is still debate as to whether the creation of a diverting stoma (DS) can reduce AL. Some randomized controlled trials reported that DS could reduce the rate of symptomatic AL[80,81], while a recent large multicenter cohort study using propensity score matching analysis indicated that DS was not associated with symptomatic AL[14]. A considerable number of retrospective studies also described the beneficial effect of DS on AL[16,20,82], while some studies stated that the creation of a DS did not reduce the rate of AL[21,83]. It is generally agreed that the creation of a DS can reduce the incidence of the severe complications of AL, including fecal peritonitis and septicemia. We need to bear in mind that even a temporarily-intended stoma can induce dehydration and renal impairment[84]. Moreover, re-operation for reversal of stoma may also be associated with morbidity and even death[85].

Transanal drainage tube (TDT)

The safety and efficacy of transanal drainage tube (TDT) placement to decrease the risk of AL after rectal cancer surgery has not been validated. In theory, TDT decreases the intraluminal pressure around the anastomotic site, and protects the anastomosis from watery stool and flatus when intestinal motility improves. There are only a few reports to investigate whether TDT can prevent AL after open LAR, but the results are inconsistent, with some studies indicating favorable outcomes[86-88], while other studies reported unfavorable outcomes[89]. Moreover, it has been reported that TDT can reduce the rate of AL after laparoscopic LAR[90]. There are slight differences in each study such as material and diameter of TDT, length of TDT insertion and duration of TDT placement. A standardized procedure for TDT should be validated and further investigation is required to elucidate its usefulness. With regard to reducing the intraluminal pressure around the anastomotic site, the concept of creating a DS is nearly the same as that for TDT. However, a DS increases patient discomfort and overall cost, and requires further surgery for closure of the DS. If the efficacy of prevention of AL is nearly equal for both procedures, it follows that TDT is superior to DS for this reason.

TDT can also be useful to cure localized peritonitis related to AL. Several reports have stated that the TDT is effective for localizing AL and controlling sepsis following LAR[91,92]. Shrinkage of an abscess by a TDT inserted into the cavity can localize inflammation, which results in a reduced incidence of re-operation.

Abdominal drains

The use of an abdominal drain has been debated widely in terms of early detection of complications as well as preventing AL. After TME surgery, a large presacral space in which a hematoma or seroma may develop constitutes a nidus for bacterial growth, which may extend to the anastomosis and cause AL. Pelvic drainage can prevent this process and help to control AL. A systematic review including several RCTs reported no significant difference in the rate of AL, concluding there was insufficient evidence to support routine drainage[93]. However, a recent meta-analysis indicated a reduction of AL rate with pelvic drainage[94]. Akiyoshi *et al*[26] reported that the presence of an abdominal drain was an independent predictive factor for AL after laparoscopic LAR. The current evidence does not support drainage of a colonic anastomosis, but the LAR case for abdominal drains is less clear.

Intestinal microbes

The human intestinal microbiome is thought to play a key ley role in the pathogenesis of obesity, gastrointestinal malignancies, and Crohn's disease[95]. Recently, the role of microflora in anastomotic healing is attracting more attention[96]. One powerful modality contributing to major alterations in composition and virulence of the gastrointestinal microflora is radiation. The susceptibility to RT-induced diarrhea could be linked to differential initial microbial colonization[97]. In a rat model of LAR, Olivas *et al*[98] demonstrated that the combination of preoperative RT and intestinal inoculation with *Pseudomonas aeruginosa* resulted in a higher rate of AL, whereas radiation alone or *Pseudomonas aeruginosa* alone did not cause AL. In an AL rat model, it has been recently reported that *Enterococcus faecalis* contributes to the pathogenesis of AL through collagen degradation and matrix metalloproteinase 9 (MMP9) activation in host intestinal tissues, and that either elimination of

Enterococcus faecalis through direct topical antibiotics or pharmacological suppression of MMP9 could prevent AL[99]. Patients undergoing colectomy are at a unique risk of *Clostridium difficile* because of the additional physical disruption of the colonic microflora. The impact of postoperative *Clostridium difficile* infection is being increasingly reported with overall worse outcome after colon resection[100]. It was reported that postoperative diarrhea or high stoma output regardless of *Clostridium difficile* infection could increase significantly more superficial surgical site infections including AL [101], which may indicate the interaction between AL and the intraluminal pressure increased by postoperative diarrhea. Further investigation focusing on intestinal microbes could be important for uncovering the elusive causes of AL.

CONCLUSION

AL remains a huge challenge despite many surgical and technological advances. Our review identified several risk factors for AL after laparoscopic LAR, all of which are readily available in clinical settings. Continued high-quality research is of paramount importance to reduce the risk and subsequent effects associated with AL.

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Table 1: Selected studies to investigate the risk factors for AL after laparoscopic LAR

Author	year	Sample size	AL rate (%)	Tumor location*	Covering stoma	Risk factors
Ito et al.[22]	2008	180	5.0	R, RS	+	anastomosis level, multiple stapler firings
Kim et al.[23]	2009	270	6.3	R, RS, S	+	tumor location
Huh et al.[24]	2010	223	8.5	R	–	tumor location, operation time
Choi et al.[25]	2010	156	10.3	R, RS	–	anastomosis level, operation time
Akiyoshi et al. [26]	2011	363	3.6	R, RS	+	tumor location, abdominal drain
Yamamoto et al. [27]	2012	111	5.4	R	+	BMI
Park et al.[28]	2013	1187	6.3	R, RS	–	male, stage, transfusion, tumor location, preoperative CRT, multiple stapler firings
Kawada et al.[29]	2014	154	12.3	R	–	tumor size, precompression before stapler firings
Katsuno et al.[30]	2015	209	15.3	R	+	male
Kim et al.[31]	2016	1154	6.7	R	+	male, smoking, alcohol intake, previous abdominal surgery, operation time, tumor location, multiple stapler firings

*; R: rectum, RS: rectosigmoid colon, S: sigmoid colon