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Review

Anastomotic leakage in colorectal cancer surgery

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ABSTRACT

The safety of colorectal surgery for oncological disease is steadily improving, but anastomotic leakage is still the most feared and devastating complication from both a surgical and oncological point of view. Anastomotic leakage affects the outcome of the surgery, increases the times and costs of hospitalization, and worsens the prognosis in terms of short- and long-term outcomes. Anastomotic leakage has a wide range of clinical features ranging from radiological only finding to peritonitis and sepsis with multi-organ failure. C-reactive protein and procalcitonin have been identified as early predictors of anastomotic leakage starting from postoperative day 2–3, but abdominal-pelvic computed tomography scan is still the gold standard for the diagnosis. Several treatments can be adopted for anastomotic leakage. However, there is not a universally accepted flowchart for the management, which should be individualized based on patient's general condition, anastomotic defect size and location, indication for primary resection and presence of the proximal stoma. Non-operative management is usually preferred in patients who underwent proximal faecal diversion at the initial operation. Laparoscopy can be attempted after minimal invasive surgery and can reduce surgical stress in patients allowing a definitive treatment. Reoperation for sepsis control is rarely necessary in those patients who already have a diverting stoma at the time of the leak, especially in extraperitoneal anastomoses. In patients without a stoma who do not require abdominal reoperation for a contained pelvic leak, there are several treatment options, including laparoscopic diverting ileostomy combined with *trans*-anal anastomotic tube drainage, percutaneous drainage or recently developed endoscopic procedures, such as stent or clip placement or endoluminal vacuum-assisted therapy. We describe the current approaches to treat this complication, as well as the clinical tests necessary to diagnose and provide an effective therapy.

1. Introduction

The safety of colorectal surgery for oncological disease has dramatically improved over the last 50 years due to a better preoperative preparation, antibiotic prophylaxis, surgical technique, and postoperative management. Since abdomino-perineal resection, new and less aggressive procedures have been developed (e.g., laparoscopic and robotic approach, endoluminal resection), always respecting the concepts of oncologically free margins (R0) and of avoiding the dissemination of cancer cells during surgery [1–7]. Several years ago, a further step forward in the field of colorectal surgery was the introduction of surgical stapler [8], which allowed surgeons to perform safer and quicker anastomoses especially during minimally invasive surgery [9–14]. Moreover, in the last decades there has been a spread of minimal invasive procedures such as the total *trans*-anal mesorectal excision with an even better clinical outcome for the patients [15–17]. There has also been the development and spread of robotic devices to aid surgical procedures [18–24].

However, complications after colorectal surgery are still inevitable. Their severity is variable ranging from mild with a minimal impact on the patient, to severe and potentially fatal, in case of anastomotic leak (AL) [25–27]. AL is one of the most severe complications for colorectal

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surgery owing to its negative impact on both short- and long-term outcomes. The incidence reported in the literature has not significantly changed in recent decades despite constant improvements in both stapled and manual sutures, in the pre-operative assessment of the patient, as well as in the surgical technique. The reported incidence is about 2.8–30% as all, of which 75% occurs in rectal anastomosis resulting in a mortality rate of 2–16.4% and in a morbidity rate of 20–35% [8,28–31].

The different ranges of AL incidence in the literature are linked to several factors such as type of disease (neoplastic or inflammatory), timing of the operation, anatomical variables such as location of the tumour, clinical presentation (occlusion, perforation), stage of the disease, surgical procedure and the type of AL reported (radiological vs clinical).

The onset of AL is also important with respect to the severity and management of this complication. AL is typically diagnosed 5–8 days post-surgery. AL was divided into "early" and "late" categories according to whether AL and AL-related complications were diagnosed within or after 30 days from surgery [32]. In other experiences AL was defined as dehiscence leading to reintervention later than 6 days postoperatively [33]. Furthermore, it has been observed that one-third of all AL were diagnosed more than 30 days after surgery, and up to 40% of these underwent surgical treatment [34]. Generally, an early AL is associated with severe peritonitis, emergency relaparotomy and increased mortality rate. By contrast, a late AL is associated with long lasting pelvic abscess [35,36]. Early AL is mostly related to technical failure of the anastomosis due to iatrogenic surgical disruption of the peri-anastomotic microvascular blood supply or tension at the anastomotic site [37], and late anastomotic leakage to pre-existing conditions in the patients, such as local sepsis, poor nutrition, immunosuppression, morbid obesity, and radiation exposure [33].

In this work, we describe the current approaches for the treatment of this complication, as well as the best diagnostic tests to provide an effective therapy.

2. Definition

AL is defined as a leak of luminal contents from a surgical join between two hollow viscera. However, there is not a univocal definition of AL in literature. Despite the fact that a standardized definition of AL was proposed by the UK Surgical Infection Study Group in 1991 [38], a review by Bruce et al. 10 years later (2001) still identified 29 different definitions of AL after lower gastrointestinal surgery [39]. The most widely adopted definition (Table 1) and classification of the severity degree (Table 2) are proposed by the International Study Group of Rectal Cancer (ISREC) [40].

In such a complex scenario, it is obviously difficult to develop an evidence based diagnostic and therapeutic algorithm for AL. In some studies, any leakage detected both clinically or radiologically is defined as AL; in others, AL is only a leakage needing and early re-do surgery.

Table 1
Definition and severity grading of anastomotic leakage (AL) after colorectal resection.

Definition	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 extra-luminal compartments. A pelvic abscess close to the anastomosis is also considered as AL.
Grade	AL requiring no active therapeutic intervention
A	AL requiring active therapeutic intervention but manageable without
B	re-laparotomy
C	AL requiring re-laparotomy

Modified from International Study Group of Rectal Cancer (ISREC) [40].

3. Risk factors

Evidence have demonstrated the risk factors for AL (Table 3) [8,14,41–51], [52–86]. Preoperative risk factors are generally divided into two types: modifiable, meaning that the patient or the physician can take measures to change them; or non-modifiable, meaning that they cannot be changed [87]. Regarding AL the Cochrane review of 2010 confirmed that male sex is an independent risk factor [88]. Obesity, diabetes, and ultra-low rectal anastomoses are other risks factors commonly reported in literature [8,89,90]. The incidence of leak was strongly associated with the distance of the anastomosis from the anal verge, with low anastomoses showing higher AL rates than right-sided resections.

Several studies underline that neoadjuvant radiotherapy is a common independent risk factor for AL in case of mid-low rectal resection [91–94]. However, a recent meta-analysis of literature from 1980 to 2015 has demonstrated no significant correlation between increased incidence of AL and neoadjuvant therapy [95]. In 2010 Zhu et al. [96] identified as further independent risk factors a tumour diameter greater than 3 cm and a local advanced disease at the time of surgical treatment.

Some authors stated that latero-lateral anastomoses have a lower leakage rate if compared to Knight-Griffen anastomoses, however the latter is commonly used in very low resections, and that could be a confounding factor for AL risk [8,97]. Some other studies suggested the importance of surgeon specialisation as a risk factor for anastomotic leak [45,98]. In addition, local conditions such as intestinal occlusion and perforation or peritoneal sepsis are well-known risk factors for AL. Sánchez-Guillén et al. stress the importance of patient optimisation in terms of blood pressure, use of inotrope and vasopressor drugs and perioperative transfusions both in elective and emergency setting to reduce AL rate [99]. Novel addictions to anastomotic technique, such as colorectal seals, polyester stents and anastomotic buttressing with absorbable materials, claim to reduce AL, but their routine use is some way off, given the lack of extensive comparative data.

4. AL in colorectal cancer surgery

To date, the multidisciplinary approach to colorectal malignancy allows surgeons and patients to achieve better oncological and functional outcomes preserving the sphincterial apparatus with a higher rate of ultra-low anastomoses (Fig. 1).

Despite these, AL is still the most severe early complication following colorectal cancer surgery as well as the main cause of mortality [100]. AL affects the outcome of surgery, worsening the prognosis in terms of short- and long-term outcomes and increasing the times and costs of hospitalization [25,101–103].

Mortality rate after AL ranges from 25 to 66% after all colorectal surgery procedures [66,104–107]. A 2010 Cochrane review shows that AL is associated with a perioperative mortality rate between 2% and 24%. Morbidity is also high and the risk of receiving a definitive ostomy can exceed 25% [88].

Bertelsen et al. found in a multicentre study a 4-fold increase in 30-day mortality in AL patients [108]. A larger recently published series reviewed leaks in 79 patients from 2001 to 2007 in a single hospital unit; the overall leak rate was 3%, with a mortality of 10.1% and a permanent stoma rate of 71.8% [109].

Moreover, several other studies demonstrated that AL in rectal cancer patients was associated with an increased risk of local recurrence and impaired long-term survival [110–114]. One large study involving 1984 patients with colorectal cancer showed that 5-year cancer-specific survival was 57.4% in those that developed an AL compared to 72% that recovered uneventfully. The 5-year rate of local recurrence was also increased from 1.9% to 4.7% in patients that developed an AL [115]. There are, however, different possible explanations to why AL may increase the risk of recurrence and thus reduce long-term survival. A biological mechanism could be advocated since surgery itself induces a

Table 2
Clinical characteristics of patients with different severity grades of anastomotic leakage (AL) after colorectal resection.

Grade	Clinical condition	Symptoms	Contents from drain	Laboratory tests	Radiologic evaluation	Treatment
A	Good	No	Serous/ fluid	Normal	Small, contained AL	No
B	Mild/ moderate discomfort	Abdominal/pelvic pain, Fever, purulent/fecal vaginal discharge (rectovaginal fistula), purulent rectal discharge.	Purulent content	Leucocytosis, C-reactive protein elevation, Procalcitonin elevation	AL may have local complications (eg, pelvic abscess)	Antibiotics, interventional drainage, transanal drainage
C	Severely impaired	Peritonitis, sepsis, multiple organ failureF	Faecal content	Leucocytosis, C-reactive protein elevation, Procalcitonin elevation, changes due to sepsis (eg., leukopenia)	AL may have generalized complications (ie, peritonitis)	Redo-surgery (laparotomy o laparoscopy) with control of septic focus, fecal diversion

Modified from International Study Group of Rectal Cancer (ISREC) [40].

systemic stress response mediated by activation of receptors for catecholamines and prostaglandins that may promote the synthesis of oncogenic growth factors while indirectly supressing anti-oncogenic factors. AL significantly increases the level of inflammation, and the diffuse peritoneal infection may thus further promote an environment suitable for tumour growth and extra-luminal implantation of micro metastasis because of increased cell migration. A favourable intra-abdominal environment for oncogenic growth may per se increase the risk of recurrence. From another point of view, the delayed starting of adjuvant chemotherapy increases the risk of recurrence [116,117]. In this respect, a Danish national cohort study demonstrated that timely administration of chemotherapy resulted in equal long-term outcomes in patients with or without AL [113]. Confirmation of this hypothesis may warrant further exploration of the long-term benefits of neoadjuvant chemotherapy compared with adjuvant chemotherapy in patients developing postoperative surgical complications. A neoadjuvant regime may eliminate the risk of omission or delay in chemotherapy.

However, the effect of AL on the long-term prognosis of the tumour remains controversial. Some studies have shown that anastomotic fistula has a negative effect on tumour recurrence and survival rate, but some show different data [117]. A previous meta-analysis indicated that AL after anterior resection for rectal cancer adversely affected cancer-specific survival and local recurrence, but not distant recurrence [118]. However, with the improvement of diagnosis and treatment, the long-term prognosis of the disease has changed [119,120].

Besides the effect of temporary stoma on recurrence and survival in AL patients is debated. In a study on 3,912 patients, Park et al. stated that rectal AL is a risk factor associated with poor overall survival in patients without a diverting stoma [28]. On the other hand, Wang et al. believe that, although diverting stomas can largely alleviate leakage-induced abdominal sepsis and possibly reduce the occurrence of systemic inflammatory reactions, the large amount of leakage caused by AL will offset beneficial effects on relapse and survival [121]. Similarly, Kulu et al. reported that in their study no temporary stoma was found to be associated with AL or changing of oncological outcomes such as local recurrence or overall survival [122].

5. Intraoperative techniques to assess integrity

To minimize the risks of postoperative anastomotic complications, surgeons have employed several intraoperative techniques to assess anastomosis integrity. These include basic mechanic patency tests, endoscopic visualization techniques, and more recently, micro perfusion assessment technology.

Basic mechanical patency tests include air and fluid leak tests including traditional air leak testing, saline leak, and methylene blue leak tests. Other methods adopted to assess blood perfusion of the intestinal stumps and the anastomotic site include visual assessment of intestinal wall color, visible peristalsis, and bleeding from the marginal arteries. These tests are limited by the fact that there is no direct visualization of the lumen. In the former, the anastomosis is assessed by occluding the proximal lumen and then filling the intraluminal cavity with air or fluid and assessing for leakage [123,124]. A systematic review of two randomized controlled trials by Beard et al. [125] and Ivanov et al. [126] assigned patients to intraoperative air leak testing vs. no testing in control group. The study found three patients in the test group requiring reoperation for a postoperative AL and one patient dying after reoperation. Conversely, the control group had a total of five reoperations for AL with a total of two deaths. The risk of a clinical AL in the tested group was 5.8% compared to 16% in the control group.

Regarding intraoperative endoscopy to visualize the anastomosis, a systematic review of five nonrandomized controlled trials enrolled a total of 950 patients and 509 patients in the tested group. The incidence of AL was 7.7% in the positive test group, 7.3% in the negative test group, and 5.9% in the control group, without significant difference in the postoperative AL rate between the groups ($P = 0.3$) [127].

A promising new technology today increasingly used and established is intra-operative fluorescence angiography with indocyanine green [128–130]. Evidence for the impact of intraoperative fluorescence angiography in reducing AL after colorectal anastomosis is growing. The procedure provides information on tissue perfusion that may help prevent AL. Intravenous indocyanine green is safe with no related adverse events observed in the literature. The PILLAR study showed a lower rate of AL when using intraoperative angiography. In this study, a low AL rate was demonstrated for left sided anastomoses reporting a 1.2% incidence for low risk and 1.9% for high-risk anastomoses (<10 cm from anal verge and/or pelvic radiation) [131]. Degett et al. [132] in their systematic review of 10 studies which included the analysis of 916 patients demonstrated that angiography with indocyanine green was associated with a reduced risk of AL of 3.3% (95%CI 1.97–4.63%) compared with standard intraoperative methods (8.5%–95% CI 4.8–12.2%) ($P = 0.005$). In another systematic review, van den Bos et al. [133] analysed 10 articles (894 patients) to determine the feasibility of intraoperative angiography in colorectal surgery and to evaluate the effectiveness of this technique in improving imaging and quantification of vascularization of colorectal anastomosis. The application of the fluorescence angiography led to reconsideration of the resection margin because of inadequate blood supply in 10.8% of cases. The AL rate was 3.5% after indocyanine green angiography and 7.4% after routine assessment of blood supply ($P = 0.002$). Shen et al. analysed four studies with a total sample size of 1,177 patients. The combined odds ratio was 0.27 (95% CI, 0.13–0.53) in favor of intraoperative angiography ($P < 0.001$) and there was no significant heterogeneity ($P = 0.48$; $I = 0$) [134]. Blanco-Colino et al. included in a meta-analysis the results of 1,302 patients from 5 non-randomized studies [135]. Fluorescence angiography significantly reduced AL rate in patients undergoing surgery for colorectal cancer (OR 0.34; 95% CI 0.16–0.74; $P = 0.006$). Low AL rates were also seen with indocyanine green angiography in rectal cancer surgery (1.1% vs. 6.1% standard methods, $P = 0.02$). The use of indocyanine green fluorescence angiography instead of standard

Table 3
Risk factor for anastomotic leakage (AL) in colorectal surgery.

Factor	
Age	The incidence of AL was 6.4% in patients <60 years old, 5.5% in patients 60–69 years old, 5.4% in patients 70–80 years old, and 4.9% in patients ≥80 years old ($P < 0.001$). Multivariate analysis showed that age was protective for AL (OR 0.965 per 5 years, 95% CI 0.941–0.985, $P < 0.001$). Mortality after AL was 1.3% in patients <60 years old, 4.8% in patients 60–69 years old, 12.3% in patients 70–80 years old, and 27.0% in patients >80 years old ($P < 0.001$). Older age was associated with mortality following AL (OR 1.497 per 5 years 95% CI 1.364–1.647, $P < 0.001$) [60].
Sex	Male sex [HR 3.468] was significantly associated with AL after laparoscopic surgery for rectal cancer [37].
Underlying disease	Diabetes was significantly and independently associated with an increased risk of AL morbidity in colorectal patients, [1.661 times in total patients (95% Cis = 1.266–2.178)] [77]. Underlying pulmonary disease and pre-existing vascular disease are both independent risk factors for AL in rectal resection. Renal disease is associated with a higher risk of AL.
Smoke	Multiple regression analysis showed that smokers, compared with non-smokers, had an increased risk of anastomotic leakage (relative risk (RR) 3.18 (95% CI) 1·44–7·00) [78].
Alcohol consumption	Alcohol history was also associated with a higher risk of AL [59]. Large quantities of alcohol consumption might be a surrogate for poor nutritional status. Multiple regression analysis has shown that heavy alcohol intake is associated with AL (relative risk 7.18, 95% CI 1·2 to 43) [78].
Nutritional status	Patients with low perioperative albumin will have increased risk factors of AL [57]. A multivariate analysis revealed that weight loss and malnutrition and fluid and electrolyte disorders were associated with a higher risk of AL [58]
Obesity	A body mass index higher than 30kg/m2 has been shown to be an independent factor for AL [46]
Anemia	Anemia has been described as a risk factor for AL. Hemoglobin is related to perfusion and oxygenation of the anastomotic margins, an essential factor for anastomotic healing. Currently, a hemoglobin level less than 11 g/dL increases risk of AL [79].
Perioperative blood transfusion	Blood transfusion (OR 10.27; 95% CI 6.82–15.45; $P < 0.001$) was associated with AL [80].
Neoadjuvant chemoradiation	Some retrospective studies have reported an association between preoperative radiotherapy and AL [37].
Immunosuppressant therapy	A systematic review found an AL rate of 6.8%t in the corticosteroid group compared with 3.3% in patients not treated with corticosteroid [76]. Recent use of chemotherapy, antiangiogenic and antimitotic agents also increase the risk AL [55].
Metastatic disease	Patients with stage IV colorectal cancer have an increased AL rate after surgery [117].
Bowel preparation	Several randomized trials have found that omitting mechanical bowel preparation does not increase the risk of AL [69,70]. A systematic review including over 5000 patients found no evidence that patients benefit from bowel preparation (either orally or by enema) [73].
Laparoscopic versus open surgery	Laparoscopic surgery has recently become popular, and many surgeons currently use this approach in colorectal pathology. Even though laparoscopic surgery for rectal cancer has technical difficulties such as pelvic approach (especially in men), lack of tactile sense or inadequate cutting angle after transection, the benefits are now widely accepted. Randomized controlled trials confirming equivalent oncological outcome and long-term survival between open and laparoscopic surgery have been published [42,51,71,83]. Laparoscopy has distinct differences from open surgery, such as the need for multiple stapler firings when transecting the rectum, which is associated with an increased AL rate, although this is likely to be reduced with advances in stapler technology. A recent meta-analysis concluded that laparoscopic rectal resection was associated with decreased blood loss, smaller incisions and longer operative times compared with the open approach. No differences were observed for postoperative morbidity and mortality between the two techniques [81]. The COLOR II trial showed statistically significant differences in terms of blood loss, bowel recovery and the length of hospital stay in favor of laparoscopic approach and no difference between open and laparoscopic rectal resection in terms of postoperative AL or mortality [82].
Handsewn or stapled anastomosis	Execution of anastomosis is a subject of debate regarding the best results on postoperative AL. Several studies assessing stapled and handsewn colorectal anastomoses found no difference in terms of postoperative AL rate between the two techniques [14,43,74]. Some authors have reported an increased risk of anastomotic leakage in stapled anastomosis using multiple firing [14].
Emergency surgery	Emergency surgery in case of peritonitis and/or bowel obstruction places patients at a higher risk of adverse postoperative events. Emergency resection was shown to be an independent risk factor for AL in some studies [47,49] and, moreover, an independent risk factor for death after leakage [52].
Surgeon's experience	Surgeon's experience in colorectal surgery has been claimed by some authors to be a risk factor for AL, with a high-volume colorectal surgeons having a smaller incidence of postoperative complications than low-volume ones [45,85]. Other authors found no statistical difference in anastomotic leak rate between consultants, trainee surgeons and independent surgeons [53].
Hospital's volume	A Cochrane review analysed the effect of hospital volume, surgeon's specialty, and surgeon's experience on outcomes following colorectal surgery. 5-year survival was significantly improved for colorectal cancer patients treated by high-volume surgeons, in high-volume hospitals, or by colorectal specialists. Hospital volume and surgeon's specialty had no effect on the AL rate, surgeon's volume was associated with a lower number of AL (relative risk 0.68) [61].
Antibiotic prophylaxis	Data from registry analysis show a beneficial effect of local antimicrobial administration on AL [62]. Local decontamination with polymyxin, tobramycin, vancomycin, and amphotericin B appears safe and effective in the prevention of AL in rectal cancer surgery [63].
Duration of surgery	Operative time longer than 3 h has also been described in the literature as being associated with an increased incidence of AL [67,84,91].
Protective ostomy	Constructing a protective ileostomy or colostomy after low anterior resection remains a subject of debate [108]. There are studies and meta-analyses that showed a decreased AL rate when surgeons used a defunctioning stoma in low anterior resection by diverting the fecal stream and reducing the intraluminal pressure of the bowel [49,56]. In a multicenter prospective study including rectal cancer patients with anastomoses below 8 cm, AL rate was 5.8% in the stoma group and 16.3% in the no stoma group [56].
Use of drain	The role of prophylactic pelvic drainage in reducing the postoperative complication rate after rectal surgery remains controversial. The role of pelvic drainage in reducing the incidence of AL and pelvic sepsis has been sustained by some authors [43,54]. A recent meta-analysis concluded that prophylactic use of pelvic drainage after extraperitoneal colorectal anastomosis has no impact on the incidence of AL (AL rate of 14.8% in the drain group and 16.7% in the no-drain group, P = 0.37) [48]. A meta-analysis by

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Table 3 (*continued*)

Factor	
Vascularization	Guerra et al. [44] suggests that pelvic drainage does not confer any significant advantage in the prevention of postoperative complications and may even add to the postoperative morbidity of patients receiving rectal surgery with extraperitoneal anastomoses. Proper vascularization of digestive segments involved in anastomosis is an important factor that can determine healing on the digestive suture. Measuring colonic blood flow by a laser-Doppler flowmetry technique before bowel manipulation and after vascular ligation and transection, it has been observed a significant difference ($P < 0.001$) in mean rectal stump flow reduction after colonic division of 16% in patients who developed AL compared with 6.2% in patients without dehiscence [86].

intraoperative methods to assess anastomotic blood perfusion in colorectal surgery leads to a significant reduction in AL and in the need for surgical reintervention for AL, especially in patients with low or ultra-low rectal resection [136].

6. Postoperative diagnosis

AL has a wide range of clinical features ranging from a radiological only finding to systemic symptoms (e.g., accelerated heart rate, tachypnea and oliguria), peritonitis, and sepsis with multiple organ failure. AL may present abruptly and with very clear clinical signs not requiring diagnostic imaging. Most patients, however, show more subtle and confusing symptoms. Most AL usually become apparent between five and seven days postoperatively. One study reported that almost one half of all leaks occur after the patient discharge, and up to 12% occur after postoperative day 30.

Most reports define AL using clinical signs, radiographic findings, and intraoperative findings [8,40,66,137]. An early detection of clinical signs such as increase of drainage output, change in the quality of the output, prolonged ileus, abdominal pain, fever, leucocytosis and anal discharge of pus, should raise suspicions of early AL and call for treatment in the following 24 h in order to avoid a worsening of the prognosis. However, clinical signs of AL are usually uncommon before the fifth post-operative day.

Over the years many risk factors have been identified (distance of anastomosis from the anal verge, gender, BMI, ASA score) but none of these allow an early diagnosis of AL. Early identification of high risk patients would help to reduce the morbidity and mortality associated with this potentially fatal complication by prompting earlier investigation and intervention.

The DUtch LeaKage (DULK) score, serum C-reactive protein and procalcitonin have been identified as early predictors for AL starting from postoperative day 2–3 [66,138]. Serum C-reactive protein levels are routinely assessed to provide information on postoperative complications. Its use in colorectal cancer surgery is still controversial, with studies demonstrating poor specificity of C-reactive protein for AL diagnosis, with levels becoming significantly raised only when symptoms become apparent [139,140]. Several other studies highlighted that procalcitonin and C-reactive protein are both reliable predictors of major AL after colorectal resection, although procalcitonin is more accurate [141–144]. Raised procalcitonin and C-reactive protein serum concentration on postoperative days 3–5 warrant a careful evaluation of the patient before discharge [145,146]. The role of C-reactive protein in the early identification of a suspected AL was reiterated in a recent Consensus Conference (Table 4) [137].

Recently, several nomograms were constructed to predict AL [147,148]. In a study enrolling 736 consecutive patients who underwent laparoscopic resection without a diverting stoma for rectal adenocarcinoma, personalized risk was calculated and surgical strategies were monitored using risk-adjusted cumulative sum (RA-CUSUM) analysis

Table 4
Recommendations on the diagnosis, and the treatment of anastomotic leakage (AL).

Category	Recommendations
Clinical parameters	Tachycardia, clinical deterioration, abdominal pain, discharge from abdominal drain, discharge from rectum, rectovaginal fistula and anastomotic defect found by digital examination contribute to the suspicion of AL
Laboratory tests	C-reactive protein and the combination of C-reactive protein and leucocytosis contribute to the suspicion of AL; Procalcitonin elevation contribute to the suspicion of AL
Radiological findings	Extravasation of endoluminal administrated contrast, collection around the anastomosis, presacral abscess near anastomosis, perianastomotic air and free intra-abdominal air are defined as AL on CT-scan
Finding during reoperation	Necrosis of anastomosis, necrosis of blind loop, signs of peritonitis and dehiscence of anastomosis are defined as AL during reoperation
Grading systems	Both the ISREC classification [40] and Clavien-Dindo classification [187] are suitable
Timing	Distinction between early and late anastomosis should be made; no fixed range of days in which AL can occur to define it as AL
Colon/rectum	Colon and rectum should be seen as separate entities

Modified from van Helsdingen et al. [137].

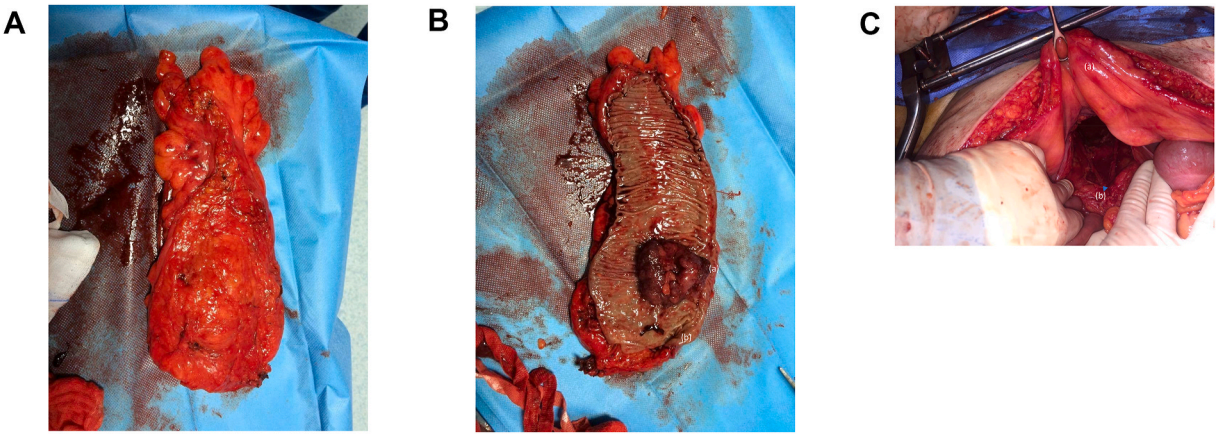

Fig. 1. A. Surgical specimen of an anterior resection of the rectum with total excision of the mesorectum; B. Same case as the previous photo. The rectal tumour is highlighted (a) with adequate and appropriate free resection margins (b). C. Intraoperative photo of pelvis at the end of anterior rectal resection. (a) Bladder. The sparing of the nerve structures (b) of the pelvis is apparent. (Personal observations - surgery performed by two senior surgeons CMM and BG).

[148]. Clinical AL occurred in 65 patients (8.8%). Sex, ASA score, operation time, blood transfusions and tumour location were identified as significant risk factors for AL. Based on these, a nomogram was created to predict AL (Fig. 2), with a concordance index (C-index) of 0.753 (95% confidence interval, 0.690–0.816). A calibration plot showed good statistical performance on internal validation (bias-corrected C-index of 0.742) [148].

However, although an early diagnosis of AL is the key point in reducing its clinical consequences, in daily practice this often happens late. To date, the diagnostic methods that are commonly used when a leakage is suspected are CT-scan, contrast enema, endoscopic examination, and reoperation. The preferred imaging tool for the detection of AL is abdominal CT-scan as it provides a more precise image of the anastomosis (Fig. 3) and perianastomotic structures (Fig. 4). In addition, CT-scan may also be useful in detecting other postoperative sequelae such as intra-abdominal abscesses or hematomas mimicking the symptoms of leakage, but the accuracy reported in the diagnosis of AL after colorectal surgery remains suboptimal [149–151]. For instance, the lowest sensitivity of CT-scan (0.15) was observed in a study by Nicksa et al. [149] who used strict criteria to define AL; after reviewing their "negative CT-scans" when using other criteria for AL (large amounts of fluid or air in the peritoneal cavity but without extravasation of contrast), their sensitivity of CT-scan increased and tripled up to 0.48. Therefore, a plea could be made for an update of the standardized definition for AL using well-defined clinical and radiological criteria.

Fig. 3. Postoperative CT-scan documenting interruption of the colorectal suture in anterior resection of the rectum for carcinoma.

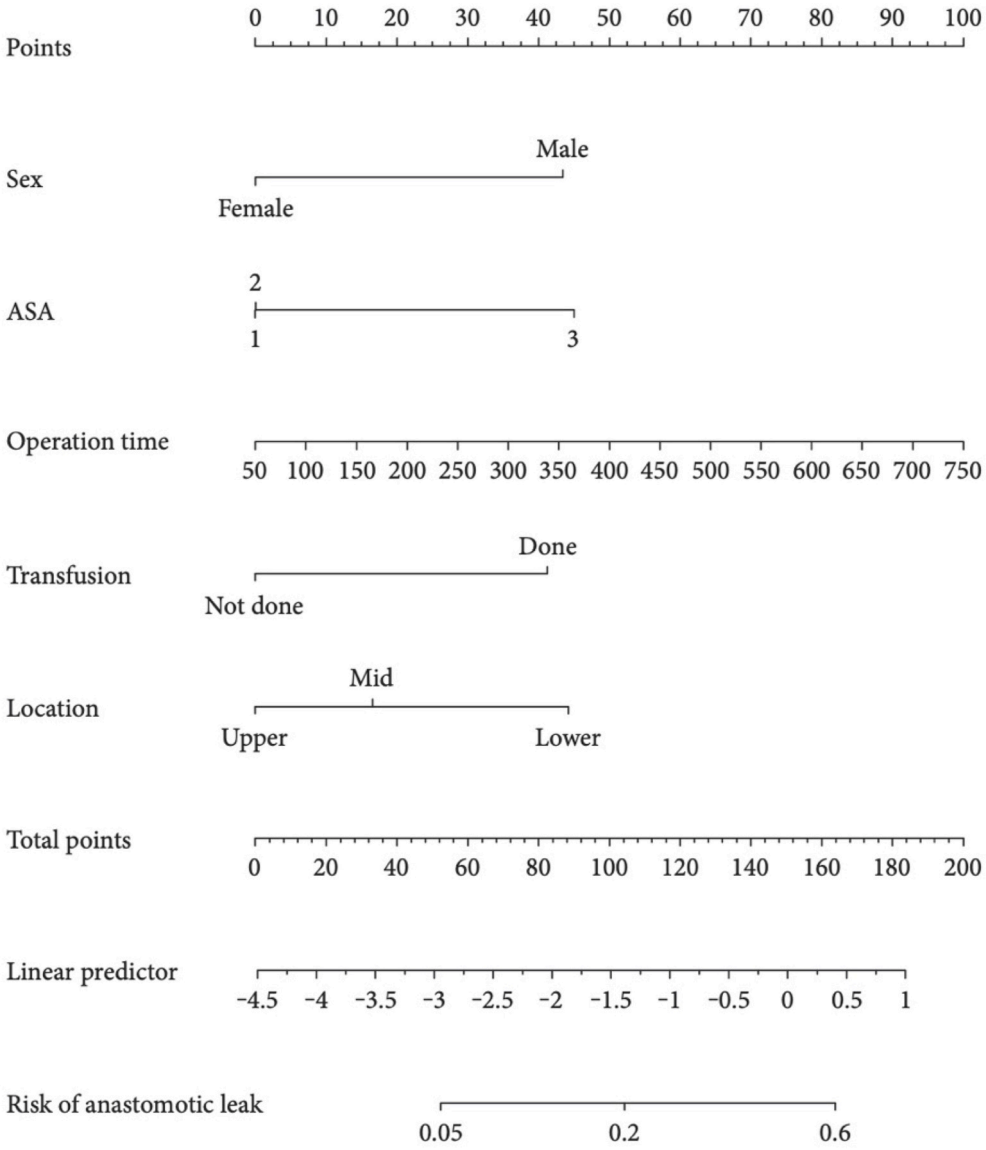

Fig. 2. Nomogram for predicting AL risk in laparoscopic resections of the rectum. Modified from Kim et al. [148].

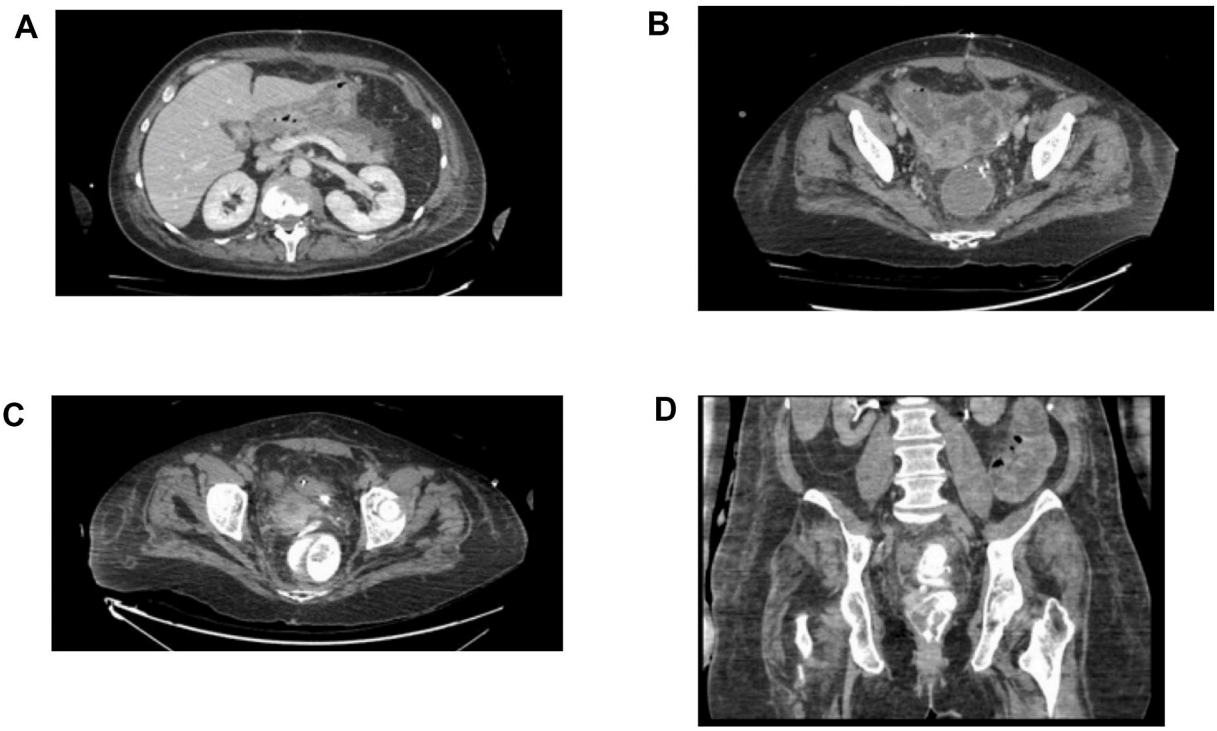

Fig. 4. A. CT-scan documenting peripancreatic collection (indirect sign of AL in a patient with dissection of the splenic flexure). B. Same case. Collection close to the colorectal anastomosis. C. CT-scan with contrast enema. The leakage of the contrast is highlighted with an initial opacification of the drainage. D. Longitudinal reconstruction of previous CT-scan.

The timing of imaging may influence the accuracy in detecting AL because, in the very early postoperative period, many obstacles to the accurate interpretation of CT-scan are present, since extravasated contrast material from the intestinal lumen into the abdomen is not always observed and similarities in CT data between patients with and without AL have also been documented [152]. A study shows an overall sensitivity of 0.59 (95% CI 0.43–0.73), a specificity of 0.88 (95% CI 0.75–0.95), positive predictive value 0.82 (95% CI 0.64–0.92), negative predictive value 0.70 (95% CI 0.57–0.81), and an accuracy of 74% of abdominal CT scan performed in patients with suspected AL [150]. In the study, a delayed reintervention for AL due to a false-negative CT outcome resulted in death in 62.5% of the patients [150].

Some studies show that contrast leakage is a strong predictor of AL when using CT imaging after colorectal surgery, even if some others underlined that contrast medium did not reach the anastomosis in more than half of considered patients.

7. The role of diverting ostomy

A diverting stoma ideally protects a low colorectal anastomosis. It is commonly fashioned through a transverse colostomy or a loop ileostomy. However, in literature, the routine use and the actual role of a protective stoma after colorectal resection is still strongly debated. Further controversy exists regarding the most optimal type of ostomy, either an ileostomy or a colostomy [72]. It has been argued that colostomies are associated with a higher infection rate than ileostomies. In contrast ileostomies have been shown to lose more fluid and electrolytes than colostomies [153]. Cochrane systematic review comparing the ileostomy and colostomy for temporary decompression of left-sided colorectal anastomosis revealed no difference in AL, reoperation rate, wound infection and mortality [72]. Although stoma prolapse was more frequent in the colostomy group, this minor complication did not provide enough evidence to recommend one ostomy type over the other [154].

Some authors report a reduction in the rate of dehiscence and re-interventions in patients with a protective ileostomy, others do not consider ostomy as a crucial factor in reducing the rate of AL [91,155]. Ostomy is useful to reduce clinical symptoms of AL by increasing the percentage of sub-clinical dehiscence, not changing the total percentage. The presence of a stoma is thought to mitigate the consequences of AL, and the ostomies are suitable for reversal once the integrity and patency of the anastomosis are confirmed by appropriate investigations. A recent metanalysis by Ahmad et al. conclude that the incidence of AL was significantly higher in the group not covered with a stoma than in the stoma-covered group, but the quality of the included RCTs may limit the clinical implications of this finding [156].

Moreover, some large-volume studies have failed to show a significant benefit of a diverting stoma in reducing the risk of AL. There is a general trend to defunction the patients who received neoadjuvant radiotherapy and those with an anastomosis closer to the anal margin. This dogma has been challenged in recent years with many authors questioning the need and perceived benefits of diversion for all patients with a low pelvic anastomosis. As now, the evidence in the literature suggests that the presence of a diverting stoma could lessen the magnitude of sepsis and morbidity that occurs if a leak does indeed develop. Some studies recommend routine use of diverting stomas. Poon et al. evaluated 148 patients and found a 3.3% rate of AL with stoma vs. 12.6% without a stoma [157]. In a large retrospective, multicentre Dutch TME trial of 924 patients, the presence of a pelvic drain and the presence of a diverting stoma decreased AL rates ($P < 0.01$) [158]. Huser et al. also performed a meta-analysis of randomized prospective studies on diverting ileostomy, which revealed a significantly lower risk of AL ($Z = 3.65$, $P < 0.01$) and lower risk of reoperation ($Z = 3.95$, $P < 0.01$) in the stoma group [159]. However, the mortality between the two groups was comparable ($Z = 0.05$, $P = 0.9$). These results were validated by a more recent Cochrane meta-analysis of more RCTs by Montedori et al. [160] of a total of six RCTs that included 332 patients in the stoma group vs. 316 in the no diversion group. The pooled analysis showed that the use of a diverting stoma resulted in less AL (relative risk (RR) 0.33; 95% confidence interval (CI) = 0.21–0.53) and less urgent reoperation (RR

0.23; 95% CI = 0.12–0.42) with no significant difference in mortality (RR 0.58; 95% CI = 0.14–2.33). On the other hand, Gastinger et al. [161] performed a retrospective multicentre study on a total of 2,729 patients where 881 received a stoma and 1,848 did not. They found no difference in overall AL rates between the two groups but did find a significantly lower reintervention rate in those patients who had a protective stoma ($P < 0.01$). Retrospective single-centre analysis of 249 patients by Leester et al. [162] and 272 patients by Rullier et al. [163] showed that a diverting stoma did not prevent AL and recommended against its routine use. Similarly, Karanja et al. [164] performed a retrospective single-centre study that evaluated 219 patients with 157 receiving a stoma. They found similar leak rates in patients who were diverted vs. those that were not. Fielding et al. [165] who evaluated 2, 057 patients found a higher leak rate with the stoma group (18 vs. 7%, $P < 0.01$). They suggested that surgeons with low individual AL rates do not need to resort to diversion. Enker et al. [166] performed a retrospective single-centre study on 681 patients and showed no reduction of AL rates in patients with stoma that underwent a low or ultra-low anterior resection. These findings were similar in a large multicentre retrospective Swedish study by Matthiessen et al. who randomly sampled 432 out of 6,833 patients for diversion but found no significant difference in AL rate (15% in stoma group vs. 12% in no stoma group) [167]. A retrospective, single-centre comparative study by Dehni et al. [168] showed a clinical leak rate of 6%with diverting stoma vs. 17% without after examining 258 consecutive cases. In conclusion, despite the potential benefits of faecal diversion for many patients undergoing colorectal surgery, the routine of an abdominal stoma while common remains fraught with complications and should not be considered trivial. However, it has been established that the septic consequences of a leak are lessened by use of a diverting stoma.

8. Treatment

AL continues to be a dreaded complication after colorectal surgery, especially in the low colorectal or coloanal anastomoses. However, there has been no consensus on the management of the colorectal AL. Disparities in treatment may result from the varying definitions of AL. In addition, the presence or absence of a diverting stoma may change the treatment algorithm as well. The management of AL has typically been surgical, with resection of the leaking anastomosis and creation of a diverting stoma. Today, however, based on the patient's presentation and the timing of the leak, there has been a gradual shift to a more conservative management, keeping surgery as the last option [156,159, 169].

Blumetti et al. showed in their study that the majority of patients do not require surgery for management of the leak and 73% of patients underwent nonoperative management [170]. Reasons for failure of nonoperative management cited in the literature include large, loculated or multiple abscesses, fistulas, and high APACHE-II scores. So, the management of the leaking low colorectal anastomosis has changed over the past several decades. Many new techniques are now available, with the goal being preservation of the anastomosis and restoration of gastrointestinal continuity with good functional outcome [171].

Patients with general peritonitis require a laparotomy (Fig. 5) and resection of the anastomosis with exteriorization of the proximal limb as an end colostomy (Hartmann's procedure). This removes the source of sepsis, but in the majority of cases, leaves the patient with a permanent stoma, with less than 50% of patients ultimately undergoing reversal. This is true above all for intraperitoneal anastomoses that have higher rates of resection compared to extraperitoneal leaks. The lowered colon ischemia, secondary to inappropriate ligation of the inferior mesenteric artery at the origin in patients undergoing anterior resection, is a further indication for early reintervention by laparotomy (Fig. 6).

In case of dehiscence of the extraperitoneal anastomosis, many authors suggest the "divert and drain" technique consisting of proximal faecal diversion with loop ileostomy, and drain placement into the pelvis, without manipulation of the pelvic anastomosis. This avoids the dangers of reoperation in an acutely inflamed field in a compromised patient. When a surgical procedure is needed to treat AL, Edden and Weiss suggest the following principles: "(1) Minimizing the extent of surgical intervention; (2) Shortening the procedure as much as possible; (3) Adequate abdominal washout; (4) Proximal faecal diversion should be favourably considered preoperatively with relevant actions such as stoma markings" [172]. A review of Fransvea et al. suggest that for those patients whose initial surgery was performed laparoscopically, a laparoscopic approach to reoperation may be performed safely at the

Fig. 5. Intraoperative photo. Abscess that is drained in AL peritonitis after anterior resection of the rectum. (Personal observations - surgery performed by two senior surgeons CMM and BG).

Fig. 6. Intraoperative photo. Ischemia of the lowered colon in a patient undergoing low anterior resection for rectal cancer. (Personal observations - surgery performed by two senior surgeons CMM and BG).

discretion of the operating surgeon. Moreover, laparoscopic reintervention can be a useful tool to achieve an early diagnosis of post-operative complications such as AL [173]. In a study by Boyce et al. concerning patients who returned to the operating room with a leak after an initial laparoscopic procedure, additional laparoscopic access to the peritoneal cavity was achieved successfully in 18 out of 28 cases (64.3%) and conversion to laparotomy was necessary in 7 cases only [174]. Marano et al. in their study showed that laparoscopic reintervention had been successfully carried out in 18/20 patients (90%) [175]. In the study of Cuccurullo et al. five patients out of 79 that underwent laparoscopic reintervention needed conversion to open surgery but no significant intra-abdominal complications were observed [176].

Reoperation for control of sepsis is rarely necessary in those patients who already have a diverting stoma at the time of the leak, especially with an extraperitoneal anastomosis. In these patients, and in those without a stoma who do not require abdominal reoperation for a contained pelvic leak, there are several treatment options, including laparoscopic diverting ileostomy combined with *trans*-anal anastomotic tube drainage, percutaneous drainage or recently developed endoscopic procedures, including stent or clip placement or endoluminal vacuum-assisted therapy. Endoscopic clip placement has been described for small defects and acute leaks. The procedure should be considered as an alternative option for the treatment of an AL in cases where conservative treatment failed [177,178]. Endoscopic therapy in selected patients is associated with high rates of technical success. Challenges remain in selecting the patients, the most appropriate strategy, and understanding the functional and long-term sequelae of this approach [179]. Further evidence from large cohort studies is needed to further evaluate the role of this therapy.

Self-expanding metal stents have been considered for the treatment of AL, placing the stent across the defect to prevent communication between the lumen and extraluminal space to protect the patient from sepsis during tissue growth [180]. The placement of covered stents provides a feasible, relatively low risk alternative to immediate surgical intervention [179]. Their use is not suitable, however, for those patients with systemic sepsis, or for an anastomosis encroaching on the anal verge. A systematic review of the use of stents for colorectal anastomotic complications including was published by Arezzo et al. [180]. Indications for stent placement included only 18 patients with AL. The overall estimated early success rate was reported as 73.3%, with 9.3% of patients requiring surgical intervention. The rate of persisting dehiscence was 25.5%. Self-expanding metal stents could be considered in the early post-operative management of AL in patients who have minimal risk of sepsis, although safety and efficacy needed to be further established.

The use of fibrin glue in colorectal AL has been reported with varying success. Its role appears to be most suitable in patients with small defects, or in combination with other treatments such as vacuum therapy [181].

Endoluminal vacuum-assisted therapy is performed by placing an open-pored polyurethane sponge in the leakage cavity through the anastomotic defect by a flexible endoscope. This treatment carries the benefits of being a less invasive approach, ensuring continuous drainage, and promoting granulation, increasing vascularity and mechanical reduction in the size of the abscess cavity [182–184]. Indications for the Endo-sponge are low, extraperitoneal leaks that are difficult to drain. The disadvantage is that the sponge must be frequently changed in the endoscopic suite, typically 8 to 10 changes over 4 weeks although sometimes longer. Complications are anastomotic necrosis and stricture. In conclusion, giving that there is no universally accepted management flowchart for AL treatment, this complication should be individualized based on the patient's general condition, anastomotic defect size and location, indication for primary resection and the presence of a proximal stoma. Non-operative management is usually preferred in patients who underwent proximal faecal diversion at the initial operation. Factors associated with failure of endoluminal vacuum-assisted therapy include neoadjuvant therapy, lack of a protective stoma before treatment, complications related to endoluminal devices and male sex. Most of these are well known risk factors for AL in general. The timing of endoluminal vacuum-assisted therapy can significantly influence success. Weidenhagen et al. [181] reported a high success rate when endoluminal therapy was started within 6 weeks of the initial operation. These results were replicated by van Koperen et al. [185] and Riss et al. [186] assessed the long-term results after primary successful endoluminal vacuum-assisted therapy in a multicentre study and found that 25% of patients developed recurrent abscesses after median follow-up of 17 months. Oncological and functional outcomes must be investigated further.

9. Conclusion

Hopefully, a surgical technology allowing surgeons to decrease the incidence of AL is going to be developed. In the meantime, the importance of AL has to be kept in mind, with the need for a prompt diagnosis and the knowledge of all possible treatment options, from the least to the most invasive in order to improve patient's outcomes in both surgical and oncological terms.

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Ethical approval

The study was a review of opinion in which we did not modify the usual treatment of this disease, so disclosures about human research (in the sense of clinical trial) are not applicable.

Author contributions

Chiarello MM and Fransvea P equally contributed in the drafting of the manuscript and must both be considered first author; Chiarello MM and Brisinda G conceived the original idea; Fransvea P, Cariati M and Bianchi V performed a comprehensive review of all available literature, and summarized the data; Brisinda G and Chiarello MM meet the criteria for authorship established by the International Committee of Medical Journal Editors and verify the validity of the results reported; Adams NJ proofread for appropriate English language usage, grammar, punctuation, and spelling. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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