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NEW TECHNOLOGY

Evaluation of the SafeHeal Colovac+ anastomosis protection device after low anterior resection for rectal cancer: the safe anastomosis feasibility evaluation (SAFE) 2019 trial

Nicolas De Hous[1] · Antonio D'Urso[2] · Guy-Bernard Cadière[3] · Benjamin Cadière[3] · Philippe Rouanet[4] · Niels Komen[1,5] · Jérémie H. Lefevre[6]

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Abstract

Background Protective ileostomy (PI) is the current standard of care to protect the anastomosis after low anterior resection (LAR) for rectal cancer, but is associated with significant morbidity. Colovac is an anastomosis protection device designed to shield the anastomosis from fecal content. A second version (Colovac+) was developed to limit the migration risk during the implantation period. The objective of this clinical trial was to evaluate the preliminary efficacy and safety of the Colovac+.

Methods This was a prospective, multicenter, pilot study aiming to enroll 15 patients undergoing LAR with Colovac+ placement. After 10 days, a CT scan was performed to evaluate the anastomosis and the Colovac+ was retrieved endoscopically. During the 10-day implantation and 3-month follow-up period, we collected data regarding predefined efficacy and safety endpoints. The primary endpoint was the rate of major (Clavien-Dindo III–V) postoperative complications related to the Colovac+ or LAR procedure.

Results A total of 25 patients were included (68% male), of whom 15 were consecutively treated with the Colovac+ and Vacuum Loss Alert System. The Colovac+ was successfully implanted in all 15 patients. No major discomfort was reported during the implantation period. The endoscopic retrieval was performed in 14/15 (93%) patients. The overall major postoperative morbidity rate was 40%, but none of the reported complications were related to the Colovac+. A device migration occurred in 2 (13%) patients, but these were not associated with AL or stoma conversion. Overall, Colovac+ provided effective fecal diversion in all 15 patients and was able to avoid the PI in 11/15 (73%) patients.

Conclusions Colovac+ provides a safe and effective protection of the anastomosis after LAR, and avoids the PI in the majority (73%) of patients. The improved design reduces the overall migration rate and limits the clinical impact of a migration.

Keywords Colovac · Low anterior resection · Rectal cancer · Protective ileostomy · Anastomosis protection device

Anastomotic leakage (AL) after low anterior resection (LAR) for rectal cancer is associated with increased morbidity, mortality and risk of permanent stoma [1, 2]. Protective ileostomy (PI) is the current standard of care to protect a low anastomosis and prevent the clinical consequences of AL [3–5]. The ileostomy, however, is associated with significant morbidity and requires a reversal procedure that is associated

Niels Komen and Jérémie H. Lefevre shared the senior authorship.

✉ Nicolas De Hous
nicolas.dehous@hotmail.com

[1] Department of Abdominal Surgery, Antwerp University Hospital (UZA), Edegem, Belgium

[2] Department of General, Digestive and Endocrine Surgery, Centre Hospitalier Régional et Universitaire (CHRU), Strasbourg, France

[3] Department of Digestive Surgery, Centre Hospitalier Universitaire (CHU) Saint-Pierre, Brussels, Belgium

[4] Department of Oncological Surgery, Institut du Cancer de Montpellier (ICM), Montpellier, France

[5] Antwerp Surgical Training, Anatomy and Research Centre (ASTARC), University of Antwerp, Edegem, Belgium

[6] Department of Digestive Surgery, Hôpital Saint-Antoine AP-HP, Sorbonne Université, Paris, France

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with complications as well [6, 7]. Therefore, avoidance of the PI could be a major benefit for these patients.

Recently, research has focused on anastomosis protection devices as an alternative to PI [8]. The Colovac Anastomosis Protection Device (SafeHeal SAS, Paris, France) is an intraluminal stent designed to shield the anastomosis from fecal content and prevent the clinical consequences of AL. A previous study with the first Colovac design demonstrated promising results [9]. Based on these initial data, a second version of the device (Colovac+) was developed to limit the migration risk during the implantation period. Colovac+ has recently been investigated in a preclinical study with excellent results in terms of safety, efficacy and device migration [10].

The objective of this second clinical study was to evaluate the preliminary efficacy and safety of the Colovac+ .

Methods

Study design

This was a pilot, prospective, multicenter, open-label, single-arm study aiming to enroll 15 patients undergoing LAR with total mesorectal excision (TME) for rectal cancer. The procedures were performed by experienced colorectal surgeons at 5 European tertiary centers: 2 in Belgium (UZA, Antwerp; CHU Saint-Pierre, Brussels) and 3 in France (CHRU, Strasbourg; ICM, Montpellier; Hôpital Saint-Antoine, Paris).

The study protocol was approved by the appropriate ethics committee and competent authorities. The study was registered online on the ClinicalTrials.gov website with the following identifier: NCT05180565. It was conducted in accordance with ISO standard 14155:2020 and the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 2013 and later revisions.

Study objectives and endpoints

The primary objective was to demonstrate the safety of the Colovac+ . Safety was assessed by recording all postoperative complications in terms of type, incidence, severity and relationship with the Colovac+ during the 3-month follow-up period. Complication severity was determined according to the Clavien-Dindo classification as either minor (grade I–II) or major (grade III–V) [11]. The primary endpoint was the rate of major postoperative complications related to the Colovac+ or LAR procedure.

The secondary endpoints regarding device efficacy and safety were the AL rate, PI avoidance rate, device migration rate, rate of patients with absence of feces between the sheath and colonic wall (before device retrieval), mucosal appearance of the anchoring site and anastomosis integrity after device retrieval, technical feasibility of device placement and retrieval, and patient tolerance of the device.

Patients

All patients who underwent LAR at the 5 participating centers and would otherwise receive a PI were considered for eligibility. The inclusion criteria were defined as follows: adult patients, eligible to undergo open or minimally invasive LAR with creation of a low (< 10 cm) anastomosis and planned PI for rectal cancer, and willing to comply with protocol-specific follow-up evaluations and sign a written informed consent. The exclusion criteria were defined as follows: inflammatory bowel disease, pregnant or nursing female patient, allergy to nickel or other Colovac+ components, concomitant major surgical procedure (e.g. hepatectomy), any medical condition increasing the risk associated with study participation (e.g. severe malnutrition), participation in another drug of medical device study, and intraoperative complications that preclude the patient from undergoing the Colovac+ procedure (e.g. bowel ischemia, blood loss, positive air leak test,…). Neoadjuvant therapy was not an exlusion criterion.

Investigational device

Colovac+ is designed to shield the anastomosis from fecal content after LAR [9]. It is a sterile, single-use, disposable intraluminal bypass device consisting of an introducer preloaded with the Colovac+ implant, and is positioned transanally (Fig. 1). The Colovac+ implant is composed of 2 elements: an anchor consisting of a covered double stent delimiting a vacuum chamber connected to 2 vacuum tubes, and a flexible cylindrical sheath attached to the anchor by 2 sealings rings, covering the anastomosis with appropriate length so that it protrudes about 5 cm outside the patient's anus. The negative pressure in the vacuum chamber is generated by 2 vacuum bottles connected to the tubes and sucks the colonic wall towards the stent, anchoring the Colovac+ in place.

The Vacuum Loss Alert System (VLAS) is an accessory device that can be used in conjunction with the Colovac+ (Fig. 1C). It is connected to the vacuum bottles and provides visual and auditory alerts when a bottle reaches a low vacuum level, allowing for continuous vacuum monitoring in the hospital room.

Device implantation procedure

Patients received a low-residue diet 2 days before surgery and mechanical bowel preparation (PEG based, 3–4 L) the day before surgery. The implantation procedure is identical

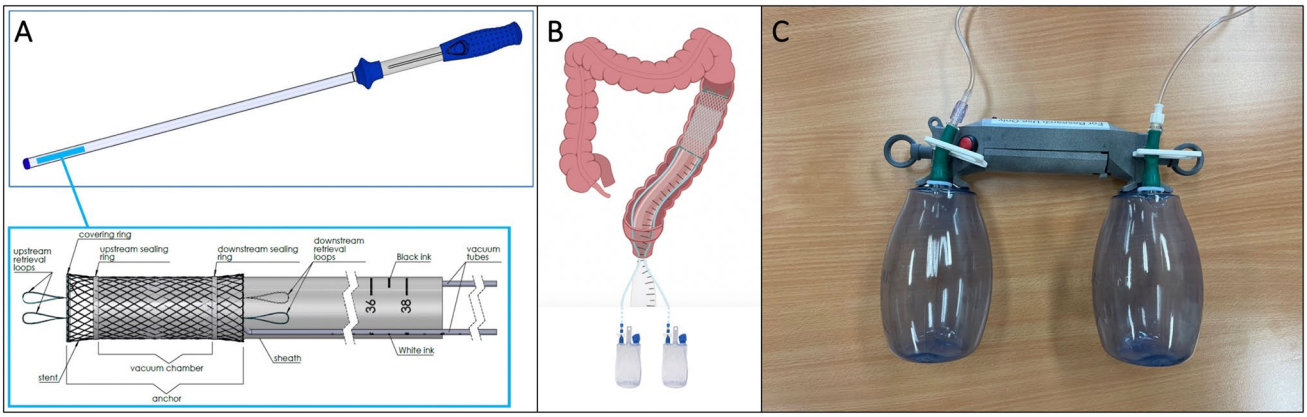

Fig. 1 The SafeHeal Colovac+ anastomosis protection device. **A** Detailed structure. **B** Device anchoring in the colon proximal to the anastomosis. **C** The SafeHeal vacuum loss alert system (VLAS) connected to the 2 vacuum bottles

to that of the first Colovac design [9]. The surgeon was asked to grade the technical ease using a 5-point Lickert scale ranked from 'very easy' to 'impossible'.

Postoperative course

The Colovac+ was left in situ for 10 days. All patients remained hospitalized and received a low-residue diet during the implantation period. Postoperative follow-up included daily clinical examinations, daily Colovac+ monitoring, and monitoring of C-reactive protein (CRP) levels on postoperative day (POD) 2, 4 and 6. Daily Colovac+ monitoring was done by checking the vacuum indicators of the bottles, presence of drainage fluid in the bottles, absence of blockage in the vacuum tubes, and length of the sheath protruding out of the anus. A clinically significant migration was defined as downstream movement of the entire stent to or below the sacral promontory (indicated by fluctuation in the length of the sheath and confirmed by radiological displacement) or as expulsion of the device, allowing fecal contents to reach the anastomosis. Patient tolerance during Colovac+ implantation was analyzed using 5-point Lickert scale ranked from 'no acceptance' to 'full acceptance'.

The day before Colovac+ retrieval, a CT scan with transanal contrast was performed to evaluate the anastomosis. The Colovac+ was retrieved on POD 10 during a colonoscopy in the operating room. First, the absence of feces between the sheath and colonic wall below the anchoring site was verified endoscopically. Next, the device was removed endoscopically through the anus by pulling on the retrieval loops located at both ends of the stent (Fig. 1). Immediately after device retrieval, an endoscopic evaluation of the anchoring site and anastomosis was performed. The surgeon was asked to grade the technical ease of the retrieval procedure using a 5-point Lickert scale ranked from 'very easy' to 'impossible'.

After hospital discharge, the patients received regular follow-up with clinical visits at 4, 6 weeks and 3 months postoperatively.

Results

Patient and surgical characteristics

Between December 2019 and November 2021, 25 patients were enrolled at the 5 participating sites (UZA, Antwerp, $n=8$; CHU St.-Pierre, Brussels, $n=8$; ICM, Montpellier, $n=3$; St.-Antoine Hospital, Paris, $n=3$; CHRU, Strasbourg, $n=3$). Patient and surgical characteristics are summarized in Table 1. Two patients were excluded after completion of the study due to major protocol deviations (insufficient bowel preparation and an intraoperative decision not to perform LAR).

The study was originally designed with a sample size of 15. However, after enrollment of the first 8 patients, the VLAS was introduced and used with the Colovac+ in the remaining 7 patients. To have a homogeneous cohort of 15 patients with the same treatment and avoid protocol violations, the overall sample size was increased to 25. The present paper reports on the 15 patients treated with the Colovac+ and VLAS.

Colovac+ implantation

The Colovac+ was successfully implanted in all 15 patients. The technical ease of the procedure was scored as 'very easy' or 'easy' by the surgeon in 13 (87%) patients (Table 2). For 2 (13%) patients, the procedure was rated as 'normal' indicating that it met the surgeon's expectations. The median duration of the implantation procedure was 7 (5–9) min.

Table 1 Patient and surgical characteristics

Item	Total cohort ($N=25$)
Gender, *n*/*N* (%)	
Male	17 (68.0)
Female	8 (32.0)
Age (years), median (IQR)	64 (57, 71)
BMI (kg/m^2), median (IQR)	24.8 (21.9, 26.1)
Clinical tumor stage, *n*/*N* (%)	
T1	3 (12.0)
T2	6 (24.0)
T3	12 (48.0)
T4	4 (16.0)
Tumor distance from anal margin (cm), median (IQR)	5 (2.5, 8)
Time from diagnosis to surgery (months), median (IQR)	6 (4, 12)
Neoadjuvant therapy, *n*/*N* (%)	
Chemotherapy only	2 (8.0)
Radiotherapy only	0 (0.0)
Chemoradiotherapy	16 (64.0)
None	7 (28.0)
Surgical approach, *n*/*N* (%)	
Laparoscopic	19 (76.0)
Robotic	6 (24.0)
Open	0 (0.0)
Anastomosis type, *n*/*N* (%)	$N=24$*
Colorectal	20 (83.3)
Coloanal	4 (16.7)
Anastomosis technique, *n*/*N* (%)	$N=24$*
End-to-end	17 (70.8)
Side-to-end	7 (29.2)
Stapled	18 (75.0)
Manual	6 (25.0)
Anastomosis distance from anal margin (cm), *n*/*N* (%)	$N=24$*
<5 cm	20 (83.3)
5–9 cm	4 (16.7)
Median (IQR)*	3 (2, 4)

*Missing data for 1 patient as no LAR was performed. This patient was eventually excluded due to a major protocol deviation

Colovac+ retrieval

The Colovac+ was removed endoscopically in 14 (93%) patients. In 1 patient, the device was removed manually during an early revision procedure for AL (see below). Consequently, the planned endoscopic evaluations of the anastomosis, Colovac+ anchoring site and space between the colonic wall and sheath could not be performed in this patient.

The technical ease of the retrieval procedure was rated as 'very easy' or 'easy' in 11/14 (79%) patients (Table 2). For 2 (14%) patients, the procedure was rated as 'normal' indicating that it met the clinician's expectations. In 1 (7%) patient, the retrieval procedure was rated as 'difficult' but the device was successfully removed. The median duration of the retrieval procedure was 20 (12–24) min.

The absence of feces between the colonic wall and sheath below the Colovac+ anchoring site was confirmed endoscopically in all patients. The endoscopic appearance of the anchoring site was rated as normal (5/14, 36%) or inflammatory (9/14, 64%) in all cases. None of the patients demonstrated bleeding lesions, ulcerations or perforations. The endoscopic appearance of the anastomosis after Colovac+ retrieval was rated as normal in 10/14 (71%) and ulcerative (minor lesions) in 2/14 (5%) patients. The remaining 2 (5%) anastomoses demonstrated partial dehiscence (see below).

Table 2 Technical ease of the Colovac+ procedure and patient tolerance

Colovac+ implantation		*N* = 15
Technical ease, *n*/*N* (%)		
Very easy		9 (60)
Easy		4 (26.7)
Normal		2 (13.3)
Difficult		0 (0.0)
Impossible		0 (0.0)
Colovac+ retrieval		*N* = 14*
Technical ease, *n*/*N* (%)		
Very easy		5 (35.7)
Easy		6 (42.9)
Normal		2 (14.3)
Difficult		1 (7.1)
Impossible		0 (0.0)
Patient tolerance	7 days	10 days
Presence of redon bottles, *n*/*N* (%)	*N* = 12**	*N* = 12**
1 (full acceptance)	9 (75.0%)	4 (33.3%)
2	2 (16.7%)	7 (58.3%)
3	1 (8.3%)	1 (8.3%)
4	0 (0.0%)	0 (0.0%)
5 (No acceptance)	0 (0.0%)	0 (0.0%)
Presence of vacuum tubes through the anus, *n*/*N* (%)	*N* = 12**	*N* = 12**
1 (full acceptance)	5 (41.7%)	3 (25.0%)
2	5 (41.7%)	3 (25.0%)
3	1 (8.3%)	3 (25.0%)
4	1 (8.3%)	1 (8.3%)
5 (No acceptance)	0 (0.0%)	0 (0.0%)

*Missing data for 1 patient as Colovac + were removed manually in the operating room without access to endoscopic evaluation

**Missing data: questionnaires have not been fully filled by all patients

Device migration

A clinically significant migration was observed in 2 (13%) patients (Fig. 2). Both migrations were radiologically confirmed and the stents were positioned close to the sacral promontory. In both cases, the Colovac+ was retrieved endoscopically without stoma creation as anastomotic healing was satisfactory. The first patient had a migration on POD 6 with an uneventful postoperative course until he was readmitted on POD 20 (see below). This migration was probably due to stool accumulation near the stent as this patient had not received the required low-residue diet or laxatives during the implantation period. The second migration was observed on POD 8. The cause of the migration remained unclear. This patient had an uneventful course after the retrieval procedure.

Patient tolerance

The Colovac+ was well tolerated by the 12 patients that completed the questionnaires (Table 2). Both at 7 and 10 days after implantation, 11/12 (92%) patients reported a high level of acceptance (1 or 2) of the vacuum system. At 7 days, 11/12 (92%) patients and at 10 days, 9/12 (75%) patients reported good acceptance (1, 2 or 3) of the vacuum tubes.

Postoperative morbidity

The overall postoperative morbidity rate was 60% (15 postoperative complications established in 9 patients) with a major (Clavien-Dindo III–V) morbidity rate of 40%. Details are presented in Table 3. None of the reported complications

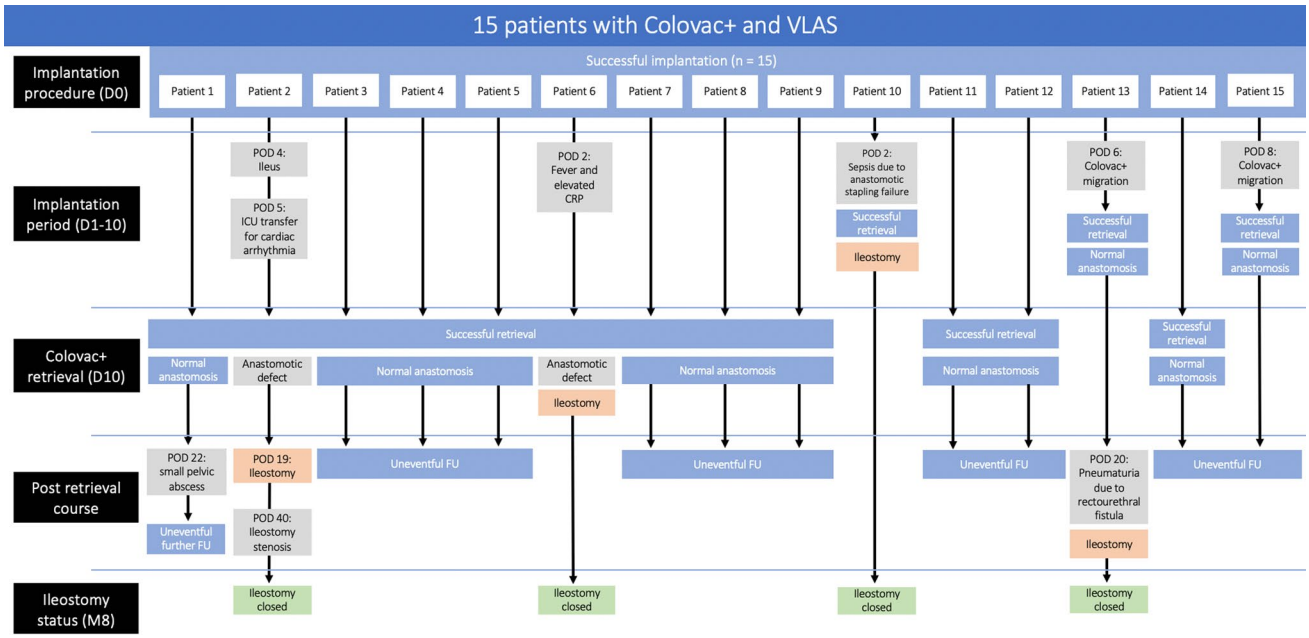

Fig. 2 Postoperative course

Table 3 Postoperative morbidity during Colovac+ implantation and follow-up

Postoperative complication, *n*/*N* (%)	Colovac+ implantation	6 weeks	3 months
Major			
Early AL	3 (21.4)		
Cardiac arrhythmia	1 (7.1)		
Late AL		1 (7.1)	
Ileostomy stenosis		1 (7.1)	
Minor			
Postoperative ileus	2 (14.2)		
Small pelvic abscess		1 (7.1)	
Urinary tract infection		1 (7.1)	2 (14.2)
Low anterior resection syndrome (LARS)		2 (14.2)	
Atrial fibrillation		1 (7.1)	

were related to the Colovac+ or the implantation and retrieval procedures (as determined by the Data and Safety Monitoring Board). The median length of hospital stay after LAR surgery was 13 (12, 16) days.

Four (27%) patients had an anastomotic defect requiring stoma conversion during the course of the study (Fig. 2). Patient 2 was diagnosed with an asymptomatic blind fistula during planned Colovac+ retrieval for which no treatment was initiated. Nevertheless, a PI was created 1 week later due to other medical reasons. Patient 6 presented with fever and elevated CRP levels on POD 2. An early leak was not expected because of the spontaneous decrease of CRP levels during the following days. During Colovac+ retrieval, a small anastomotic defect was established and the patient was immediately converted to PI. Patient 10 presented with an early leak and sepsis due to anastomotic stapling failure on POD 2 and was converted to PI on the same day. The stapling donuts were described as relatively thin by the surgeon. Patient 13 presented with a rectourethral fistula 20 days after surgery and was also converted to PI.

Patient 1 was diagnosed with a small pelvic abscess 22 days after surgery without radiological signs of AL and was treated with antibiotics alone.

Overall, Colovac+ provided effective fecal diversion in all 15 patients during the 10-day implantation period and was able to avoid the PI in 11/15 (73%) patients (Fig. 2). All ileostomies had been reversed within 8 months after surgery.

Discussion

A pilot study with the initial Colovac design already showed promising results: effective fecal diversion was observed in 100% of cases and the PI was avoided in 67% of patients [9]. A limiting factor was device migration from the anchoring site downstream in the colonic lumen, potentially leading to an unprotected anastomosis. Of the 15 implanted devices, 3 (20%) migrated before the end of the implantation period. Two migrations were attributed to a vacuum defect, and 1 was caused by device misplacement during implantation.

In response to these results, a second version of the device (Colovac +) was developed with technical changes in order to limit the migration risk and facilitate the early detection of migration [10]. These changes include modifying the anchor to an overlapping configuration of 2 stents to create additional passages for air evacuation when the vacuum is applied, adding a second vacuum tube and bottle, and use of the VLAS accessory to provide continuous vacuum monitoring.

In the present study with the Colovac+ , 2 (13%) of the 15 implanted devices migrated. None of these migrations were associated with AL or stoma conversion during Colovac+ implantation. In contrast, the 3 migrations in the first Colovac study were all associated with AL and stoma conversion. The limited clinical impact of the Colovac+ migrations can be attributed to the improved design. The reinforced vacuum anchor reduces the tendency of the device to migrate. The improved detection of migration allows a rapid device retrieval with verification of the anastomosis, preventing a migration from manifesting itself clinically in case anastomotic healing is incomplete.

The present study demonstrated that the Colovac+ is an effective measure to protect a low anastomosis and is able to avoid the creation of a PI in the majority (73%) of patients that would otherwise receive an ileostomy per standard of care. Effective fecal diversion with the Colovac+ was observed in 100% of cases. Of the 3 (20%) patients diagnosed with AL during Colovac+ implantation, only 1 (7%) was symptomatic. These results are comparable to those of randomized studies with the PI, although our study population is small and there are few published studies on this subject [12]. It is important to remind that the objective of preventive measures after LAR, such as the PI and Colovac, is to prevent the clinical consequences of AL, and not to reduce the overall leakage rate (including grade A, radiological leaks) [13].

There are several studies describing the occurrence of late AL after early closure of the PI. Some studies report leakage rates between 1 and 4% after early (between 7 and 14 days) stoma closure [14, 15]. Nelson et al. reported an intra-abdominal collection rate of 14% after early (between 14 and 28 days) stoma closure [16]. Similarly, it is anticipated that some patients will demonstrate late AL after Colovac+ retrieval regardless of the device's efficacy at protecting the anastomosis. In the present study, there was 1 patient presenting with a rectourethral fistula 20 days after surgery. In such cases, creation of a PI can still be performed—and is required—to provide long-term anastomosis protection. One of our patients presented with a small pelvic abscess 3 weeks after surgery, but this was not considered as a leak because the CT scan showed no anastomotic fistula or luminal contrast extravasation.

Regarding technical feasibility, this study showed that both the implantation and retrieval procedures are feasible and safe. There was no anastomotic trauma or collateral damage to the colonic wall, except for minor inflammatory changes at the anchoring site after device retrieval. The short and consistent procedural times signify the simplicity of the Colovac+ procedure, especially because 5 different clinicians placed and retrieved the devices. In 1 case, Colovac+ retrieval was more difficult and took more time. This can be attributed to the learning curve effect, since colonic stent removal is not routinely performed in the standard practice [9].

Furthermore, this study also confirmed that the Colovac+ is well tolerated by patients. Limited discomfort related to the presence of the vacuum tubes and sheath through the anus was reported during the implantation period. However, this can be easily counterbalanced by the discomfort associated with the PI that is present for a much longer time. For the purpose of the study, patients were not discharged before the end of the Colovac+ implantation period.

There are some limitations to this study. The study population is small and consists of convenient rectal cancer patients treated at 5 expert centers. The results may not be generalizable to all rectal cancer patients and other centers. Furthermore, there was no direct comparison between the Colovac+ and PI. More research is needed to confirm our preliminary results and demonstrate the value of the Colovac+ as an alternative to PI. A larger, randomized study (SAFE 2 trial, NCT05010850) is ongoing.

Conclusion

Colovac+ provides a safe and effective protection of the anastomosis during the healing period after LAR. This minimally invasive approach avoids the PI in the majority (73%) of patients without anastomotic complications and allows safe conversion to the standard of care PI for patients requiring longer anastomosis protection. The improved design of the Colovac+ reduces the overall migration rate and limits the clinical impact of a migration. Colovac+ could become

a valuable treatment alternative after LAR for rectal cancer in selected patients.

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Declarations

Disclosures This study was funded by SafeHeal SAS, the company that manufactures the Colovac. Jérémie H. Lefevre is a consultant for SafeHeal. Nicolas De Hous, Antonio D'Urso, Guy-Bernard Cadière, Benjamin Cadière, Philippe Rouanet and Niels Komen have no conflicts of interest to disclose.

Ethical approval This study was approved by the ethics committee of each participating hospital.

Informed consent Informed consent was obtained from all patients prior to study enrollment.

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