Surgical Innovation
1–7

DOI: 10.1177/1553350615617250
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Feasibility of an Intraluminal Bypass Device in Low Colorectal Anastomosis: Preliminary Results in a Porcine Model

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Abstract

Background: The Cologuard CG-100 is a novel intraluminal bypass device designed to reduce the clinical outcomes associated with low colorectal anastomotic leak. The device is inserted transanally, anchored to the colon above the anastomosis, and deployed intraluminally to cover the anastomosis from within. The purpose of this study was to evaluate the safety and performance of the device in a porcine model. *Method*: Twelve pigs underwent low colorectal anastomosis with insertion of the Cologuard CG-100 device. Contrast material injection, abdominal X-ray, and histologic studies were used to evaluate sealing quality, device positioning, and tissue damage, respectively. The surgeons completed a usability and satisfaction questionnaire after completion of the procedure. *Results*: Absolute sealing was observed in all 4 animals euthanized immediately after surgery. In the other 8 animals, the device was kept in situ for 10 days and then extracted. X-ray films with injection of contrast material through a designated injection tube before device removal showed that the sheath and ring were correctly placed. No leak was demonstrated. There were no device-related adverse events, and no critical histological abnormalities were noted in the bowel area that was compressed by the device. The device was found to be easy to insert, position, and extract. *Conclusion*: The Cologuard CG-100 device efficiently reduced contact between fecal content and low colorectal anastomosis in a porcine model and is easily deployed and extracted. It holds promise for possible clinical use pending further studies.

Keywords

colorectal surgery, anastomotic leak, intraluminal device

Introduction

Anastomotic leakage is a devastating complication of low anterior resection of the rectum, with a reported incidence of 11%.[1,2] It has a negative prognostic impact on both local recurrence of rectal cancer and long-term cancer-specific survival,[3] and it is a major cost driver in the health system.[4] Therefore, it is common practice to create a temporary stoma during surgery to protect the anastomosis.[5] However, diverting stomas themselves are associated with a 17% rate of complications,[6] and they considerably affect patient quality of life. These factors are particularly important, as almost 20% of temporary diversions become permanent[7] and 4% to 10% fail to prevent sepsis.[8] Alternative strategies to lower the incidence of anastomotic leakage, such as staple-line reinforcement, transanal decompression devices, and intraluminal devices, have not been widely accepted.[9]

The CG-100 (Cologuard Ltd, Kfar Saba, Israel) is a single-use intraluminal bypass device intended to reduce the contact of fecal content with an anastomotic site following colorectal surgery (open or laparoscopic). It can be used in anastomoses located up to 20 cm from the anal verge with an internal colon lumen diameter of 25 to 34 mm. The CG-100 has putative advantages of easy installation, strong aligned fixation, and simple recovery. Furthermore, it allows for radiologic testing of the anastomosis integrity prior to its removal.

The purpose of the present study was to evaluate the safety and performance of the CG-100 device in a porcine model. The study was reviewed by the

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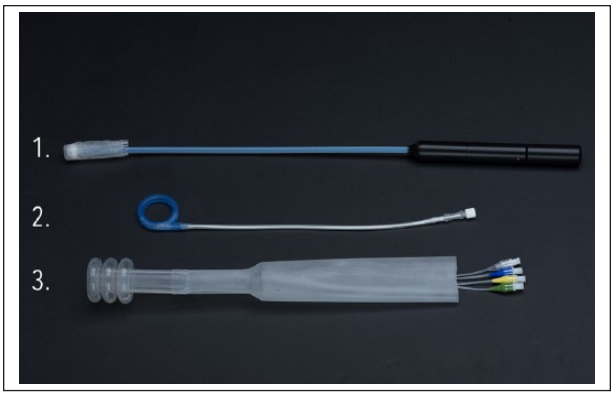

Figure 1. The CG-100 device: (1) delivery system; (2) removable external ring; (3) internal silicone sheath.

Conformité Européene (CE) in order to obtaining a CE mark and was reviewed and approved by the CE notified body.

Materials and Methods

General Device Description

The CG-100 device is composed of 3 main components (Figure 1): The first component is an internal silicone sheath, 350 mm long and 25 mm in diameter, with 3 rounded inflatable balloons, each 48 mm in diameter, at one end (this end is placed internally in the colon), and 4 silicon catheters with valve mechanism at the other end (this end of the sheath is extracted through the anus). Three catheters are designated to fill each balloon with fluid separately, and the fourth catheter is placed between the silicon sheath and the colon mucosa and serves to inject contrast material to that space. The second component is a delivery system to guide the sheath into the lumen and through the anus and the anastomosis site. The third component is a removable fixating ring located outside the colon and proximal to the anastomosis, equipped with a locking mechanism.

Placing the Device. After the colorectal anastomosis is created (up to 20 cm from the anal verge), the external ring is introduced through a mesenteric window 10 cm proximal to the anastomosis to encircle the colon externally. The ring is locked with a pin that is controlled from the end of the ring's connecting tube (this part will be placed out of the abdomen to allow to opening of the pin and withdrawal of the ring). The silicon sheath is introduced transanally using the delivery system until the balloons are placed proximal to the external ring. The balloons, which are folded within the delivery system, are filled with 15 mL of diluted contrast fluid each. The balloons are preventing the silicon sheath from moving downstream beyond the external ring. The balloons and the sheath can still move freely inside the colon, preventing damage to the colon wall (Figure 2). The ring's connecting tube is then delivered through the abdominal wall and fixed to the skin. After 10 days, when the risk for leakage is reduced, the device is extracted with no need for surgical intervention. The ring is opened from the outside and extracted like a surgical drain. The balloons are then deflated, and the sheath is pulled out from the rectum through the anus.

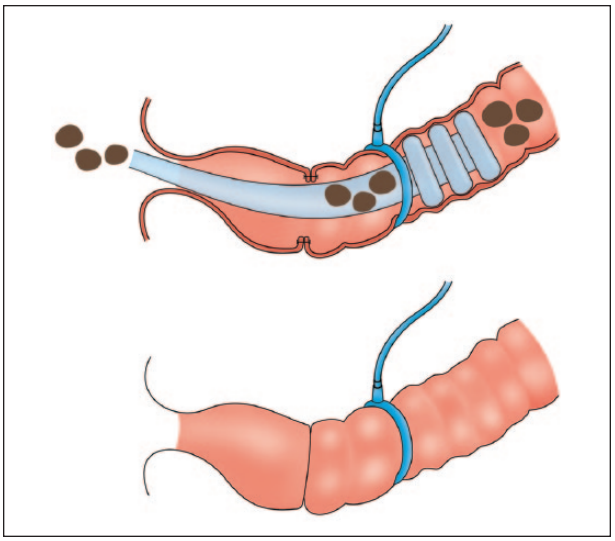

Figure 2. The CG-100: intraluminal fixation.

Animals

The study was performed in the Institute of Animal Research at Lahav CRO in adherence with Good Laboratory Practice for Nonclinical Laboratory Studies. The protocol was approved by the national ethics committee.

Twelve pigs aged 6 to 7 months and weighing 50 to 70 kg were included. All animals underwent a 7-day acclimation period prior to the procedure, which consisted of a comprehensive medical examination, dispensation of medication, and a uniform feeding program. Bowel preparation was started 3 days before the surgery by means of a laxative (Soffodex) and enema. The animals were held in an isolated area in the animal facility of Lahav CRO, and the clinical procedures (detailed below) were performed in the Lahav CRO animal operating room.

Anastomosis Procedure and Device Placement

After a midline abdominal incision, the rectum was incised about 15 cm from the anus with a 60-mm blue linear stapler. The external ring of the CG-100 device was

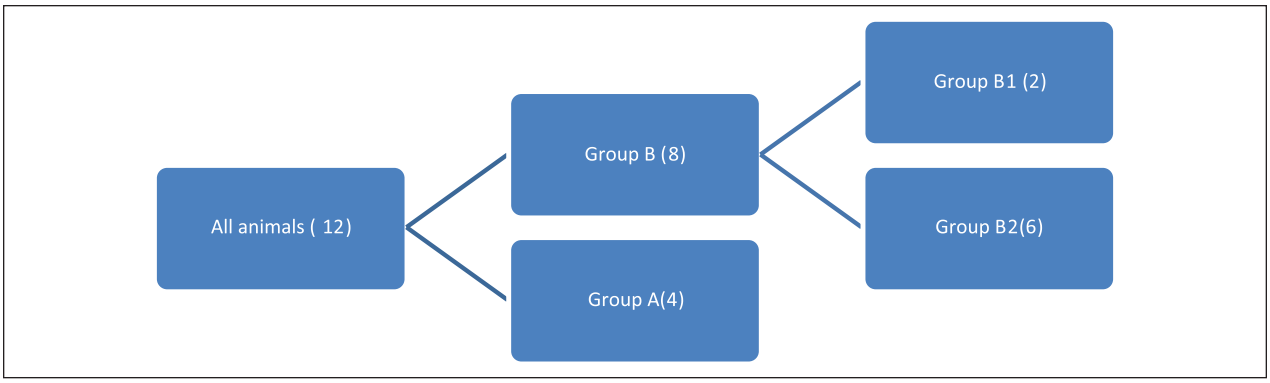

Figure 3. Subgrouping of animals.

introduced through a small channel created in the mesentery of the colon, about 10 cm from the resection line, and closed. The location of the ring was marked at 3 different points on the circumference of the colon using a standard needle and India ink. The anvil of a circular staple (28.5/31.5 mm) was secured at the colon edge, and the colorectal anastomosis was completed by a double-stapling technique through the anus. The integrity of the anastomosis was checked by a standard running-fluid test and closing the proximal end of the colon with a bowel clamp.

Experimental Procedure

The animals were divided to 2 main groups (Figure 3).

Group A (n = 4). To study the immediate sealing ability of the CG-100 sheath, a controlled opening of significant size of approximately 20 mm in length was made at the anastomosis site with scissors, and the sheath was introduced through the anus as described above, without exteriorizing the connecting tube of the external ring. A second opening was then created in the colon with scissors, approximately 10 cm proximal to the most cranial balloon, and saline mixed with methylene blue was injected via a catheter filling the colon to a significant diameter with tension to check the device's sealing capability. The animals were euthanized postoperatively.

Group B (n = 8). To evaluate the long-term effect of the device, the CG-100 sheath was introduced as described above. The abdominal cavity was closed in a conventional manner using a nylon loop suture, and the skin was closed with a Vicryl suture. The balloon inflation tubes were fixed by a tie. The external end of the sheath was trimmed so that only 3 to 4 cm remained below the level of the porcine anus.

Analgesics and antibiotics were administrated postoperatively to all animals, and a uniform feeding program was followed. Data were collected on a daily basis as follows: clinical symptoms, presence and appearance of stool, amount of uneaten food, signs of bowel content leakage, incision healing, and in situ distance of the device from the anus.

After 10 days, the animals were anesthetized and contrast material was injected through the fourth catheter into the space between the internal sheath and bowel mucosa to check for a leak. Abdominal X-ray was performed to determine the location and position of the device and balloons. Thereafter, the external locking mechanism was released, and the ring was extracted from the abdominal cavity. The balloons were deflated, and the sheath was pulled out of the rectum.

Following device removal, group B animals were further divided into 2 subgroups. Two animals (group B1) were immediately euthanized with an overdose of intravenous sodium pentobarbital potassium chloride, and 6 animals (group B2) were maintained for another 20 days under normal conditions (regular diet) and checked daily for general behavior, signs of pain, uneaten food, and feces, and weekly for body weight and complete blood count. They were euthanized on the 30th postoperative day in the same manner as group B1. On the day of euthanization, the pelvis was visually checked for marks of anastomotic leak.

Histology samples were taken from the anus and rectum, up to 15 to 20 cm proximal to the location at which the external ring had been positioned. In addition, approximately 50 mm of unexposed control tissue was collected from a location 10 cm proximal to the location at which the cranial balloons had been positioned.

Outcome Measures

Measures of device success were as follows: sealing quality; safety and speed of deployment; intraoperative or immediate postoperative complications; long-term (10-30 days) complications, such as leaks, obstructions, or abdominal infections; clinically significant damage to tissue in

contact with the device compared to control tissue; physician satisfaction. Physician satisfaction questionnaire was completed at the end of each procedure (including device removal). Answers were ranked on a 1- to 5-point scale (1 = *Must improve*, 5 = *Intuitive/Memorable*).

Histology tests were performed on bowel areas exposed to the device and control sections retrieved from each animal for assessment. Exposed areas included CG-100 balloons, ring, and anastomotic site; the control section was taken from a location more proximal to the CG-100 balloons area. No scale for anastomosis healing was used, and the histology results are descriptive.

Sample size calculations and rationale was done according to the requirements posed by the CE authorities.

The planned sample size for group A was 4 animals. The objective of this group was to demonstrate performance. This group was not expected to show statistical significance or statistical power, only demonstrate performance.

The sample size for group B was 8 animals. The rational for the sample size calculation was based on demonstrating zero (0) failures in the device within 10 days with 95% confidence interval.

The expected proportion of failures in a sample size of 8 items was 0%. The success of this study enables us to declare that in larger samples there will be no more than 2 failures.

Sample Size Justification

When the sample size is 8, a one-sided 95% confidence interval for a single proportion using the large sample normal approximation will extend 0.25 from the observed proportion for an expected proportion of 0 (Reference: nQuery Advisor 2.1).

The data were analyzed using the SAS version 9.1 (SAS Institute, Cary NC).

Results

All animals completed the study, with no cases of death, animal-related serious adverse events, or device-related adverse effects. Two animals had a postoperative ventral hernia that was not treated. In 2 cases, the external ring had to be resutured to the skin postoperatively and the bandage changed. The surgeons reported that the device was easy to introduce and extract, with high usability.

Overall, the time added to the procedure because of CG-100 device deployment ranged from 2 to 11 minutes. In the 4 animals examined immediately postoperatively, injection of methylene blue through an enterotomy after deliberate induction of an anastomotic tear yielded no evidence of leakage or obstruction during or after surgery. Abdominal X-ray performed after 10 days in the animals in which the device was left in situ showed that the sheath and ring were correctly positioned.

No evidence of anastomotic leak was seen in any of the 8 animals in group B either during postoperative X-ray exam and or during extraction of device at day 10 postoperatively (Figure 4). In all cases, the device was extracted without complications.

Only low-grade changes were noted on histologic study at 10 days after surgery (2 animals, group B1), which were not unexpected for this type of procedure. There was no evidence of mucosal ulceration or necrosis in the areas in contact with the balloons or ring (Figure 5). At 30 days (6 animals, group B2), the study and control sections of mucosal epithelium appeared normal, and lamina propria regeneration in the area of the anastomosis was almost complete. There was some fibrosis in the colonic wall and serosa, as expected after resection and anastomosis.

Discussion

Intracolonic devices are intended for use in colorectal surgery to prevent leakage of fecal materials to the peritoneal cavity thorough a disrupted anastomosis. They may also prevent anastomotic separation by shielding the anastomosis from contact with bowel content.[10]

In 1984, Ravo and Ger[11] described the first intraluminal colonic tube (the Coloshield) designed specifically to prevent anastomotic leaks. It consisted of a latex sleeve that is fixed to the colonic mucosa with absorbable sutures and is expelled naturally with bowel movement. Good results were reported in these studies and others employing a similar and other devices in both animal and human experiments using different types of materials.[12-15] However, none of these devices has been widely accepted, perhaps owing to the low level of evidence (mostly animal models and underpowered human studies). More recently, Oliveira et al[16] used an intraluminal device fashioned from a biological membrane to protect colonic anastomoses in dogs, with few complications and better healing than in controls. In 2011, researchers introduced the C-seal, a biodegradable intracolonic device that is glued to the anvil of a circular stapler for application to the bowel lumen. The C-seal was found to be safe and effective in human studies.[17,18]

In the present study, we examined the safety and performance of a new intracolonic sheath, the CG-100, in a porcine model. The CG-100 is indicated for single use for temporary intraluminal bypass in order to reduce fecal material and other substances from coming into contact with the anastomotic site. The device met all our success criteria. Transanal introduction of the device through the anastomosis may theoretically pose some risk to its integrity. Nevertheless, it was easily deployed, with no

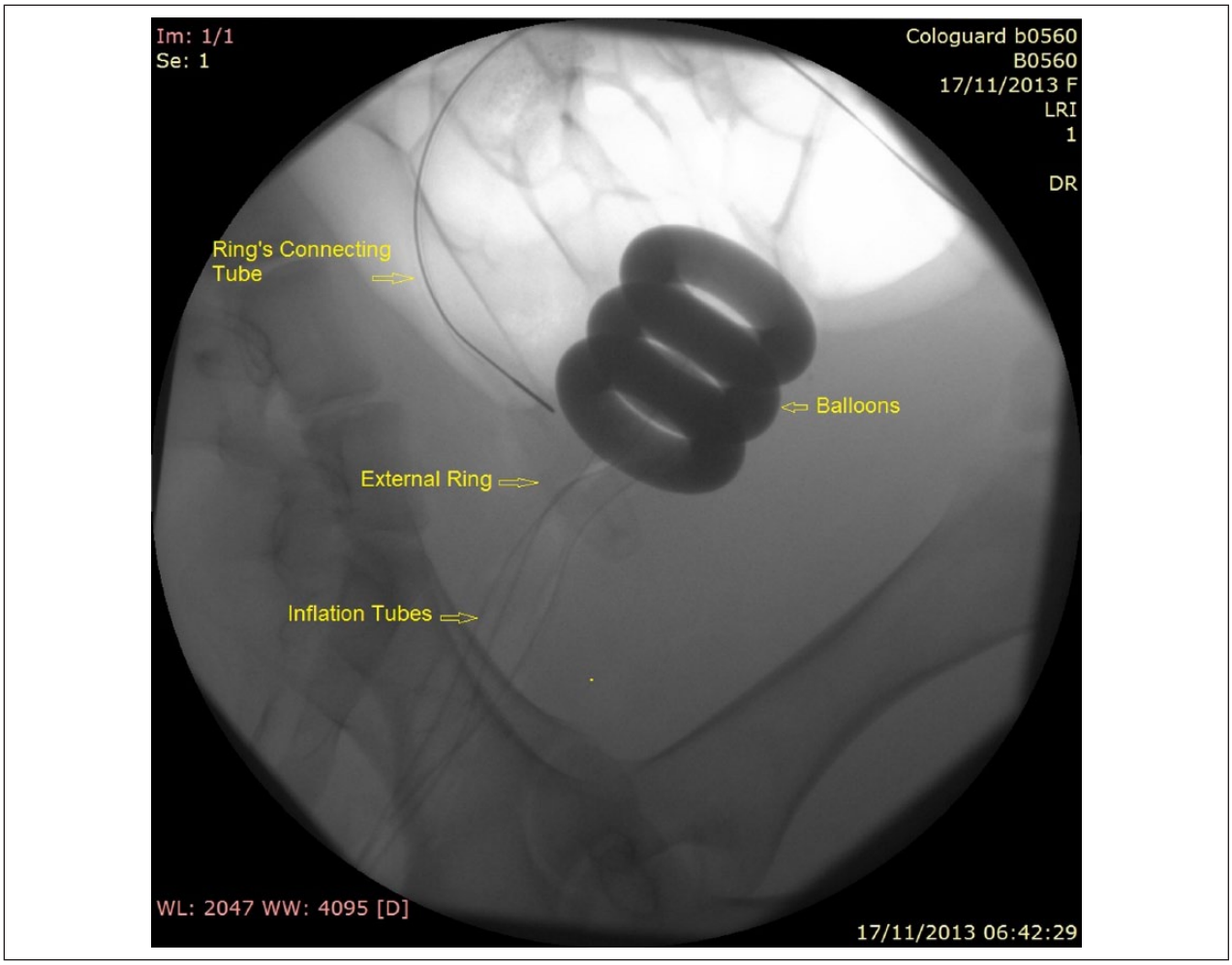

Figure 4. Abdominal X-ray showing intracolonic positioning of the sheath and the ring.

technical difficulties or operational complications, easily extracted, and caused no damage to the anastomosis site. There were no intraoperative or postoperative device-related complications. None of the pigs in the short- and long-term groups had an anastomotic leak. Anastomotic leakage was tested under tension in group A but was descriptive without pressure measurement.

Except for primates, the pig is the laboratory animal nearest to humans in terms of anatomy and physiology of the gastrointestinal tract. While healthy pigs rarely show an anastomotic leak, studies have demonstrated that higher rates of an anastomotic leak may occur after manipulating the anastomosis and using the pig as a model for clinical colon anastomotic leakage is feasible.[19,20] Accordingly, an artificial defect at the anastomosis was made in the current study to check the sealing capabilities of the CG-100 device.

Most anastomotic leaks become apparent between days 5 and 8 after surgery.[21] Clinical signs of leakage are uncommon after that, although there are rare reports of leaks even as late as day 12.[22] Therefore, to test the performance of the CG-100 device, we left it in situ for 10 days in some of the animals. The device remained well positioned during this time, and no leaks or complications were found even after a total of 30 days of follow-up. Histologic study confirmed the absence of significant device-induced tissue damage in the colon wall or other structures. Furthermore, we were able to evaluate the device radiologically before its extraction by injection of contrast material to the space between the internal sheath and bowel mucosa. In contrast to other intracolonic devices, the CG-100 is actively extracted and is not dependent on material or suture degradation. Potentially, in cases of a radiologically confirmed anastomotic leak, the device can be kept in situ even longer than 10 days, but this needs to be tested in further studies.

In summary, the present experimental study demonstrates that the CG-100 device can safely and efficiently reduce contact between fecal content and the anastomotic site and may prevent the clinical outcomes associated

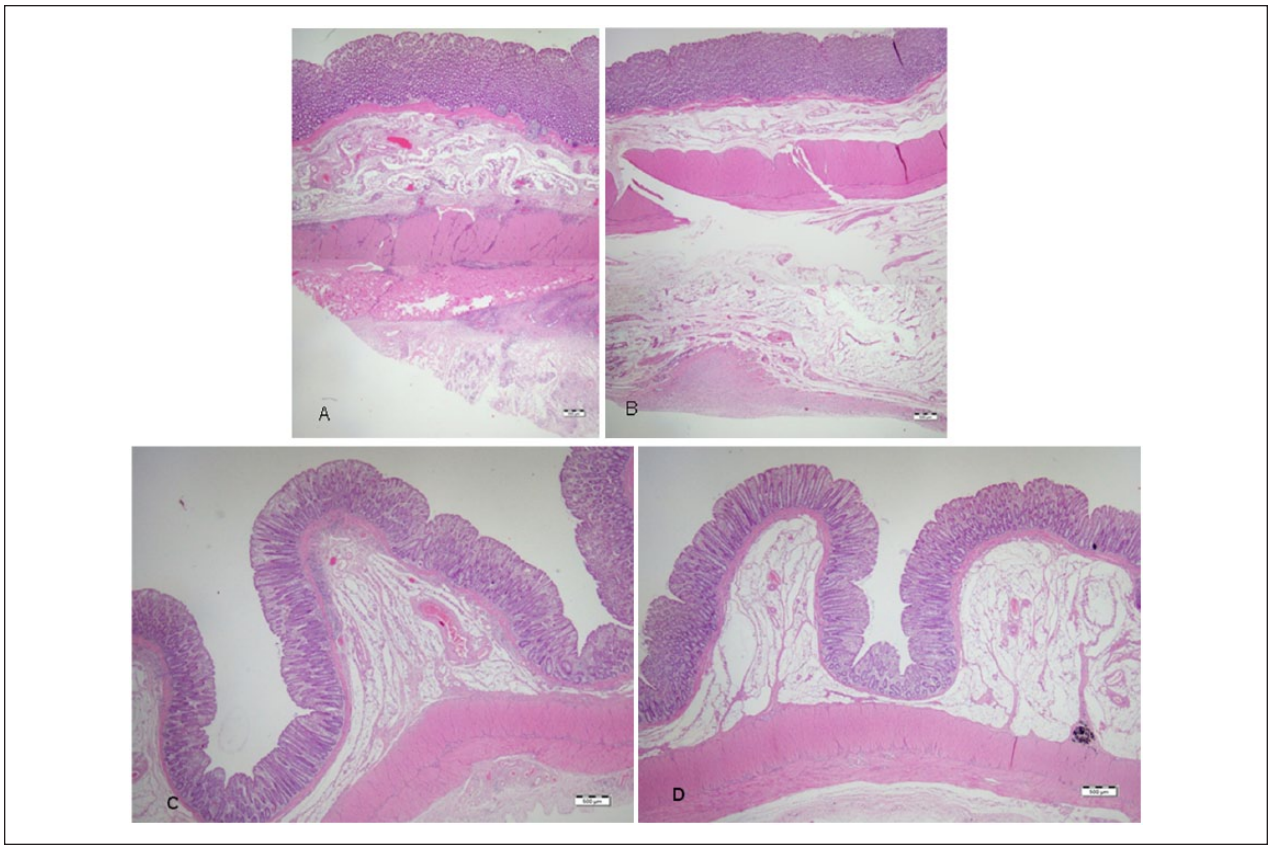

Figure 5. Histology findings.
(A) Ring area after 10 days: The mucosa is within normal ranges. There is leukocyte infiltration (inflammation) in the submucosa, tunica muscularis, and serosa. (B) Ring area after 30 days: All tissue layers are within normal ranges. (C) Cranial balloon area after 10 days: The tissue is within normal ranges with minimal mucosal edema and mild lymphoplasmacytic infiltration. (D) Cranial balloon area after 30 days: The tissue is within normal ranges.

with an anastomotic leak after colorectal surgery. Its introduction, deployment, and extraction is easily and consistently performed. The device holds promise for clinical use and warrants further study. The CG-100 gained a marketing approval after the study and a multicenter safety study has been initiated.

Authors' Note

Nir Wasserberg and Udi Willenz equally contributed to the article.

Author Contributions

Study concept and design: Ron Greenberg, Udi Willenz
Acquisition of data: Ron Greenberg, Udi Willenz, Nir Wasserberg, Ana Maria Botero-Anug
Analysis and interpretation: Nir Wasserberg, Ana Maria Botero-Anug
Study supervision: Ron Greenberg, Udi Willenz

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The study was sponsored by Cologuard Ltd.

References

1. Paun BC, Cassie S, MacLean AR, Dixon E, Buie WD. Postoperative complications following surgery for rectal cancer. *Ann Surg*. 2010;251:807-818.
2. den Dulk M, Marijnen CA, Collette L, et al. Multicenter analysis of oncological and survival outcomes following anastomotic leakage after rectal cancer surgery. *Br J Surg*. 2009;96:1066-1075.
3. Mirnezami A, Mirnezami R, Chandrakumaran K, Sasapu K, Sagar P, Finan P. Increased local recurrence and reduced survival from colorectal cancer following anastomotic leak systematic review and meta-analysis. *Ann Surg*. 2011;253:890-899.
4. Koperna T. Cost-effectiveness of defunctioning stomas in low anterior resections for rectal cancer. *Arch Surg*. 2003;138:1334-1338.
5. Paun BC, Cassie S, MacLean AR, Dixon E, Buie WD. Postoperative complications following surgery for rectal cancer. *Ann Surg*. 2010;251:807-818.

6. Chow A, Tilney HS, Paraskeva P, Jeyarajah S, Zacharakis E, Purkayastha S. The morbidity surrounding reversal of defunctioning ileostomies: a systematic review of 48 studies including 6,107 cases. *Int J Colorectal Dis*. 2009;24:711-723.
7. den Dulk M, Smit M, Peeters KC, et al; Dutch Colorectal Cancer Group. A multivariate analysis of limiting factors for stoma reversal in patients with rectal cancer entered into the total mesorectal excision (TME) trial: a retrospective study. *Lancet Oncol*. 2007;8:297-303.
8. Tan WS, Tang CL, Shi L, Eu KW. Meta-analysis of defunctioning stomas in low anterior resection for rectal cancer. *Br J Surg*. 2009;96:462-472.
9. Morks AN, Havenga K, Ploeg RJ. Can intraluminal devices prevent or reduce colorectal anastomotic leakage: a review. *World J Gastroenterol*. 2011;17:4461-4469.
10. Ravo B, Metwally N, Castera P, Polansky PJ, Ger R. The importance of intraluminal anastomotic fecal contact and peritonitis in colonic anastomotic leakages. An experimental study. *Dis Colon Rectum*. 1988;31:868-871.
11. Ravo B, Ger R. A preliminary report on the intracolonic bypass as an alternative to a temporary colostomy. *Surg Gynecol Obstet*. 1984;159:541-545.
12. Ravo B. Colorectal anastomotic healing and intracolonic bypass procedure. *Surg Clin North Am*. 1988;68: 1267-1294.
13. Ross H. The effect of an intraluminal tube used as an internal drain on the healing of the rat colon. *Dis Colon Rectum*. 1987;30:591-594.
14. Serra J, Capella G, Esquius J, Montañes R, Rius X. Experimental study of the efficacy of the endoluminal prosthesis in colonic anastomoses. *Int J Colorectal Dis*. 1992;7:21-25.
15. Yoon WH, Song IS, Chang ES. Intraluminal bypass technique using a condom for protection of coloanal anastomosis. *Dis Colon Rectum*. 1994;37:1046-1047.
16. Oliveira AL, Jamel N, Lacombe DP, et al. Use of intraluminal protection in colonic anastomosis in dogs. *Acta Cir Bras*. 2007;22:57-62.
17. Kolkert JL, Havenga K, ten Cate Hoedemaker HO, Zuidema J, Ploeg RJ. Protection of stapled colorectal anastomoses with a biodegradable device: the C-Seal feasibility study. *Am J Surg*. 2011;201:754-758.
18. Morks AN, Havenga K, ten Cate Hoedemaker HO, Leijtens JW, Ploeg RJ; C-Seal Study Group. Thirty-seven patients treated with the C-seal: protection of stapled colorectal anastomoses with a biodegradable sheath. *Int J Colorectal Dis*. 2013;28:1433-1438.
19. Pommergaard HC, Rosenberg J, Schumacher-Petersen C, Achiam MP. Choosing the best animal species to mimic clinical colon anastomotic leakage in humans: a qualitative systematic review. *Eur Surg Res*. 2011;47:173-181.
20. Nordentoft T, Sørensen M. Leakage of colon anastomoses: development of an experimental model in pigs. *Eur Surg Res*. 2007;39:14-16.
21. Komen N, Dijk JW, Lalmahomed Z, et al. After-hours colorectal surgery: a risk factor for anastomotic leakage. *Int J Colorectal Dis*. 2009;24:789-795.
22. Hyman N, Manchester TL, Osler T, Burns B, Cataldo PA. Anastomotic leaks after intestinal anastomosis: it's later than you think. *Ann Surg*. 2007;245:254-258.