

## Outcomes of surgical treatment for enterovesical fistula in Crohn's disease

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### ABSTRACT

Enterovesical fistula (EVF) in Crohn's disease (CD) often does not improve with medical treatment and requires surgical treatment. The surgical treatment strategy for EVF in CD is definitive resection of the intestinal tract side, and performing a leak test using dye injection into the bladder after EVF dissection to determine the appropriate surgical procedure for the bladder side. This study aimed to evaluate the outcomes of surgical treatment for EVF in CD. Twenty-one patients who underwent surgery for EVF between 2006 and 2021 were included and retrospectively evaluated for clinical background, surgical procedures, and postoperative complications. The most common origin of EVF was the ileum (17 cases; 81%), and the most common site of EVF formation was the apex (12; 57%). Surgical approaches were laparotomy in 11 (52%) cases and laparoscopy in 10 (48%). Surgical procedures on the bladder side were fistula dissection in 13 (62%) cases and sutured closure of fistula in 8 (38%). A comparison of approaches revealed no significant difference in operative time, but the amount of blood loss was significantly less in the laparoscopy ( $p < 0.01$ ). There was no significant difference in the occurrence of postoperative complications between approaches. Postoperative anti-TNF- $\alpha$  antibody agents were used in 17 (81%) cases, and there were no cases of recurrent EVF. In conclusion, definitive resection of the intestinal tract and minimal treatment on the bladder side were sufficient to achieve satisfactory outcomes for EVF in CD.

Keywords: Crohn's disease, enterovesical fistula, surgical treatment, laparoscopic surgery

Abbreviations:

CD: Crohn's disease

EVF: enterovesical fistula

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### INTRODUCTION

Crohn's disease (CD) is an idiopathic chronic inflammatory condition affecting the gastrointestinal tract anywhere from the mouth to the anus, potentially causing stricture and fistula

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formation.<sup>1,2</sup> Fistulae are abnormal communications between two epithelial surfaces, and patients with CD may develop different types of fistulae: perianal, enterovesical or colovesical, enterovaginal or rectovaginal, enteroenteric or enterocolic, and enterocutaneous.<sup>3</sup> Enterovesical fistula (EVF) is a relatively rare condition in CD. Epidemiological data on EVF are contradictory, with published studies reporting variable incidence rates, ranging from 1.6 to 7.7%.<sup>4-16</sup> EVFs are most commonly diagnosed based on clinical symptoms, but diagnostic studies are required for confirmation. At present, there is no consensus on the optimal diagnostic algorithm. Medical therapy, including immunosuppressants and anti-tumor necrosis factor (TNF)- $\alpha$  antibodies, has led to long-term remission in some patients, but surgery is indicated for patients with intractable EVF. The optimal strategy for treating EVFs is also still being debated. This present study aimed to evaluate diagnostic approaches and surgical outcomes for EVF in CD.

## METHODS

### *Ethics*

Written informed consent for surgery and use of their clinical data were obtained from all the patients according to the requirements of the Institutional Review Board of Nagoya University.

### *Patient population*

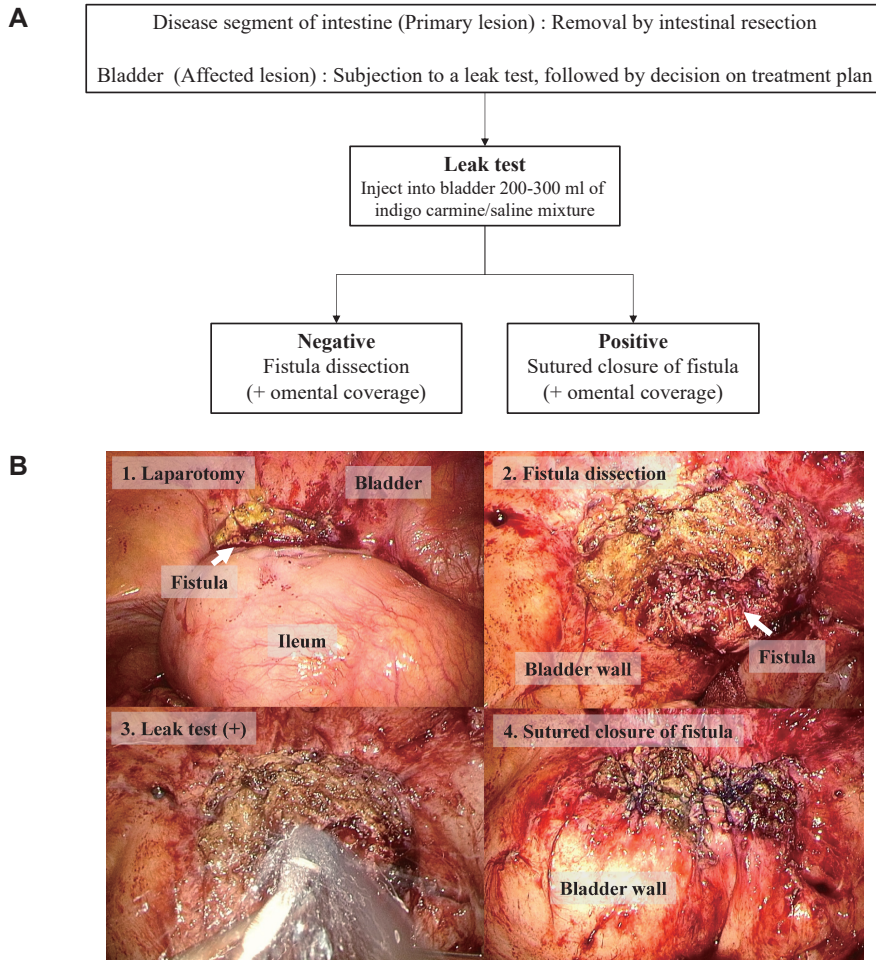
This was a retrospective study of adult CD patients undergoing elective surgery for EVF between January 2006 and December 2021 at the Nagoya University Graduate School of Medicine (Nagoya, Japan).

### *Surgical treatment strategy*

Surgery for EVF began with dissection of the bowel lesion and bladder. The diseased segment of the intestine (primary lesion) was then resected and a primary anastomosis was performed. The bladder (affected lesion) was filled with 200–300 mL of indigo carmine/saline mixture to test for leakage. Fistula dissection alone was performed for cases with no identifiable defect (leak test negative). However, if a defect was clearly identifiable (leak test positive), then sutured closure of fistula was performed using absorbable sutures. After sutured closure of fistula, the leak test was repeated to confirm the lack of an identifiable defect. An omental pedicle was used to cover the repaired portion of the bladder if the greater omentum could be taken down to the pelvic floor (Figs. 1A, 1B). As there was no institutional policy before 2015, bladder drainage via a transurethral route, performance of a cystogram, and timing of removal of the urinary catheter were all performed at the discretion of the surgeon. After 2015, all patients underwent a cystogram on postoperative day 7, and if there was no leakage of contrast agent, the urinary catheter was removed on the same day.

### *Statistical analyses*

Categorical variables are expressed as frequencies and percentages. Differences in characteristics between the two groups were analyzed using the  $\chi^2$  test for categorical variables and the Mann-Whitney U test for continuous variables. *P*-values less than 0.05 were considered statistically significant. Statistical analyses were performed using JMP software version 15 (SAS Institute Inc, Cary, NC, USA).



**Fig. 1** Surgical treatment strategy and procedures for enterovesical fistula in Crohn's disease

**Fig. 1A:** Surgical treatment strategy.

**Fig. 1B:** Surgical findings.

This is a case of ileo-vesical fistula. The small intestine and bladder were dissected. A leak test was performed, which revealed positive findings. Sutured closure of fistula was performed.

## RESULTS

### *Patient characteristics*

Among the 409 cases of bowel resection for CD between January 2006 and December 2021, surgery for EVF was performed in 21 (5.1%). The characteristics of these 21 cases are summarized in Table 1. The median age at diagnosis of CD was 24 years (range, 10–33). The median interval between CD diagnosis and surgery for EVF was 10.5 years (range, 0.08–24.9). The most common presenting symptoms were pneumaturia (71%), followed by faecaluria (67%), fever (29%), dysuria (24%), and suprapubic pain (24%). In all cases, either pneumaturia or faecaluria was present. The most common origin of EVF was the ileum (81%), followed by the

sigmoid colon (14%) and rectum (5%). Preoperatively, fistula was treated with anti-TNF- $\alpha$  agents in 14 cases (67%). Nine cases received infliximab (IFX) and 5 received adalimumab (ADA).

**Table 1** Patient characteristics

	N = 21
Gender, n (%)	
Male/Female	17 (81)/4 (19)
Age at CD diagnosis, years	
Median (range)	24 (10–33)
Age at surgery, years	
Median (range)	33 (24–49)
Duration of illness, years	
Median (range)	10.5 (0.08–24.9)
Location of CD, n (%)	
Ileal/Ileocolonic/Colonic	4 (19)/16 (76)/1 (5)
Symptoms*, n (%)	
Pneumaturia	15 (71)
Faecaluria	14 (67)
Fever	6 (29)
Dysuria	5 (24)
Suprapubic pain	5 (24)
Origin of EVF, n (%)	
Ileum/Sigmoid/Rectum	17 (81)/3 (14)/1 (5)
Preoperative medical treatment*, n (%)	
5-ASA	21 (100)
Steroid	7 (33)
Immunomodulators	6 (29)
Nutrition therapy	17 (81)
Anti-TNF agents	14 (67)
IFX	9 (43)
ADA	5 (24)

N: total number of patients

n: number of patients

CD: Crohn's disease

EVF: enterovesical fistula

5-ASA: 5-aminosalicylic acid

anti-TNF agents: anti-tumor necrosis factor agents

IFX: infliximab

ADA: adalimumab

\*Multiple symptoms and medical treatments for certain patients.



*Diagnostic investigations of EVF*

A summary of diagnostic investigations, examination findings, and location of EVF formation are shown in Table 2 and Fig. 2. Gastrointestinal contrast studies and computed tomography (CT) scans were conducted for all cases, while cystoscopy was performed in 15 (72%). Gastrointestinal contrast studies confirmed the inflow of contrast agent into bladder in 8 cases (38%), cystoscopy detected the fistula in 5 (24%), and CT examination showed bladder wall thickening and air in the bladder leading to a suspicion of fistula in 13 (62%). The final diagnosis regarding the location of EVF formation was made by preoperative examinations and intraoperative findings. The most common location of EVF formation was the apex (57%), followed by the posterior wall (29%) and trigone (14%). All 6 cases (28%) in which cystoscopy was not performed had the fistula at the apex.

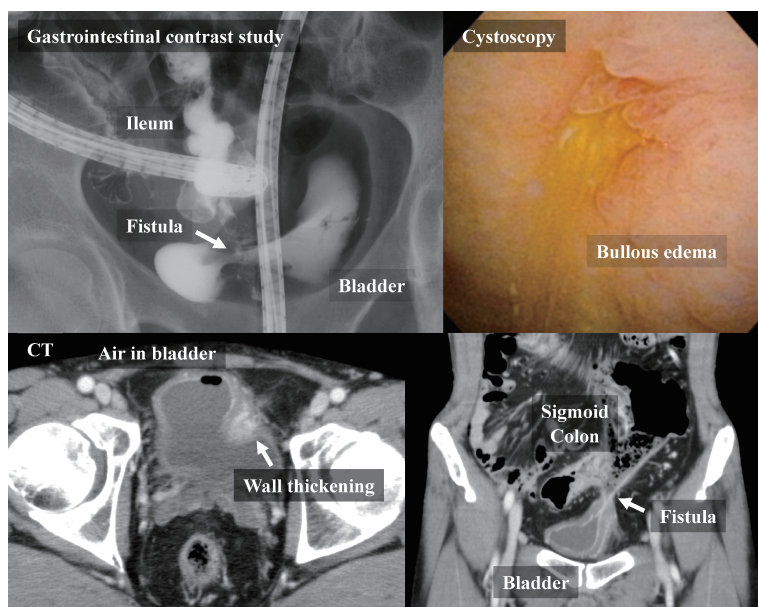
**Table 2** Diagnostic investigations and location of EVF

	n (%)
Diagnostic test	
Gastrointestinal contrast study	21 (100)
Contrast agent inflow into bladder (+)	8 (38)
Contrast agent inflow into bladder (–)	13 (62)
Cystoscopy	15 (72)
Edematous bladder mucosa	10 (48)
Detection of fistula	5 (24)
CT examination	21 (100)
Bladder wall thickening	8 (38)
Bladder wall thickening, air in bladder	13 (62)
Location of EVF formation	
Apex	12 (57)
Posterior wall	6 (29)
Trigone	3 (14)

n: number of patients

EVF: enterovesical fistula

CT: computed tomography



**Fig. 2** Imaging findings of EVF

EVF: enterovesical fistula

### *Surgical procedures*

Surgical indication in this study was as follows: EVF only: 4 cases (19%), EVF with other intestinal stricture: 3 (14%), EVF with other enteroenteric fistula: 7 (33%), and EVF with other intestinal stricture and enteroenteric fistula: 7 (33%). Since 2013, our department has implemented laparoscopic surgery for all elective surgery cases regardless of stricturing/penetrating type. Of the study population, 10 cases (48%) underwent laparoscopic surgery. We compared surgical procedures and outcomes by surgical approach, ie, open surgery (Open group) and laparoscopic surgery (Lap group).

Surgical indications differed according to the surgical approach. In the Open group, there were significantly more cases with other stricturing and/or penetrating CD lesion. As for previous surgery, 8 cases had surgical history of CD related intestinal resection. Initial surgery was performed in 5 cases (45%) in the Open group and 8 (80%) in the Lap group, with no significant difference between the two groups. Intestinal resection was performed in all cases, although various surgical procedures were performed for the intestinal tract. Regarding treatment for EVF, fistula dissection was performed in more than half of the cases in both groups. Omental coverage was performed in 8 cases (73%) in the Open group and 3 (30%) in the Lap group, with no significant difference between the two groups ( $p = 0.05$ ). In addition, there were no cases in which partial cystectomy or urinary diversion was performed (Table 3).

### *Surgical outcomes*

A comparison of the Open and Lap groups revealed no significant difference in operative time, but the amount of blood loss was significantly less in the Lap group ( $p < 0.01$ ). In the Lap group, one case converted to open surgery. In this particular case, the ileovesical fistula-rectum formed an inflammatory mass in the pelvis, and scope-assisted detachment was difficult (Table 4).

**Table 3** Surgical procedures

	Open group (N =11)	Lap group (N =10)	<i>p</i> value
Surgical indication, n (%)			
EVF only	0 (0)	4 (40)	0.01
EVF with other CD related lesion	11 (100)	6 (60)	
Previous surgery, n (%)			
First	5 (45)	8 (80)	0.10
2nd	6 (55)	2 (20)	
Surgical procedures for intestinal tract*, n (%)			
Ileocecal resection	4 (36)	6 (60)	
Ileal resection	8 (73)	1 (10)	
Colectomy	0 (0)	3 (30)	
Rectal resection	3 (27)	0 (0)	
Subtotal colectomy	0 (0)	1 (10)	
APR	2 (18)	1 (10)	
Treatment EVF, n (%)			
Fistula dissection	7 (64)	6 (60)	0.86
Sutured closure of fistula	4 (36)	4 (40)	
Omental coverage	8 (73)	3 (30)	0.05

N: total number of patients

n: number of patients

CD: Crohn's disease

Lap: laparoscopy

APR: abdominoperineal resection

EVF: enterovesical fistula

\*Multiple procedures for certain patients.

**Table 4** Surgical treatment outcomes

	Open group (N = 11)	Lap group (N = 10)	<i>p</i> value
Operative time, min			
Median (range)	254 (129–405)	210 (133–377)	0.50
Blood loss, mL			
Median (range)	437 (153–1900)	118 (15–798)	< 0.01
Conversion to open surgery, n (%)	–	1 (10)	–
Overall complications, n (%)	5 (45)	2 (20)	0.21
Ileus	1	0	
Abdominal abscess	1	0	
Anastomotic leakage	1	0	

Enterovesical fistula in Crohn's disease

Bladder wall leakage	1	0	
Wound infection	0	1	
Urinary tract infection	1	0	
Postoperative bleeding	0	1	
Mortality, n (%)	0 (0)	0 (0)	1.00
<hr/>			
Urinary catheter replacement period, days			
Median (range)	10 (7–37)	7 (4–30)	0.05
Hospital stay, days			
Median (range)	26 (12–54)	15 (12–20)	0.01

N: total number of patients

n: number of patients

Lap: laparoscopy

Postoperative complications were observed in 5 cases (45%) in the Open group and 2 (20%) in the Lap group, with no significant difference between the two groups. In the Open group, anastomotic leakage and bladder wall leakage were observed in one case each. The bladder wall leakage was healed by decompression with cystostomy, and we could remove cystostomy catheter after one month of indwelling. Median hospital stay was significantly shorter in the Lap group compared to the Open group (15 days vs 26 days;  $p < 0.01$ ; Table 4).

For postoperative treatment, all cases were treated with 5-aminosalicylic acid (5-ASA) and nutritional therapy. Anti-TNF- $\alpha$  agents were used in 81% of cases, including 6 cases (29%) treated with IFX and 11 (52%) treated with ADA (Table 5). The median length of follow-up was 54 months (range, 0.65–174), and no recurrence of EVF was observed.

**Table 5** Postoperative medical treatment

	N = 21
Postoperative medical treatment*, n (%)	
5-ASA	21 (100)
Steroid	1 (5)
Immunomodulators	5 (24)
Nutrition therapy	21 (100)
Anti-TNF agents	17 (81)
IFX	6 (29)
ADA	11 (52)

N: total number of patients

n: number of patients

5-ASA: 5-aminosalicylic acid

anti-TNF: agents anti-tumor necrosis factor agents

IFX: infliximab

ADA: adalimumab

\*Multiple medical treatments for certain patients.

## DISCUSSION

Among the 409 CD cases of surgery in this study, the incidence of EVF was 5.1%. There currently is no consensus on the optimal diagnostic procedure for EVF, and the rate of EVF detection using our methods was low. In treating EVF, our policy of resecting the lesion in the intestinal tract and minimally treating the bladder side based on the leak test resulted in satisfactory outcomes.

All cases in the present study had either pneumaturia or faecaluria. A gastrointestinal contrast study and CT scan were performed for all cases, but contrast agent flow into the bladder or air in the bladder, which infers the presence of EVF, was found in about 40% and 60% of cases, respectively. Cystoscopy was performed in 70% of cases, and fistulas were identified in less than half, consistent with previous reports.<sup>17,18</sup> The rate of fistula detection was low, with several cases presenting only with clinical symptoms and no detectable EVF in imaging studies. Moving forward, evaluation of fistulas using MRI will need to be considered.<sup>19-21</sup> Another useful diagnostic method of EVF is to observe whether the charcoal is excreted in the urine after oral intake of medical charcoal.<sup>22,23</sup> Since it is difficult to diagnose EVF, a comprehensive diagnosis based on a combination of multiple imaging studies, clinical symptoms, and intraoperative findings is important.

Although anti-TNF- $\alpha$  antibodies and surgery can be used to treat EVF, the efficacy of anti-TNF- $\alpha$  antibodies has not been established. Several retrospective studies have compared treatment with anti-TNF- $\alpha$  antibodies versus surgery in CD with EVF.<sup>15,16,24</sup> Although results varied across studies, about 29–45.4% of patients were reported to maintain remission without the need for surgery, and 44.1–81.4% required surgery.<sup>15,16,24</sup> Factors independently associated with the need for surgery include the presence of other complications of CD such as bowel obstruction and abscess formation, higher CD activity index, and longer duration from the diagnosis of fistula.<sup>15,24</sup>

The majority of patients with EVF must undergo surgery, which requires a definitive small extent resection of the “primary lesion” (intestinal tract side) and treatment of the “affected lesion” (bladder side) involved in the primary lesion. In principle, the “affected lesion” does not need to be resected to a large extent, since it will improve once the causative intestinal tract is resected.<sup>10,11,25</sup> As shown in Fig. 1, our policy is to perform a leak test after dissection of the fistula to consider which procedure is appropriate for the bladder side. None of our cases underwent partial cystectomy or urinary tract alteration, and bladder leakage was observed in only one case, which improved with cystostomy. Thus, minimal treatment for the bladder side is likely to be sufficient. Regarding the approach, laparoscopic surgery was performed in 47.6% of cases (first surgery: 80%, second surgery: 20%). Compared to the Open group, there was no significant difference in the occurrence of postoperative complications in the Lap group, and the length of hospital stay was significantly shorter in the Lap group. These results are similar to those reported in previous studies comparing laparoscopic and open surgery for CD.<sup>26,27</sup> Some reports have demonstrated the usefulness of laparoscopic surgery even in cases of recurrent CD,<sup>28-30</sup> and thus we plan to expand the indication for laparoscopic surgery to recurrent cases in the future.

Omental interposition likely reduced bladder wall leakage in our study population. Bladder wall leakage occurred in only one case (4.7%), and omental coverage was performed in just over half of the cases. This technique may reduce the risk of recurrent fistulas by placing healthy, well-vascularized tissue over the surface of the bladder to improve healing.

There is no consensus regarding the duration of balloon catheter placement. According to a study by de Moya et al, there were no significant differences in bladder-related complications between patients who had their catheters removed before or on postoperative day 7.<sup>31</sup> The authors concluded that leaving the catheter in for longer than 7 days has no discernible advantage.<sup>31</sup>

Another study found that routine postoperative cystography after surgery for EVF may not be necessary for all patients if the bladder is drained for 1–2 weeks after bowel resection.<sup>32</sup> Since 2015, our policy has been to perform cystography on postoperative day 7 and remove the catheter after confirming the absence of leakage, and no case of delayed suture failure at the bladder site has been observed.

CD has a high rate of postoperative recurrence requiring reoperation. Therapies which have been reported to prevent postoperative recurrence include 5-ASA, thiopurines, anti-TNF- $\alpha$  antibody agents, and enteral nutritional therapy. Meta-analyses have shown that anti-TNF- $\alpha$  antibody agents (IFX and ADA) are effective in preventing clinical and endoscopic recurrence.<sup>33,34</sup> Moreover, combination therapy with nutritional therapy has been reported to be superior to infliximab alone for remission induction and remission maintenance.<sup>35</sup> In the present study, anti-TNF- $\alpha$  antibodies were administered postoperatively in 81% of cases and enteral nutritional therapy was used in all cases. Thus, combination therapy was used in more than 80% of cases, which may have contributed to the lack of EVF recurrence.

This study has some limitations. First, we retrospectively collected data from a small sample of patients who underwent surgery at a single center. Second, the total number of patients who received medical therapy, including anti-TNF- $\alpha$  antibodies, for EVF was unknown. Therefore, the proportion of patients treated for EVF who were able to avoid surgery is unclear.

In conclusion, definitive resection of the lesion in the intestinal tract, and fistula dissection and suture closure as minimal treatment on the bladder side, was sufficient to achieve satisfactory outcomes in treating EVF in CD patients. The lack of EVF recurrence even after long-term observation suggests that our department's treatment policy is effective. Given that some CD patients with EVF are successfully treated with medical therapy, well-designed prospective studies to determine the exact role of medical and surgical treatments for EVF in CD patients are warranted.

## CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest.

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