


ORIGINAL ARTICLE

Long-term outcomes of anti-tumor necrosis factor therapy and surgery in nonperianal fistulizing Crohn's disease

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Introduction

Crohn's disease (CD) is a chronic, progressive, relapsing, and debilitating disorder of the gastrointestinal tract, with varied manifestations and severity, depending upon the pattern of involvement along the longitudinal and transverse axes of the gastrointestinal (GI) tract.¹ Although luminal phenotype and the mild disease course are most common, this can progress to or present with transmural inflammation in the form of strictures or fistulae. In population-based studies, the cumulative risk of developing any kind of fistula is 33% at 10 years and 50% at 20 years.² Perianal fistula is the most common type of fistula associated with CD,³ being present in up to one-fourth of patients, and has been well characterized in terms of its natural history and treatment outcomes.³ However, nonperianal fistulae

Abstract

Background: Unlike perianal fistula, long-term outcomes of nonperianal fistulae (NPF) in Crohn's disease (CD) are not clear. We aimed to compare the outcomes of medical and surgical therapies in patients with NPF.

Methods: We retrospectively analyzed the records of patients of CD with NPF who were prospectively followed from January 2005 to December 2018.

Results: Of the 53 patients with NPF [mean age at presentation: 29 ± 14 years; 54.7% male; median duration of follow-up: 47 months (interquartile range [IQR]: 26–76-months)], enteroenteric fistula (37.8%) was the most common presentation. Of 22 patients treated with anti-tumor necrosis factor (TNF) therapy, complete response was achieved in 40.9% (*n* = 9). Overall probability of maintaining response was similar between the anti-TNF and surgical groups (95.2% vs 82.4%; 71% vs 76%; and 63% vs 69% [*P* = 0.8] at 1, 2, and 3 years, respectively), with only 13.6% of patients treated with biologicals requiring surgery over 56 months. Twenty-one patients required upfront surgery (small bowel or ileocolonic resection with/without diversion; 28.5% emergent), with 47.6% postoperative recurrence over 36 months, of which nine patients required biologicals (77.7% response to anti-TNF therapy). Long-term outcome was comparable between medically and surgically treated patients; 6.4% developed tuberculosis on anti-TNF therapy. Two patients (3.7%) developed malignancy (one - enteroenteric, one - colovesical).

Conclusion: Anti-TNF therapy appears to be as effective as surgery in this retrospective analysis of patients with NPFCD, and it may be indicated in the absence of abscess and other complications. These patients are at higher risk of fistula-associated malignancy, which requires a lower threshold for suspicion, especially over the long term in the presence of nonresponse to medical therapy.

(NPF), which can be internal (enteric, vaginal, and vesical fistulae) or external (enterocutaneous fistulae) depending on the organ of origin and termination, are equally morbid, and unlike perianal fistulae, their disease course, behavior, and long-term treatment outcomes and complications are sparsely reported, especially from the developing world where the disease burden of inflammatory bowel disease (IBD) is on the rise.⁴ The risk of intestinal and extraintestinal malignancy is increased in patients with IBD because of inflammatory damage to the intestine and complications of long-term immunosuppressive medications.⁵ However, the frequency and type of malignancy in nonperianal fistulizing CD is rarely reported.⁶

Despite the advances in immune pathogenesis and targeted therapies for IBD, the treatment options for nonperianal fistulizing CD remain limited to anti-tumor necrosis factor (TNF)

therapy and surgery, which was the only option before the advent of anti-TNF agents.⁷ Moreover, the progressive nature of CD in the postoperative period,⁸ requirement for repeated resections, and significant morbidity are major limitations to considering surgery the first-line therapy for fistulizing CD. The evidence of anti-TNF agents in patients with nonperianal fistulizing CD is also limited to a few retrospective cohort studies,^{9–12} with most prospective controlled studies including perianal fistulae and excluding internal fistulae.^{13–15} Furthermore, the efficacy of anti-TNF is considered low in this subgroup,^{13,14,16} and it is limited by infectious side effects, including the high risk of tuberculosis (TB), especially in TB-endemic Asian countries.¹⁷ The limitations of both treatment options make it difficult for the clinician in selecting the right option for the patient, and comparative studies are required in this aspect. The present multicenter study was therefore designed to evaluate the long-term outcomes and complications following surgery and anti-TNF therapy in patients with nonperianal fistulizing CD, following up at tertiary care centers in northern and western India.

Materials and methods

Study population. This multicenter study included patients with nonperianal fistulizing CD who were being followed up at the IBD clinic, Department of Gastroenterology, All India Institute of Medical Sciences (AIIMS), New Delhi, and P. D. Hinduja National Hospital & Medical Research Centre, Mumbai, India, from January 2005 to December 2018. Patients with clinical, endoscopic, radiological, or cystoscopic evidence of fistula were included in the analysis. Details of patients with incomplete records were excluded.

Study design and data collection. It was a retrospective analysis of a prospectively maintained database of patients with nonperianal fistulizing CD (including enteric, vesical, vaginal, and cutaneous fistulae). The database is maintained through a paper file system, wherein data are entered by a team of gastroenterologists running the IBD clinic. Patient files contain all dated information concerning the demographic profile, disease and its distribution, including history, medical examination, test results, follow-up symptom assessment, treatment types (both medical and surgical), and their outcomes. The following parameters were extracted from the database: demographic features, disease characteristics (including location, extent, severity, behavior), types of fistulae, radiological details, treatment, response, and long-term complications. Any missing data were confirmed by interviewing the patient in person. Disease characteristics, complications, and long-term response were compared between patients who received surgery as first-line treatment *versus* those who received anti-TNF therapy.

Ethical considerations. Ethical approval was obtained from the Institutional Ethics Committee (IRB No: IECPG-134/19.4.2018, RT-2/2018).

Definitions

Crohn's disease. Diagnosis of CD was made as per European Crohn's and Colitis Organization (ECCO) guidelines, based on characteristic clinical, radiologic, endoscopic, and histologic

features.¹⁸ Disease activity was measured by the Crohn's disease activity index (CDAI).¹⁹ Disease location and behavior were classified on the basis of Montreal classification.²⁰

Definitions of types of fistulae and their response

1. **Enteric fistula:** Communication between one part of the small intestine and another part of the bowel, demonstrated by imaging, endoscopy, or during surgery
 - a. **Complete response:** Complete resolution of symptoms with CDAI <150
 - b. **Partial response:** Decrease in CDAI by ≥ 100 points but not below 150
2. **Enterocutaneous fistula:** Communication between bowel and skin demonstrated radiologically or clinically
 - a. **Complete response:** 100% decrease in discharge with complete closure of fistulous openings
 - b. **Partial response:** $\geq 50\%$ decrease in the number of fistulous openings or $\geq 50\%$ decrease in fistulous discharge (in case of single fistula)
3. **Vesical fistula:** Communication between the bowel and urinary bladder demonstrated radiologically or during surgery or cystoscopy
 - a. **Complete response:** 100% resolution of urinary symptoms (fecaluria, pneumaturia, recurrent urinary tract infection [UTI]) with or without radiological demonstration of the disappearance of fistula with CDAI <150
 - b. **Partial response:** Significant decrease in urinary symptoms or significant resolution on imaging without complete disappearance of the fistulous tract
4. **Vaginal fistula:** Communication between bowel and vagina causing vaginal discharge
 - a. **Complete response:** 100% resolution of symptoms (Vaginal discharge, passage of feces or gas through the vagina) with or without radiological demonstration of the disappearance of fistula with CDAI <150
 - b. **Partial response:** Significant decrease in vaginal symptoms or significant resolution on imaging without complete disappearance of the fistulous tract
5. **Mixed fistula:** Presence of more than one type of fistula

Clinical relapse. Recurrence of discharge (for vaginal fistula, enterocutaneous fistula), urinary symptoms (for vesical fistula), or increase in CDAI by >100 points with total score > 150 after achieving clinical remission was considered clinical relapse.

Statistical analysis. Categorical variables were expressed as percentages, and continuous variables were expressed as mean \pm SD or median (range) as appropriate. A chi-square test was used to compare categorical variables between patients who were treated with medical therapy at the beginning *versus* those who were treated with surgical therapy, and Student t-test or Mann-Whitney U-test was used to compare continuous variables as appropriate. $P < 0.05$ was considered statistically significant. Survival analysis was conducted to compare the response with therapy in both groups. SPSS software version 21.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis.

Results

This study included 53 patients diagnosed with nonperianal fistulizing CD (40 patients were from AIIMS, New Delhi, and 13 patients were from PD Hinduja hospital, Mumbai).

Baseline demographic and clinical profile. The mean age (at the time of presentation) was 29 ± 14 years, and 54.7% ($n = 29$) patients were males. The median disease duration and the median follow-up duration were 96 months (interquartile range [IQR]: 48–156) and 47 (IQR: 26–76) months, respectively. Small bowel involvement was seen in 77.3% ($n = 41$) patients. The most common symptom at the time of presentation was

diarrhea ($n = 28$; 52.8%) followed by abdominal pain ($n = 16$; 30.2%) (Table 1). The most common type of fistula was enteric fistula ($n = 20$; 37.8%) followed by enterocutaneous fistula ($n = 9$; 17%) (Table 1); 22.6% ($n = 12$) patients had mixed fistulae, and 11.3% ($n = 6$) had associated perianal fistula (Table 2). Maximum patients ($n = 43$; 81.2%) developed fistula after a median of 36 (12–72) months since the onset of luminal symptoms, and only 18.8% ($n = 10$) of patients presented with fistula at the disease onset. Of the patients, 39.6% ($n = 21$) were empirically treated with antitubercular therapy (ATT) before being diagnosed with CD; 30.2% ($n = 16$) patients had associated extraintestinal manifestations (EIMs), with arthralgia (22.6%) being the most common EIM [(arthralgia-12(22.6%); aphthous ulcers-1(1.9%); deep venous thrombosis-3 (5.7%)].

Table 1 Baseline characteristics of patients with nonperianal fistulizing Crohn's disease

Parameter	N (%) ($n = 53$)
Age at presentation (mean \pm SD) (years)	29 ± 14
Gender, n (%)	
Male	29 (54.7%)
Female	24 (45.3%)
Median (interquartile range) duration of disease (months)	96 (48–156)
Median (interquartile range) duration of follow-up (months)	47 (26–76)
Smoking, n (%)	5 (9.4%)
Alcohol, n (%)	6 (11.3%)
Presenting symptom, n (%)	
Pain abdomen	16 (30.2%)
Diarrhea	28 (52.8%)
Perianal symptoms	1 (1.9%)
Intestinal obstruction	2 (3.8%)
Others	6 (11.3%)
Disease location (L), n (%)	
Ileal (L1)	9 (17.0%)
Colonic (L2)	12 (22.6%)
Ileocolonic (L3)	24 (45.3%)
Upper gastrointestinal (L4)	1 (1.9%)
L1 + 4 (with upper GI modifier)	4 (7.5%)
L3 + 4 (with upper GI modifier)	3 (5.7%)
Type of fistulae, n (%)	
Enteric fistulae	20 (37.8%)
Mixed fistulae	12 (22.6%)
Cutaneous fistulae	9 (17%)
Vaginal fistulae	7 (13.2%)
Vesical fistulae	5 (9.4%)
Median (interquartile range) duration of disease onset to identification of fistula (months)	36 (12–72)
Mode of detection, n (%)	
Clinical	26 (49.1%)
Radiological	24 (45.3%)
Others	3 (5.6%)
History of antitubercular therapy, n (%)	21 (39.6%)
Extraintestinal manifestations, n (%)	16 (30.2%)
Malignancy, n (%)	2 (3.8%)
Death, n (%)	1 (1.9%)

Treatment outcomes

Response to anti-TNF therapy. Twenty-two patients were managed with upfront anti-TNF (infliximab [IFX]: 17; adalimumab [ADA]: 2; both: 3) therapy (median duration of therapy: 15.5 [IQR: 8–36] months) (Fig. 1). Overall complete response was achieved in 40.9% ($n = 9$) and partial response in 54.5% ($n = 12$) patients, which was sustained for a median of 22 months (IQR: 14–46). Patients who achieved complete response with biologicals maintained response for a median duration of 47 months (IQR: 25–69 months). Primary nonresponse to anti-TNF in the entire cohort (including patients who received biologicals in surgery group) was 14% for IFX and 27% for ADA at 8 weeks. Eight patients had a secondary loss of response at a median follow-up of 20 months (IQR: 14–43). Among them, 25% ($n = 2$) of patients responded after switching to another anti-TNF; 31.8% ($n = 7$) of patients stopped anti-TNF after a median duration of 11 months (three patients underwent surgery, and the remaining patients were maintained on immunomodulators). Surgery was required in three patients (13.6%, two with partial response and one with primary nonresponse) and could be avoided in the remaining patients over a median follow-up of 56 months. None of the factors, such as age at presentation, gender, type of fistula, duration of disease, duration of disease onset to initiation of anti-TNF, extent, and presence of mixed fistulae, could predict complete response to anti-TNFs (Table SS1).

Complications in biological group. Among all the patients who received biologics (including patients who received biologics in surgery group; $n = 31$), complications were noted in 19%

Table 2 Distribution of the types of fistulae among patients with mixed fistulae

Type of fistula	n (%)
Enteroenteric + enterocutaneous	2 (3.7%)
Enteroenteric + enterovesical	2 (3.7%)
Enterocutaneous + rectovaginal	1 (1.9%)
Enterocolic + enterovesical	1 (1.9%)
Enteroenteric + ileovaginal	1 (1.9%)
Enterovesical + enterocutaneous	1 (1.9%)
Enteroenteric + enterocolic + enterovesical	1 (1.9%)
Enterocolic + enterocutaneous + colovesical	1 (1.9%)

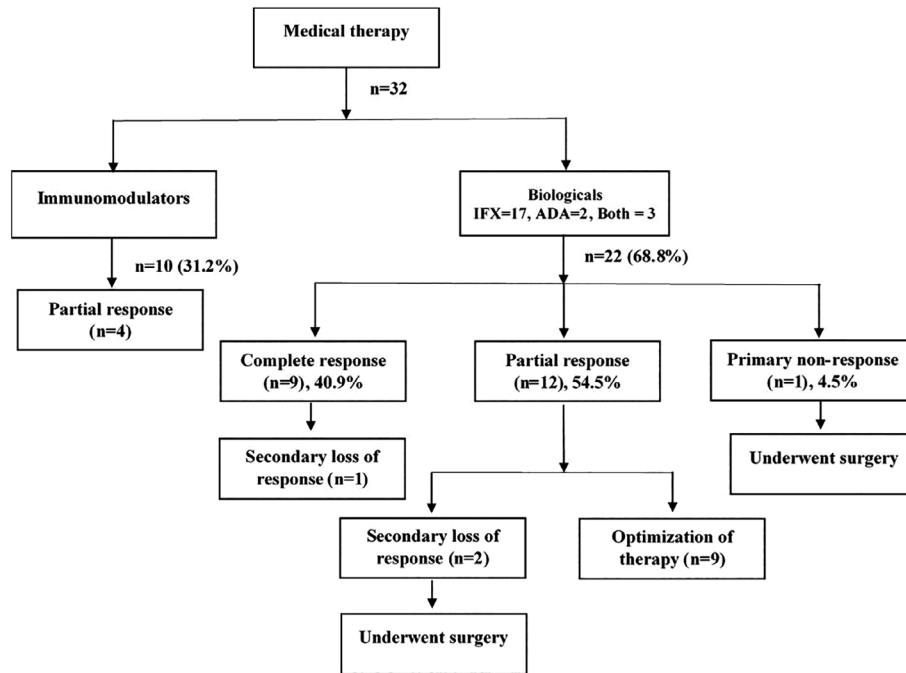


Figure 1 Details of medical therapy in patients with nonperianal fistulizing Crohn's disease.

(n = 6) patients, of which 6.4% (n = 2) patients developed TB (pulmonary and endobronchial) despite screening for latent TB. Other notable complications include avascular necrosis,

herpes zoster, intra-abdominal abscess, and recurrent UTIs that were managed conservatively and required transient stoppage of anti-TNFs.

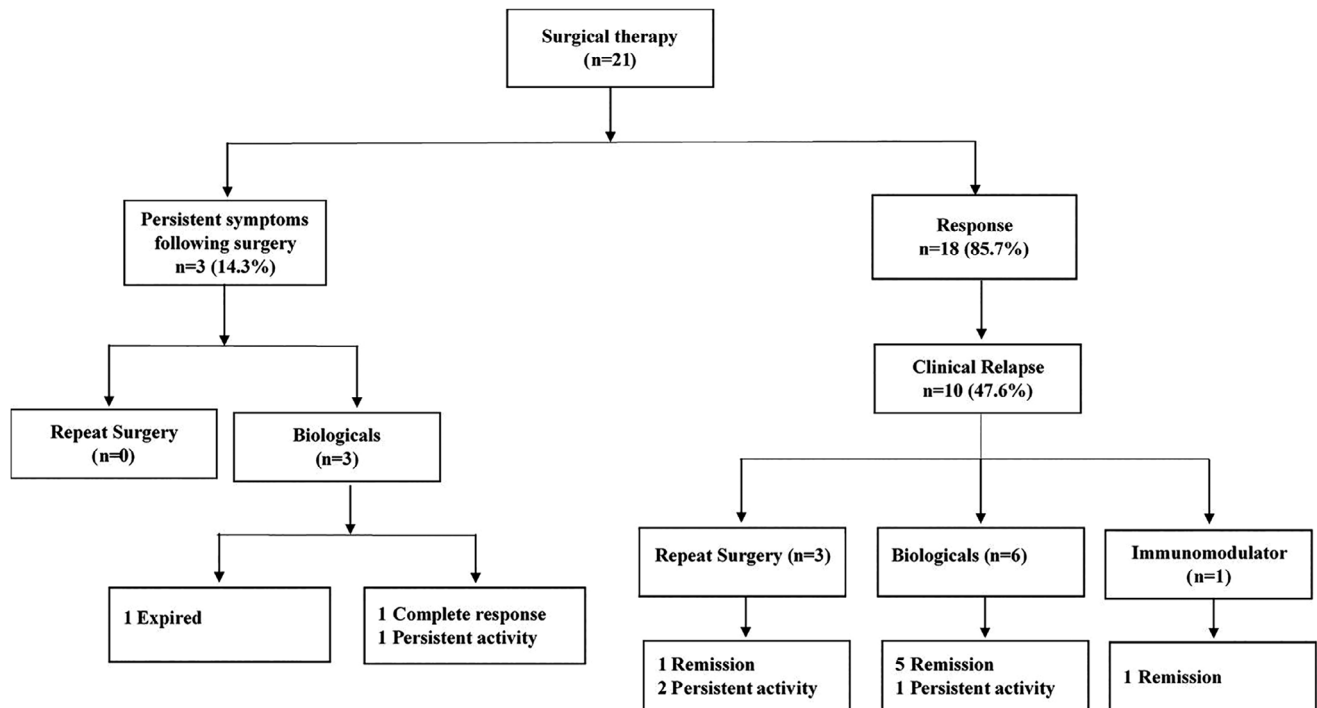


Figure 2 Details of surgical therapy in patients with nonperianal fistulizing Crohn's disease.

Table 3 Comparison of baseline characteristics and treatment response between anti-tumor necrosis factor (TNF)-first strategy and surgery-first strategy

Parameter	Anti-TNFs first (<i>n</i> = 22)	Surgery first (<i>n</i> = 21)	<i>P</i> value
Gender, <i>n</i> (%)			
Male	8 (36.4%)	14 (66.7%)	0.04
Female	14 (63.6%)	7 (33.3%)	
Mean (\pm SD) age at presentation (years)	25 \pm 14	31 \pm 15	0.2
Median (interquartile range) duration of disease (months)	96 (52–156)	144 (80–204)	0.3
Median (interquartile range) duration of follow-up	48 (29–90)	44 (26–81)	0.7
Small bowel involvement, <i>n</i> (%)	16 (72.7%)	18 (85.7%)	
Type of fistula, <i>n</i> (%)			
Enteric	8 (36.4%)	8(36.4%)	0.6
Vesical	1 (4.5%)	3 (14.2%)	
Vaginal	2 (9.0%)	2 (9.5%)	
Cutaneous	5 (22.7%)	2 (9.5%)	
Mixed	6 (27.3%)	6 (28.5%)	
Perianal fistulae, <i>n</i> (%)	1 (4.5%)	4 (19%)	0.1
Mixed fistulae, <i>n</i> (%)	6 (27.3%)	6 (27.3%)	>0.9
Associated bowel stricture, [†] <i>n</i> (%)	30%	33.3%	0.5
Median (interquartile range) duration between disease onset and fistula identification (months)	36 (6–72)	36 (12–72)	0.8
Median (interquartile range) duration between symptom onset and primary therapy (surgery or biologics) (months)	36 (7–58)	24 (15–72)	0.6
Malignancy	0	2	0.2
Median (interquartile range) duration of overall response (months)	22 (14–46)	36 (6–54)	0.8
Change to another mode of therapy (surgery to medical/medical to surgery), <i>n</i> (%)	3 (13.6%)	10 (47.6%)	0.02

[†]Stricture data available for all patients in surgery group and 10 patients in medical group.

Response to surgery as the first treatment strategy.

Twenty-one patients were managed with upfront surgery (Fig. 2). The median duration between the onset of CD and surgery was 24 (13–73) months. The most common surgeries performed were small bowel resection (*n* = 7; 33.3%) and diversion with or without resection of fistula (*n* = 7; 33.3%) (Fig. 3). In 28.5% (*n* = 6) of patients, surgery was performed for emergency indications such as bleeding, obstruction, and perforation. Overall, 28.5% (*n* = 6) required ≥ 2 surgeries. Of patients, 47.6% (*n* = 10) relapsed after a median duration of 36 months (7 received post-operative prophylaxis) and required either repeat surgery (*n* = 3) or medical therapy (anti-TNFs:9; immunomodulator:1). Cumulative probabilities of recurrence after surgery were 17.6, 31, and 39% at 1, 3, and 5 years, respectively. None of the factors, such as age at onset, gender, type of fistula, smoking, EIMs, presence of mixed fistulae, presence of perianal fistulizing disease, duration between onset of CD and fistula, ileocolonic disease, and postsurgery prophylaxis, could predict postsurgery recurrence (Table S2). Of nine patients who received anti-TNFs following surgical recurrence, 77.7% (*n* = 7) of patients had complete response, which was maintained for a median duration of 28 months (14–40).

Anti-TNF versus surgical therapy. Except for gender distribution, there was no statistically significant difference between

anti-TNF and surgical groups for baseline characters such as duration of disease, duration of follow-up, age at presentation, type of fistula, and duration between CD onset and fistula identification (Table 3). Although the median duration of response was numerically higher in the surgical group (36 vs 22 months), it did

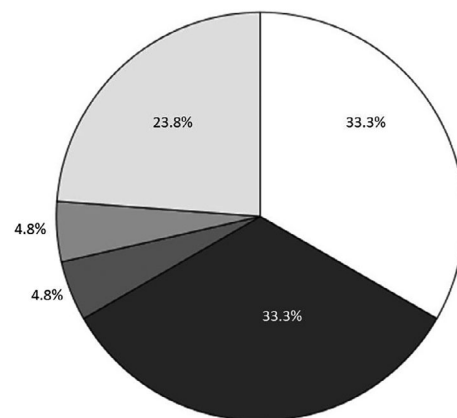


Figure 3 Pie diagram showing different types of surgeries in non-perianal fistulizing Crohn's disease. □ Small bowel resection. ■ Diversion. ■ Colectomy. ■ Resection of fistula. □ Ileocolonic resection.

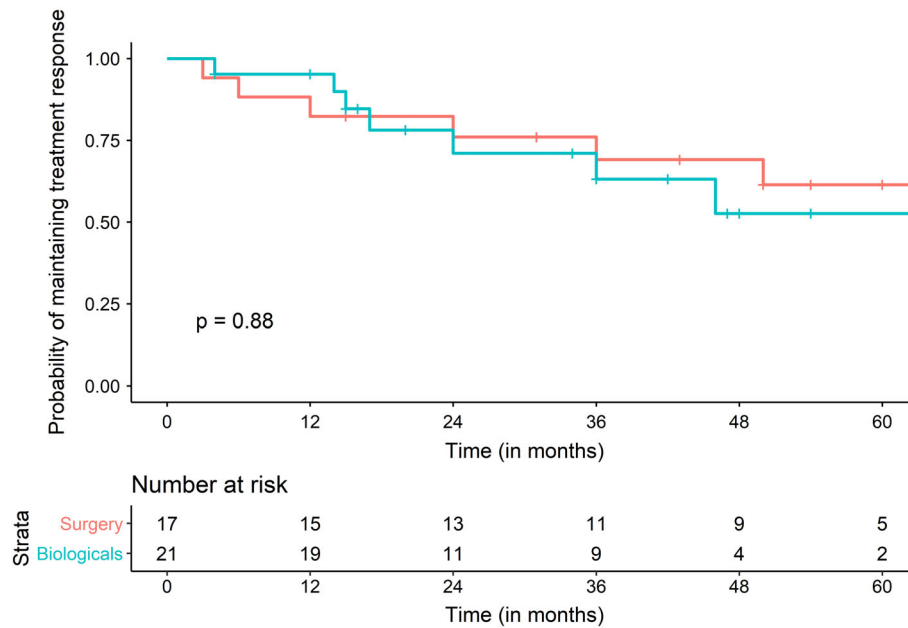


Figure 4 Kaplan Meier curve comparing overall probability of maintenance of treatment response between anti-tumor necrosis factor (TNF)- and surgery-first strategies. —+— Strata. —+— Surgery. Biologicals.

not achieve statistical significance ($P = 0.8$) (Fig. 4). The overall probability of maintaining response at 1, 2, and 3 years was 95.2% versus 82.4%, 71% versus 76%, and 63% versus 69% ($P = 0.8$) between the anti-TNF and surgical groups, respectively.

Response with immunomodulators. Ten patients received immunomodulators (IM) (azathioprine/6-mercaptopurine/methotrexate) as the primary therapy. Among these patients, 40% ($n = 4$) had a partial response, which was maintained for a duration of 54 months, and in the rest of the patients, there was no response. One patient in the surgery group achieved complete response with IM after clinical relapse following surgery.

Complications in surgery group. Intra-abdominal abscess was present in five patients (three patients were managed with surgery, and two patients were managed with percutaneous drainage). Thromboembolic complications were seen in 5.6% of patients. Fistula-associated cancer developed in two patients (3.7%). The first patient had prolonged disease course (disease duration 38 years) and underwent multiple abdominal surgeries. Enterointestinal fistula was identified during the third surgery (18 years from onset of disease), which was resected along with segment of bowel. Histopathology showed features of well-differentiated adenocarcinoma arising from fistulous tract. The other patient developed mucinous adenocarcinoma in colovesical fistula associated with perianal fistula. He was symptomatic for 24 months with chronic diarrhea before developing symptoms of colovesical fistula (pneumaturia, fecaluria) and perianal fistula.

Discussion

CD is a heterogeneous disorder in terms of extent, severity, and long-term disease course. Fistulizing disease lies at the extreme end of the severity spectrum and, as per population-based studies, can develop in 35% patients over 25 years, of which 46% of fistula are nonperianal in nature.² Unlike perianal fistula, the disease course, treatment outcomes, and complications in patients with nonperianal fistulizing CD are not well characterized, and the present study has tried to fill this knowledge gap by analyzing these patients from two different regions of India.

Of the 53 patients with NPF, more than 80% developed it later in the disease course, over a follow-up duration of 3 years. The overall proportion of NPF in the present cohort may be slightly lower than other series, probably because of relatively short follow-up period, and numbers may increase with time. Enteric fistulae were the most common type, followed by cutaneous fistulae, and the distribution matched the other reports.²¹ About 40% of patients received ATT before the diagnosis of CD, which could be higher than the previous reports of ATT trial in patients with CD.²² This could reflect tertiary care bias as most of the patients had received ATT before being referred to this hospital.

Approximately 40% of patients (22/53) were treated with upfront anti-TNF therapy (median duration of 15 months), which is significantly higher than the overall proportion of patients treated with anti-TNFs at our centers.¹⁷ Of the patients treated, 40.9% achieved complete remission, and more than 90% of patients had at least a partial response. The overall response was sustained over 22 months, whereas among those patients who achieved complete remission, it was maintained for 47 months. Overall, only three patients (13.6%) required surgery,

and the majority of patients could avoid surgery over a follow-up of approximately 5 years. These results were consistent with results from the west and other Asian centers.²³ Response to anti-TNF therapy in fistulizing CD depends on the type of fistulae,²³ with perianal fistulae responding better than NPF.^{13,14} Kobayashi *et al.* demonstrated a 5-year cumulative closure rate of 29% with anti-TNF therapy in the CD-associated internal fistulae, with 47.2% patients requiring surgical therapy due to failure of anti TNFs. Complications, including abscess formation, obstruction, and exacerbation of symptoms, were seen in 17% of patients.⁹ A study by the GETAID group showed complete closure of enterocutaneous fistula in 33%, of which half of the patients relapsed during follow-up, and surgical resection was required in 54%.¹⁰ Another multicenter study from Spain revealed lower remission rates of only 16.7% with anti-TNF therapy in patients with genital fistulae.²⁴ Long-term results from CHARM and ADHERE studies have also shown similar response rates with ADA, with 24% healing of draining fistulae at 4 years of follow-up.²⁵ Although the anti-TNF response rates in the present study match the other reports, the rates of surgery due to anti-TNF failure (13.6%) and development of abscesses after anti-TNF therapy are much lower. This could be explained by less frequent coexisting strictures in the present cohort (30%) compared to other studies, where >50% of patients had a coexisting stricture.⁹

Twenty-one patients were managed with surgery as first-line therapy, and the most common type of surgery was small bowel resection with or without diversion, and 28.5% surgeries were performed for emergent indications. About half of patients relapsed after a median duration of 36 months. Overall, one-third of surgeries performed in CD are due to intra-abdominal fistulae.²⁶ Presence of strictures, multiple fistulae, and vesical fistulae are predictive factors for surgery in this group of patients.²⁷ In a surgical series by Yoon *et al.*, 40% of surgeries were performed for intra-abdominal abscess or obstruction, and only 12% were done for medically intractable disease. Postoperative complications were seen in 16% of patients, and 9% required repeat surgery for recurrent disease.²¹ In the present study, although the postoperative recurrence rate was 47.6%, only three patients required repeat surgery, which is similar to the above report. Lower frequency of postoperative complications in the present study could be due to a lower proportion of emergent surgery compared to the study by Yoon *et al.*

Overall probability of maintaining response at 1, 2, and 3 years was comparable between the medically and surgically treated patients. Another interesting finding in our study is that anti-TNFs are effective in treating postoperative recurrence in nonperianal fistulizing CD with a 70% complete response.

Complications in NPF could be disease or treatment related. In the present study, overall complications were noted in 19% of patients treated with anti-TNFs, of which 6.4% of patients developed TB (pulmonary and endobronchial). A recent study from our institute also showed a high incidence of TB reactivation (11.6%) following anti-TNFs in patients with IBD (CD and ulcerative colitis [UC]).¹⁷ Another striking finding was the development of malignancy in 3.7% ($n = 2$) patients. However, there is evidence to suggest that the risk of small bowel cancers (SBCs), colorectal cancer, and fistula-associated cancer increases in CD, however, unlike UC,²⁸ and the risk of

malignancy in CD is not well defined.²⁹ Regarding SBCs, three meta-analyses have suggested risk estimates between 27.1 and 33.2, and the postulated risk factors have been young age, male gender, long duration of disease, associated fistula, prior stricturoplasty, bypassed bowel loop, etc.^{30–33} The reports on fistula-associated cancer are mostly related to perianal fistula, and there are very few case reports or case series that have described the incidence of malignancy in NPF.

Although retrospective, the data were extracted from a prospectively maintained database with a reasonably long follow-up and results on treatment outcomes and complications, including malignancy. The study, however, is limited by small sample size, although it represents two different parts from a country that is experiencing a rise in disease burden of IBD. Furthermore, the response was assessed clinically, and follow-up images were not available for all patients. Definitions of fistula closure are not uniform across various studies, which need to be standardized for comparison of results.

To conclude, nonperianal fistulizing CD has an aggressive course with limited treatment options and requires individualized treatment. In this retrospective analysis, both anti-TNF therapy and surgery appear to have an equal response, which needs to be confirmed in prospective studies. These patients are at higher risk of fistula-related malignancy, and the threshold of suspicion should be low in patients with longer disease duration, especially in the presence of nonresponse to medical therapy.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Table S1. Factors associated with complete response with biologicals

Table S2. Factors associated with postsurgery recurrence