

ORIGINAL RESEARCH ARTICLE

## Risk factors for recurrence of Crohn's disease requiring surgery in patients receiving post-operative anti-tumor necrosis factor maintenance therapy

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### Abstract:

**Objectives:** Anti-tumor necrosis factor (TNF) antibodies have shown efficacy in the prevention of recurrence of Crohn's disease after intestinal resection. However, some patients develop surgical recurrence despite this therapy. We aimed to evaluate the risk factors for recurrence of Crohn's disease requiring surgery while receiving post-operative anti-TNF therapy. **Methods:** We performed a retrospective evaluation of 164 patients who had received post-operative anti-TNF maintenance therapy between 2002 and 2016. We classified Crohn's disease-related re-operation as surgical recurrence and analyzed its risk factors using the Cox proportional hazard model. **Results:** Of the 164 participants, 128 had received infliximab and 36 had received adalimumab maintenance therapy. We obtained follow-up data over a mean of 60.2 months. The proportion of patients with surgical recurrence at 5 years was 14.9%. The only independent risk factor for surgical recurrence, which we identified was post-operative smoking habit (odds ratio, 5.03; 95% CI, 1.14-12.8; P=0.033). **Conclusions:** Post-operative smoking may be a significant risk factor for post-operative surgical recurrence of Crohn's disease while receiving anti-TNF maintenance therapy.

### Keywords:

Crohn's disease, operation, recurrence, anti-TNF therapy, smoking

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### Introduction

Crohn's disease (CD), a chronic, lifelong, inflammatory bowel disorder, is characterized by repeated relapse and remission; and most patients require bowel resections<sup>1,2)</sup>. Resection of the affected intestine is the ultimate option for refractory segmental CD and the requirement for further surgery remains the most objective endpoint in studies regarding disease recurrence. Without further treatment, 25 to 30% of post-operative patients with CD will require further surgery by 5 years<sup>3)</sup>. Thus, post-operative recurrence of CD is an important management challenge. In recent years, anti-tumor necrosis factor (TNF) antibodies, namely infliximab (IFX) and adalimumab (ADA), have shown efficacy in the prevention of CD after intestinal resection<sup>4,7)</sup>. We have previously reported that post-operative IFX maintenance therapy reduces the incidence of surgical recurrence of CD<sup>8)</sup>.

However, some patients do develop surgical recurrence despite post-operative anti-TNF antibodies maintenance therapy. Therefore, this retrospective study aimed to evaluate the risk factors for surgical recurrence of CD in patients receiving post-operative anti-TNF antibody maintenance therapy.

### Methods

All patients in our institution's database with CD who had undergone bowel resection at Mie University Hospital between May 2002 and February 2016 were considered for inclusion in this retrospective study. A total of 180 patients underwent 247 CD surgeries during the study period. The 164 cases (146 patients, including 16 patients with two operations and 1 patient with three operations) who had received post-operative anti-TNF antibody maintenance therapies from within 6 months of primary surgery were included

in the present analysis.

Diagnoses of CD were based on clinical, radiographic, endoscopic, and pathological data and had been established according to the accepted criteria<sup>9,10</sup>, the Montreal classification being used to assess the behavior, severity, extent, and location of disease<sup>11</sup>.

All patients provided written informed consent for using their data in this study. The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board.

Indications for post-operative anti-TNF antibody maintenance therapy were considered as a high risk of CD recurrence because of having undergone multiple operations within a short period, requiring early surgery despite aggressive medical treatment, or having a longer than usual portion of bowel being affected. With regard to the selection of an anti-TNF antibody, patients who had been receiving anti-TNF antibodies prior to surgery were prescribed the previously administered drug as soon as possible. Anti-TNF antibody-naïve patients chose between IFX and ADA themselves after receiving an explanation that large clinical trials comparing both these agents found similar efficacy in induction and maintenance of remission for patients with moderate to severe CD, and adverse effects of these drugs are also comparable. The previously unused anti-TNF antibody was selected for post-operative therapy in patients with a history of episodic administration or long breaks from an anti-TNF antibody.

The induction phase for IFX was defined as the administration of a standard regimen of three IFX infusions (5 mg/kg) at 0, 2, and 6 weeks, and subsequent maintenance infusions (5 mg/kg) every 8 weeks. Patients with loss of response (LOR) to 5 mg/kg of IFX had their dose escalated to 10 mg/kg. ADA induction was with subcutaneous injections of 160 mg in week 0, 80 mg in week 2, and then 40 mg every other week. Patients showing LOR to 40 mg every other week of ADA had their doses escalated to 40 mg every week. Patients who did not tolerate IFX (i.e., by infusion reactions) were switched to ADA.

The following characteristics were recorded for all participants: Gender, age, and disease location and behavior at diagnosis (Montreal classification)<sup>11</sup>, age, strictureplasty, ileocecal resection, presence of anal lesions at operation, smoking habit after primary surgery, and post-operative concomitant use of thiopurine and an elemental diet. The primary outcome event was defined as re-operation for CD recurrence, confirmation of such recurrence being based on pathological examination of the resected specimen.

Statistical analysis was performed using IBM SPSS statistics ver. 22 (IBM). Surgical recurrence-free survival was calculated as the time from the date of primary operation to the date of re-operation or last follow-up. Univariate analysis of the probability of re-operation-free survival was performed by the Kaplan-Meier method and the risk of CD-related re-operation was analyzed by the Cox proportional hazard model. A *P* value of less than 0.05 was considered signifi-

cant.

## Results

A total of 112 initial operations and 52 re-operations was included in the 164 cases. Anti-TNF antibody maintenance therapy comprised IFX in 128 cases and ADA in 36 cases (including 10 patients who did not tolerate IFX and were switched to ADA). Relevant baseline characteristics are shown in Table 1. Follow-up data were obtained over a mean of 60.2 months (range 8-206 months). By the end of follow-up, 18 patients had required re-operation while receiving post-operative anti-TNF antibody maintenance therapy. The percentages of patients with surgical recurrence at 1, 3, 5, and 10 years were 1.3%, 5.9%, 14.9%, and 16.7%, respectively (Figure 1).

Results of univariate analysis of factors associated with surgical recurrence after intestinal resection for CD are shown in Table 2. The only independent risk factor significantly associated with surgical recurrence was post-operative smoking habit (odds ratio, 5.03; 95% CI, 1.14-12.8; *P*=0.033) (Figure 2). There was a non-significant tendency for surgical recurrence to occur more frequently in patients without large intestinal involvement (Montreal L1) (odds ratio, 2.38; 95% CI, 0.94-6.05; *P*=0.068) (Figure 3).

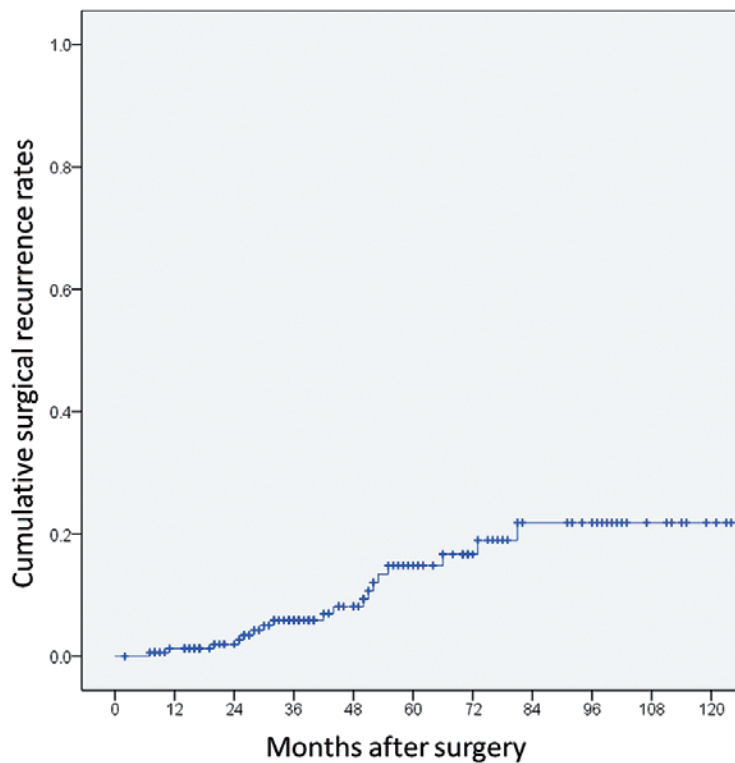
## Discussion

Post-operative recurrence of intestinal CD can be defined as endoscopic, histological, clinical, radiological, or surgical. Anti-TNF antigens have recently been shown to be effective in preventing endoscopic and clinical recurrence of CD. In a randomized, placebo-controlled study conducted over 1 year, Regueiro et al.<sup>4</sup> reported that administration of IFX after bowel resection was effective in reducing the incidence of endoscopic (9.1% vs. 84.6%, *P*=0.0006) and histological (27.3% vs. 84.6%, *P*=0.01) recurrence of CD. Savarino et al.<sup>6</sup> have reported that post-operative ADA is also effective. In their prospective, open-label, randomized trial with a 2-year follow-up, they found significantly lower rates of endoscopic and clinical recurrence in patients receiving ADA (6.3% and 12.5%, respectively) than in those receiving azathioprine (64.7% and 64.7%, respectively) or mesalazine (83.3% and 50%, respectively).

In a retrospective direct comparison between IFX and ADA therapy after ileocecal resection, there was no significant difference between the two anti-TNF agents in terms of early post-operative endoscopic recurrence rates (12% vs. 32%, *P*=0.815)<sup>12</sup>. With regard to surgical recurrence, Regueiro et al.<sup>13</sup> reported a prospective, open-label study with follow-up for at least 5 years after surgery: They found a significantly lower surgical recurrence rate in patients who had received IFX during most of the follow-up than in patients who had received it for shorter periods (20.0% vs. 64.3%, *P*=0.047). Our previous retrospective case-control study showed a lower incidence of surgical recurrence of

**Table 1.** Clinical Characteristics of Patients with Crohn’s Disease Receiving Post-operative Anti-TNF Antibody Maintenance Therapy.

Variable		N=164 (%)
Gender	Male	120 (73.2)
	Female	44 (26.8)
Age at primary operation (years)		35.5 (range 14-65)
Age at diagnosis	≤40 yrs	149 (90.9)
	>40 yrs	15 (9.1)
Disease location	Terminal ileum	61 (37.2)
	Colon	17 (10.4)
	Ileum and colon	86 (52.4)
Disease behavior	Non-stricturing	4 (2.4)
	Stricturing	80 (48.8)
	Penetrating	80 (48.8)
Presence of anal lesions	Yes	71 (43.3)
	No	93 (56.7)
Type of operation	Initial surgery	112 (68.3)
	Reoperation	52 (31.7)
Ileocecal resection only	Yes	16 (9.2)
	No	148 (90.8)
Strictureplasty	Yes	26 (15.9)
	No	138 (84.1)
Post-operative smoking habit	Yes	6 (3.7)
	No	158 (96.3)
Post-operative thiopurine use	Yes	34 (20.7)
	No	130 (79.3)
Post-operative elemental diet use	Yes	57 (34.8)
	No	107 (65.2)



**Figure 1.** Kaplan-Meier plots illustrating cumulative surgical recurrence rates in patients with Crohn’s disease receiving post-operative anti-TNF maintenance therapy.

**Table 2.** Results of Univariate Analysis of Factors Associated with Surgical Recurrence after Intestinal Resection for Crohn's Disease in Patients Receiving Post-operative Anti-TNF Maintenance Therapy.

Variable	OR	95% CI	P
Gender			
M/F	2.04	0.59-7.09	0.259
Age at primary surgery			
<40 years/≥40 years	1.65	0.25-12.5	0.657
Age at diagnosis			
<40 years/≥40 years	1.23	0.47-3.44	0.628
Post-operative smoking			
Yes/No	5.03	1.14-22.2	0.033
Small intestinal involvement			
Yes/No	2.38	0.026-40.5	0.361
Large intestinal involvement			
No/Yes	2.38	0.01-37.4	0.068
Multiple stenoses in small intestine			
No/Yes	1.23	0.41-3.75	0.713
Disease behavior			
Non-penetrating/Penetrating	1.34	0.53-3.45	0.534
Perianal disease			
No/Yes	1.13	0.45-2.87	0.797
Type of operation			
Reoperation/Initial surgery	1.21	0.47-3.12	0.696
Strictureplasty			
Yes/No	1.60	0.56-5.24	0.343
Ileocecal resection only			
No/Yes	1.70	0.23-12.8	0.608
Receiving elemental diet			
Yes/No	2.28	0.90-5.77	0.082
Thiopurine use			
Yes/No	1.12	0.40-3.15	0.831

Cox proportional hazard model

CD in patients receiving post-operative IFX maintenance therapy than in control patients at 36 months follow-up (6.0% vs. 68.0%,  $P=0.002$ ). In addition, in this retrospective study, the cumulative rates of surgical recurrence while receiving post-operative anti-TNF antibody maintenance therapy were 5.9% and 14.9% at 3 and 5 years follow-up, respectively. These data indicate that post-operative anti-TNF antibody maintenance therapy is highly effective in minimizing surgical recurrence of CD; however, this treatment is ineffective in some patients.

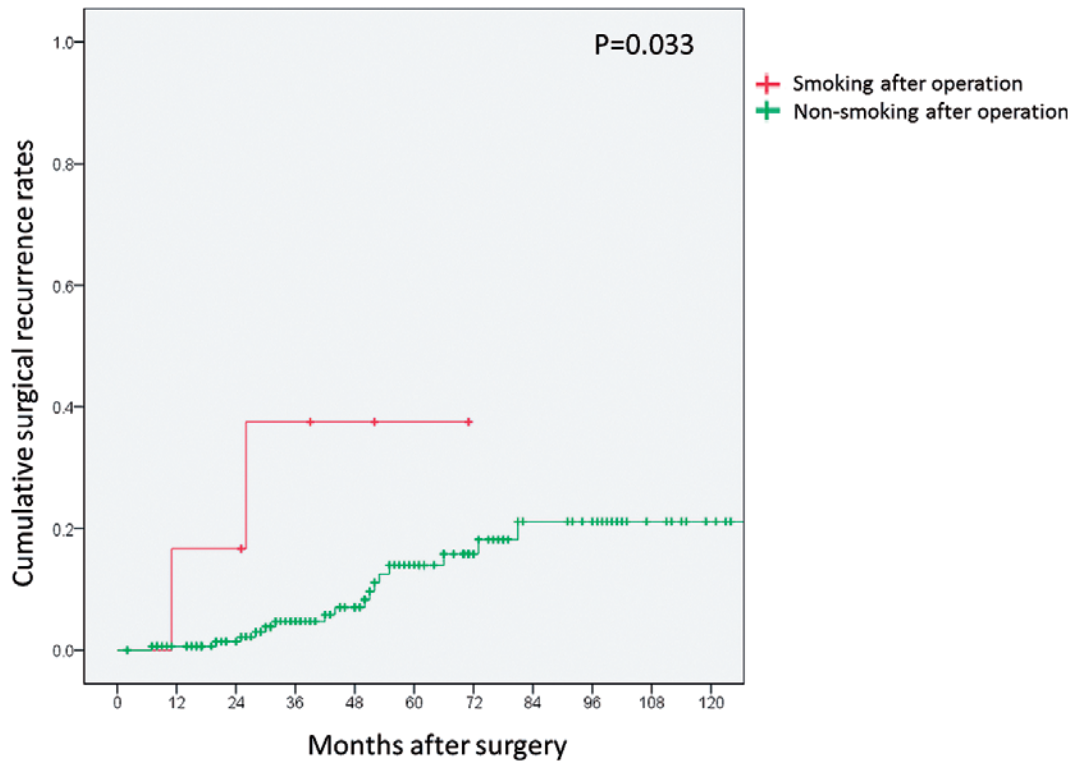
In this study, we found that post-operative smoking was a significant risk factor for post-operative surgical recurrence of CD while receiving maintenance therapy with anti-TNF antibodies. Previous studies have shown that smoking is both a risk factor for relapse of CD in general and for surgical recurrence in particular<sup>14-17</sup>. A recent multicenter prospective cohort study showed that despite the widespread use of immunosuppressants and anti-TNF antibodies, smokers with CD have a more severe disease course, including greater requirements for treatment, than non-smokers<sup>18</sup>. Furthermore, a retrospective study conducted to evaluate the effects of

smoking at diagnosis on the clinical outcomes after endoscopic dilation found that smoking doubles the risk of recurrent stricture formation requiring further intestinal resection or strictureplasty. Maintenance therapy with azathioprine did not influence the subsequent course or the need for new interventions<sup>19</sup>.

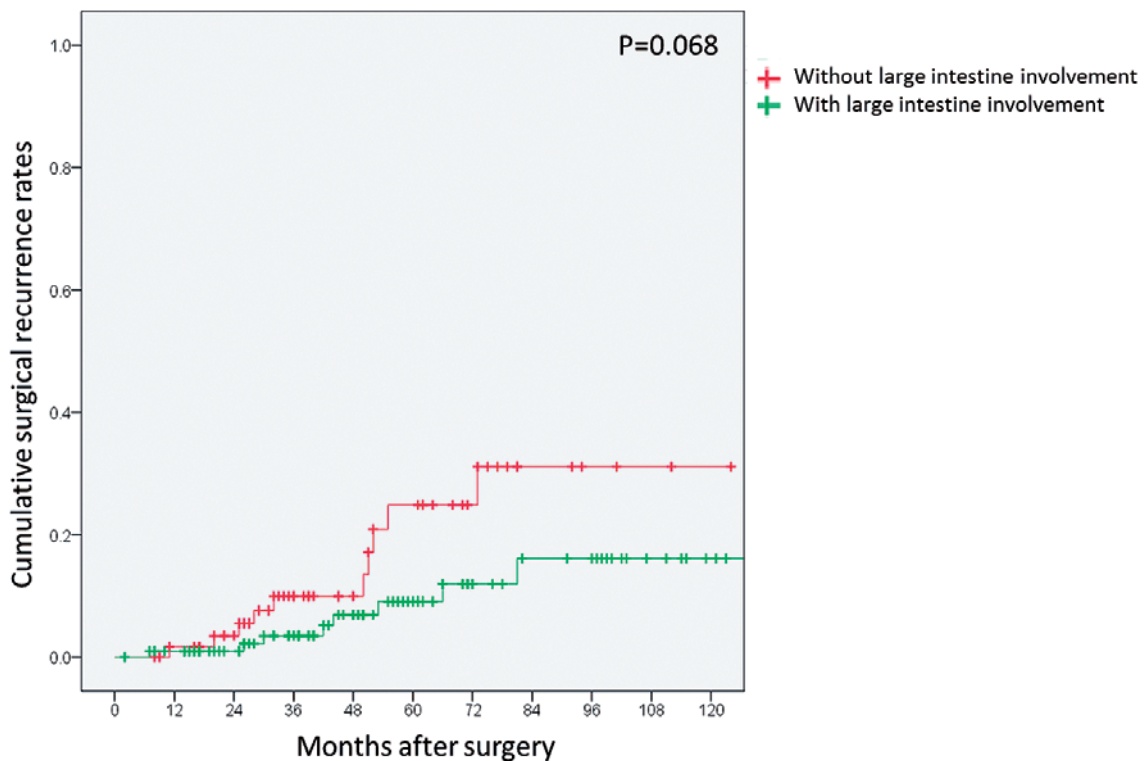
Our current data support the finding that smoking habit adversely affects the risk of recurrence despite anti-TNF maintenance therapy.

On the other hand, evidence for routine use of azathioprine in post-operative patients with CD is not definitive<sup>20,21</sup>. ADA has been shown to be superior to thiopurines in preventing early post-operative CD recurrence in high-risk patients<sup>22</sup>. Moreover, several studies have shown that elemental diet therapy is effective in minimizing endoscopic recurrence<sup>23</sup> and reducing the incidence of second resections<sup>24,25</sup>.

However, we found no association between concomitant use of azathioprine or elemental diet and surgical recurrence. Because the indications for use of these concomitant drugs were not standardized, there is probably some bias in the present data. Our findings should, therefore, be assessed



**Figure 2.** Kaplan-Meier plots illustrating cumulative surgical recurrence rates of Crohn's disease in patients receiving post-operative anti-TNF maintenance therapy grouped by post-operative smoking or non-smoking. Post-operative smoking habit was an independent risk factor for surgical recurrence (odds ratio, 5.03; 95% CI, 1.14-12.8;  $P=0.033$ ).



**Figure 3.** Kaplan-Meier plots illustrating cumulative surgical recurrence rates in patients with Crohn's disease who received post-operative anti-TNF maintenance therapy grouped by presence or not of large intestinal involvement. There was a non-significant tendency toward higher rates of surgical recurrence in patients without large intestinal involvement (Montreal L1) (odds ratio, 2.38; 95% CI, 0.94-6.05;  $P=0.068$ ).



by further controlled studies.

In this study, we identified a non-significant tendency for surgical recurrence of CD to occur in patients without large intestinal involvement, that is, with ileal disease (Montreal L1), despite anti-TNF maintenance therapy. Recurrence after resection is considered to occur more frequently with small bowel disease, as previously stated<sup>26</sup>. In addition, several studies have shown that the extent of ileal involvement is a predictor of early post-operative recurrence<sup>27,28</sup>. Likewise, ileal disease location is a significant risk factor for a second ileocolic resection<sup>29</sup>. Although, our data did not confirm that small intestinal involvement is a significant risk factor for surgical recurrence of CD while receiving post-operative anti-TNF maintenance therapy, CD limited to the small intestine should probably be managed by more aggressive post-operative therapy.

### Conclusion

Post-operative smoking may be a significant risk factor for post-operative surgical recurrence of patients with CD receiving maintenance therapy with anti-TNF antibodies. Although further larger studies are necessary to assess this apparent disadvantage, we believe that all high-risk patients with CD should be encouraged to quit smoking after surgery.

#### Conflicts of Interest

The authors declare that there are no conflict of interest.

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