

## Special Article - Crohn's Disease and Colitis

# Risk Factors of Surgical Recurrence after Resection for Crohn's Disease

**Makni A\*, Magherbi H, Heni AE, Haddad A, Awali M, Daghfous A, Ksantini R, Fteriche F, Jouini M, Kacem M, Rebai W, Daghfous A and Safta ZB**  
Department of General Surgery 'A', La Rabta Hospital, Tunisia

\*Corresponding author: Makni Amin, Department of General Surgery 'A', La Rabta hospital, Tunis El Manar University, Jabbari 1007, Tunis, Tunisia

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## Abstract

**Objective:** The surgery is required in more than 80% of patients with Crohn's disease. Crohn's disease is associated with high rates of postoperative recurrence. The aim of the study was to identify, the risk factors of postoperative 'surgical recurrence' after the first resection for Crohn's disease.

**Methodology:** We report a retrospective study from January 1998 to September 2010 that studied 226 patients originated only from Tunisia (in North Africa), operated on for MC. We had been interested to the risk factor of surgical recurrence of Crohn's disease.

**Results:** Mean age was 33 years. The average time between the onset of the disease and the surgical procedure was 31 months. The diagnosis of CD was established preoperatively in 213 patients (94%). The diagnosis was made intraoperatively because of an acute complication in 5 cases (2.2%) and postoperatively in 8 cases (3.5%). The most common location was the ileocecal junction in 184 cases (81.4%). The most common type of lesion was the mixed form (stricture and fistula) in 123 cases (54.4%). Operative mortality was 0.04% (n=1). Specific morbidity was 8.4% (n=19). In long term, a surgical recurrence was noted in 18 patients (8%). In multivariate analysis, independent risk factors for recurrence were: smoking (p=0.012, ORs=3.57) and post-operative medical treatment (p=0.05, ORs=2.6).

**Conclusion:** Our series is unique for a lower rate of the postoperative recurrence (8%). The two risk factors of recurrence are smoking and the necessity of postoperative medical prophylaxis.

**Keywords:** Crohn's disease; Surgery; Recurrence

## Introduction

The surgery is required in more than 80% of patients with Crohn's disease (CD) [1]. The aim of surgery is to treat complicated lesions [2]. The most important principle of the surgery is to perform an intestinal resection as limited as possible. Crohn's disease is associated with high rates of postoperative recurrence. At 10 years after surgery, 75% of patients suffer recurrence and 45% of these require re-intervention. The aim of the study was to identify, the risk factors of postoperative 'surgical recurrence' after the first resection for Crohn's disease.

## Methods

### Study design and patient selection

This is a retrospective study, with prospective collection of data, conducted from January 1998 to September 2010, which included all patients undergoing surgery for primary CD. All patients born and living in Tunisia in North Africa. The diagnosis of CD was confirmed in all cases by histological examination of endoscopic biopsies or specimen after bowel resection. We excluded from this study, patients initially operated in another center and patients operated on for isolated anoperineal lesions of CD. The management was multidisciplinary and standardized for all patients.

### Definition of 'surgical recurrence'

Many definition of recurrence exist in the literature: endoscopic recurrence, clinical recurrence and surgical recurrence. We defined surgical recurrence as the need for repeat surgery [3].

### Risk factors

All of the potential risk factors studied were divided in four groups. Factors related to the patient (cigarette smoking), to the disease (duration of disease, anatomical site of disease, type of disease: stricturing, penetrating, mixte or inflammatory disease), to the type of surgery (extend of bowel resection, the type of anastomosis and the involvement of section margins) and to the pharmacological treatment after surgery.

### The postoperative course

A protocol was established to ensure regular monitoring during the postoperative period. Patients were followed both by the surgical team than gastroenterology. All results of clinical, biological and endoscopic have been noted and transcribed on patient records.

### Statistical analysis

All data were reported as mean (with standard deviation (SD)) and/or median (with range value). The data were analyzed by means of SPSS 9.00 statistical package for Windows. Chi-square test (Fisher

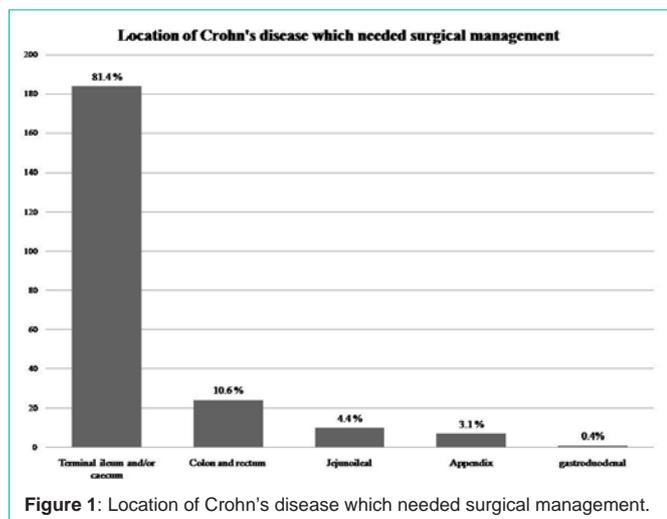


Figure 1: Location of Crohn's disease which needed surgical management.

exact test in the case of small numbers) was used for group comparison and Student's *t* test to analyze normally distributed quantitative data.  $P < 0.05$  was considered statistically significant.

The final date for follow-up was December 2015. Follow-up information was obtained regularly from outpatient clinical visits. To identify risk factors of the surgical recurrence of CD, we performed in the first step, univariate analysis: The survival rates and 95% confidence intervals [CI] were calculated using the Kaplan-Meier method. The Kaplan-Meier method was used for the management of patients lost who were considered as such during the follow-up. Differences in survival were compared by the Log Rank test. Next, the multivariate analysis was performed using Cox's proportional-hazards regression model.

## Results

### Characteristics of patients (with and without surgical recurrence)

The median age at diagnosis was 33.6 years (SD=12.2 years). They were 103 women and 123 men. The notion of smoking was present in 59 patients (26.1%).

In almost all cases (n=213, 94%), patients were monitored, before surgery, by a gastro-enterologist. Rarely, the diagnosis of CD was made during an emergency laparotomy performed for an acute complication (n=5, 2.2%) [Peritonitis (n=3), acute bowel obstruction (n=2)] or after histological examination of removed specimen (n=8, 3.5%) [Appendectomy (n=7), ileal resection for a migration of mesh in the gastrointestinal tract (n=1)].

Among the 226 patients, 102 (45.1%) were receiving at least one medical treatment for CD. Corticosteroid therapy was prescribed in 86 patients (38.1%), whereas the immunosuppressive treatment was prescribed in 23 patients (10.2%).

Anoperineal lesions were present in 45 patients (19.9%). One or more extra-intestinal manifestations were present in 39 patients (17.2%) [Rheumatologic (n=19), dermatological (n=12), ophthalmic (n=7), hematologic (n=3), hepatobiliary (n=2), nephrological (n=2), neurological (n=1) and gynecological such as primary infertility (n=1)].

Table 1: Characteristics of fistulizing form of Crohn's disease.

| Characteristics of fistulizing form | Number of patients (rate %) |
|-------------------------------------|-----------------------------|
| <b>Location of fistula</b>          |                             |
| Abdominal fistula                   | 130 (58)                    |
| Internal fistula                    | 119 (53)                    |
| Blind fistula                       | 76 (34)                     |
| Entero-sigmoid fistula              | 17 (8)                      |
| Entero-enteric fistula              | 12 (5)                      |
| Entero-transverse fistula           | 8 (4)                       |
| Entero- or colo-vesical fistula     | 7 (3)                       |
| Entero- rectal fistula              | 2 (0.8)                     |
| Entero- or colo-gastric fistula     | 1 (0.4)                     |
| Entero-cutaneous fistula            | 17 (8)                      |
| Anoperineal fistula                 | 45 (20)                     |
| <b>Number of abdominal fistula</b>  |                             |
| Blind fistula                       | 76 (34)                     |
| Between 2 anatomic areas            | 54 (24)                     |
| One fistula                         | 44 (20)                     |
| Two fistula                         | 10 (4)                      |

(† some patients had more than one fistula)

Table 2: Indications for surgery in 226 Crohn's disease patients.

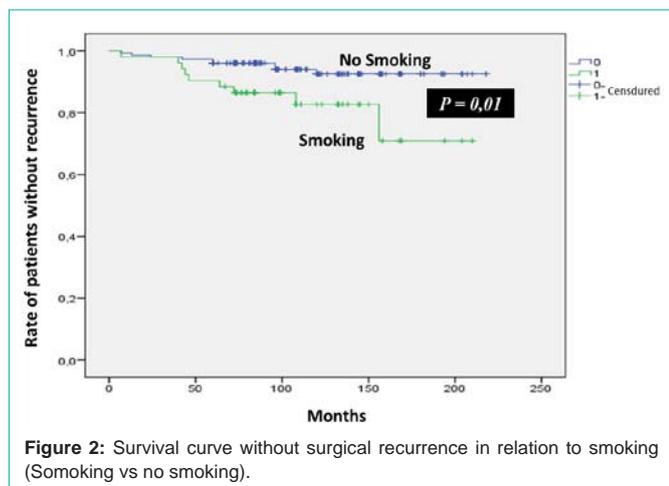
| Indication of surgery           | Number of patients (Rate %) |
|---------------------------------|-----------------------------|
| Elective situation              | 204 (90)                    |
| Mixed form                      | 114 (50)                    |
| Stenosing form                  | 72 (31.8)                   |
| Fistulizing form                | 6 (3)                       |
| Failure of medical treatment    | 7 (3)                       |
| Degeneration of Crohn's disease | 3 (1.3)                     |
| Suspected tumour                | 2 (1)                       |
| Emergency context               | 22 (10)                     |
| Free perforation                | 8 (3.5)                     |
| Small bowel obstruction         | 8 (3.5)                     |
| Suspected acute appendicitis    | 5 (2.2)                     |
| Acute intestinal bleeding       | 1 (0.4)                     |

Of the 226 patients, Crohn's disease was complicated by intra-abdominal abscess in 65 patients (28.8%).

Regarding the topography of lesions, the CD was single or multifocal. The distribution of the surgical lesions was ileocecal (n=184; 81%), colic (n=24; 10%), jejuno-ileal (n=10; 4%), appendicular (n=7; 3%) or duodenal (n=1; 0.4%) (Figure 1). Table 1 summarizes characteristics of fistulizing form of Crohn's disease. Table 2 summarizes indications for operations in 226 patients with Crohn's disease.

Two hundred four patients (90.2%) had uneventful postoperative course. At least one complication was present postoperatively in 22 patients (9.7%). Among them, 19 (8.4%) were infectious. Mortality was 0.4% (n=1).

Postoperative therapy was indicated in 75 patients (33.1%)



[Immunosuppressive (n=44), amino-salicylates (n=26)].

### The long-term outcomes

The mean follow-up was 110 months (SD=48 months), the number lost to follow-up was 21 patients (9.2%). Acute adhesive obstruction of the small intestine was occurred in 17 patients (7.5%)

including one patient (0.4%) who had required resection of necrotic small bowel of 3 m, and currently he is still alive after falling 36 months of the occlusive episode, with a short bowel syndrome (small bowel remaining length=0.5 m). Incisional hernia was occurred in 13 patients (5.7%). Surgical recurrence had occurred in 18 patients (8%) (Figure 2). It was an anastomotic recurrence in 76.6% of cases (n=13). The anastomotic recurrence was occurred only in patients who initially had an ileocecal resection. The median time to onset of surgical recurrence was 60 months (Min=7 months, Max=156 months).

### Risk factors of surgical recurrence

Regarding risk factors of surgical recurrence in univariate analysis, it had been retained: laparotomy approach, smoking, anoperineal lesions, postoperative medical treatment and extra-digestive manifestations such as: dermatologic and ophthalmologic manifestations. In multivariate analysis, the independent risk factors for surgical recurrence were: smoking (p=0.012, ORs=3.57) (Figure 2) and post-operative medical treatment (p=0.05, ORs=2.6) (Figure 3).

Table 3 shows data studied as risk factors of surgical recurrence in univariate analysis.

**Table 3:** Risk factors of surgical recurrence in univariate analysis.

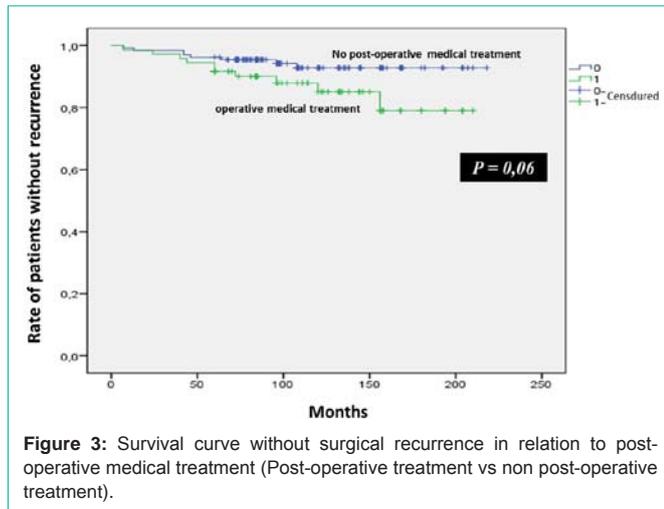
|                                  | No recurrence |          | Recurrence |         | P value | Odds ratio (CI‡) |
|----------------------------------|---------------|----------|------------|---------|---------|------------------|
|                                  | n=186         | 91.2 (%) | n=18       | 8.8 (%) |         |                  |
| Gender (M/F)                     | 1.04          |          | 2          |         | 0.20    | 0.52 [0.18–1.44] |
| Age (Year) ± SD†                 | 33 ± 12       |          | 37 ± 14    |         | 0.20    |                  |
| Age of onset                     | 30 ± 11       |          | 33 ± 13    |         | 0.47    |                  |
| Duration of the disease (months) | 29 ± 45       |          | 30 ± 31    |         | 0.97    |                  |
| Smoking                          | 43            | 23       | 9          | 50      | 0.01*   | 3.33 [1.25–9]    |
| Abdominal mass                   | 45            | 24       | 4          | 22      | 0.54*   | 0.85 [0.33–3.35] |
| Medical treatment before surgery | 81            | 43       | 9          | 50      | 0.59    | 1.29 [0.49–3.23] |
| Intra-abdominal abscess          | 50            | 26       | 5          | 27      | 0.56*   | 1.11 [0.35–3.12] |
| Emergency surgery                | 21            | 11       | 0          | 23.5    | 0.12*   | 1.11 [1.06–1.16] |
| Laparoscopy approach             | 69            | 37       | 0          | 0       | 0.001   | 1.25 [1.11–1.33] |
| Ileo-caecal location             | 150           | 80       | 15         | 83      | 0.53*   | 1.25 [0.31–4.36] |
| Appendicular involvement         | 17            | 10.4     | 3          | 25      | 0.14*   | 2.94 [0.71–11.6] |
| Healthy slice section            | 143           | 76.9     | 17         | 94.4    | 0.06*   | 5.26 [0.66–40]   |
| Disease (kind of lesion)         |               |          |            |         |         |                  |
| Stricture                        | 167           | 89       | 17         | 94      | 0.45*   | 1.96 [0.24–15.3] |
| Fistula                          | 102           | 54       | 13         | 72      | 0.15    | 2.17 [0.73–6.25] |
| E-D manifestations               | 29            | 15       | 7          | 38      | 0.02*   | 3.44 [1.23–9.61] |
| Dermatologic manifestation       | 8             | 4.3      | 3          | 16      | 0.06*   | 4.42 [1.06–18.5] |
| Ophthalmologic manifestation     | 4             | 2.2      | 3          | 16      | 0.01*   | 9.09 [1.88–50]   |
| AP lesions                       | 34            | 18       | 8          | 44      | 0.01*   | 3.57 [1.31–10]   |
| Postoperative digestive fistula  | 6             | 3.2      | 2          | 11.1    | 0.15    | 3.84 [0.69–20]   |
| Postoperative medical treatment  | 62            | 33       | 10         | 55      | 0.06    | 2.50 [0.94–6.66] |

\* Fisher exact test

‡CI: Confident interval at 95%

† SD: Standard Deviation

E-D: extra-digestive; AP: Anoperineal



**Table 4:** Risk factors of surgical recurrence in multivariate analysis.

|                                 | <i>P value</i> | Odds ratio | Confident interval at 95% |
|---------------------------------|----------------|------------|---------------------------|
| Smoking                         | 0.01           | 3.57       | 1.32–9.52                 |
| Postoperative medical treatment | 0.05           | 2.61       | 1–6.83                    |

Table 4 shows data studied as risk factors of surgical recurrence in multivariate analysis.

## Discussion

The postoperative recurrence is a major problem especially common in the management of this disease. Results depend of definition of recurrence. Using, the need for a second resection as the definition for recurrent disease, authors found a recurrence rate of about 20% at 5 years and 35% at 10 years [4,5-13]. In the present study the risk of recurrence was lesser than the previous reports, it was about 7.5%.

### Patient related factors

**Age:** Subjects with a diagnosis of CD at a young age have higher rates of recurrence in some studies [14,15] but neither in others [16,17] nor in the present study.

**Smoking:** Smoking is associated with an increased risk of developing CD, and a significant predictive risk factor for surgical recurrence in this study and others [18-21].

### Disease related factors

**Type of disease:** Penetrating disease type have, in some studies, a higher risk and an earlier appearance of surgical recurrence [22,23].

**Duration of disease:** Several trials suggest the existence of a correlation between disease duration and risk of surgical recurrence [16,23]. In literature, we can find studies reporting an increased risk in patients with short duration of disease.

**Anatomical site and extension of the disease:** Some Authors reported an increased risk of surgical recurrence in patients with ileal disease and in patients with ileo-colic disease [15,24].

ECCO report that extent of disease of more than 100 cm is considered as a risk factor for recurrence [25].

In the present study, none of the studied factors related to the disease is considered as a risk of surgical recurrence.

### Factor related to surgery

**Involvement of the margins of the section:** Some Authors report a lower incidence of recurrence when the margins of the section were healthy [26].

**Type of anastomosis:** A longer follow-up showed a significantly lower incidence of reoperations in patients with side-to-side anastomosis, both manual and mechanical, compared with that of patients with mechanical end-to-side anastomosis [27].

**Laparoscopy or laparotomy:** Makni, et al. reported lower rates of recurrence with laparoscopic surgery compared to those obtained with open surgery in short and middle term [12].

In the present study, only laparoscopy is considered as a risk of surgical recurrence at univariate analysis.

### Factors related to postoperative medical treatment

Several randomized trials have shown that medical treatment (5-ASA, Immunosuppressants, Antibiotics, Steroids, budesonide, Anti-TNF and Probiotics) could be effective not only in reducing the incidence of surgical recurrence, but also decreasing the severity of the lesions.

However, in the present study, post-operative medical treatment was an independent risk factor of surgical recurrence. It could be because of the severity of lesions, which were indicating the pharmacological prophylaxis.

## Conclusion

In this study, stricturing and penetrating form of terminal ileum was the most common. Conservative management based on stricturoplasty is rarely indicated. Surgical recurrence was 8%, and the two independent risks for recurrence were: smoking and post-operative medical.

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