



Alimentary Tract

Previous colonic resection is a risk factor for surgical relapse in Crohn's disease



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ABSTRACT

Background: Despite the improvement of medical therapies, nearly half of patients with Crohn's disease require surgery within 10 years after diagnosis. However, intestinal resection is not curative and recurrence may occur.

Aims: To evaluate post-surgical outcomes for patients with Crohn's disease in a large monocentric cohort, and to identify variables associated with clinical and surgical relapse.

Methods: Patients with Crohn's disease who had surgery for ileal and colonic Crohn's disease between 2004 and 2016 and on at least one-year follow-up following surgery were included.

Results: One hundred ninety-three patients were included in the study. Crohn's disease recurrence concerned 53% of patients after a median 56-month (6–158) follow-up and 29% of patients required a second surgical intervention. At logistic regression analysis, active smoking and young age at diagnosis were identified as independent risk factor for post-surgical relapse ($p = 0.01$), while colonic or ileocolonic resection was recognized as a risk factor for surgical Crohn's disease relapse ($p = 0.003$).

Conclusions: Post-surgery recurrence is frequent for patients with Crohn's disease. Active smoking and young age at diagnosis are risk factors for Crohn's disease recurrence. As compared with patients undergoing small-bowel surgery, patients with colonic resection are prone to relapse requiring a second surgical intervention.

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1. Introduction

In spite of the increasing use of thiopurines and anti-tumor necrosis factor (TNF) drugs, population-based studies indicate that nearly half of patients with Crohn's disease (CD) require surgery within 10 years from diagnosis [1,2]. As known, the surgical resection of the inflamed bowel in CD is not curative, and patients remain at risk for post-operative relapse. This is characterized by the recurrence of CD-related lesions in the pre-anastomotic area (endoscopic recurrence), eventually followed by symptoms (clinical recurrence) and potentially by repeated surgical interven-

tions (surgical recurrence), which cause CD patients sources of disability and decreased quality of life. Studies suggest that the risk of endoscopic recurrence in CD is as high as 75% one year after resection, while clinical and surgical recurrences occur in up to 80% and 50% of cases, respectively, over a follow-up period of 20 years [2]. Several variables leading to an increased risk of post-surgery relapse for CD patients have been identified. These include: cigarette smoking, disease location, disease behavior, number of previous surgical interventions, and presence of NOD2 mutations [1,2]. Noteworthy, the severity of endoscopic relapse at the anastomosis site 6–12 months after surgery has been found to predict the risk of clinical relapse [3], and ileocolonoscopy findings are now being used to guide CD therapeutic management in the post-surgery setting. Given the clinical relevance of post-surgery relapse for CD patients, therapeutic strategies have been adopted with the aim to prevent its occurrence, including the use of antibiotics,

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mesalamine, thiopurines and antibodies against tumor necrosis factor [4–10].

While the incidence and risk factors for clinical and endoscopic CD relapse have been extensively studied, little data is available with regard to surgical CD recurrence. This can be due to a number of issues, including the need for large cohorts of patients and extensive follow-up periods, as surgical recurrence is characterized by lower incidence than clinical and endoscopic relapse. Moreover, heterogeneous indications as to surgery and surgical techniques constrain the reliability of large multicenter studies. In our paper we have analyzed the incidence and risk factors for surgical CD recurrence in a large retrospective single-center cohort.

2. Materials and methods

A retrospective monocentric cohort study was conducted at Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (Milan). Patients with age of >18 years and histological diagnosis of CD, who had undergone one or more surgical interventions for CD between June 2004 and July 2016, and on follow-up for at least 6 months, were included in this study.

The data were extracted from an electronic database describing all surgical interventions and clinical data. The surgery reports were reviewed for data concerning: indication for surgery, timing (elective or urgent surgery), type of operation (resective or non-resective) and surgical technique (laparoscopic or open). Additionally, clinical data were collected about: sex, age at diagnosis, localization according to the Montreal classification, perianal or upper GI disease, extra-intestinal manifestations, smoking habits before and after surgery.

"Ileal surgical intervention (ISI)" was defined as surgical intervention for ileal or limited ileocaecal CD, as confirmed by endoscopy, cross-sectional imaging and histological evaluation of the surgical specimen. "Colonic surgical intervention (CSI)" was defined as surgical intervention of any extension performed for CD involving the colon (excluding the caecum) as confirmed by endoscopy, cross-sectional imaging and histological evaluation of the surgical specimen. Any patients who had undergone surgery exclusively for perianal disease, upper gastrointestinal disease, stoma creation or bowel re-canalization were excluded. Both medical and surgical recurrences of CD were analyzed. Medical recurrence was defined as clinical and endoscopic recurrence requiring a change in medical therapy or endoscopic dilation. Surgical recurrence was defined as CD-related surgery required because of refractoriness to medical therapy or CD-related complications. Patients with multiple recurrences were also separately analyzed. The term Crohn's disease recurrence implied medical recurrence, unless specified otherwise.

Continuous variables were summarized as medians and categorical variables by means of frequencies. For the purpose of statistical analysis, multi-categorical variables were reduced to binary variables according to appropriate clinical criteria and continuous variables were categorized by approximated medians. Data were analyzed with non-parametric tests; demographic data between the two groups were compared with Mann-Whitney's U-test and univariate analysis was carried out using Fisher's exact test (two ways). P values < 0.05 were considered statistically significant. All the data are given as mean \pm standard deviation [SD], unless specified otherwise. Statistical analysis was performed using t-test, one-way analysis of variance [ANOVA], or Mann-Whitney's test in order to compare continuous variables. Univariate and multivariate linear regression analysis was carried out to estimate the relationship between surgical recurrence and clinical parameters (e.g. sex, age at diagnosis, disease duration, smoking status, disease location, disease behavior, concomitant therapy, anti-TNF therapy). Kaplan-Meier's analysis was carried out to estimate the survival

Table 1

Clinical characteristics of the enrolled patients at baseline.

Clinical parameter	N = 193
Male/Female, n	107/86
Age at diagnosis	
\leq 40 years	141
40 years	52
Age at enrolment, median (range) – years	49 (23–88)
Smoking status before surgery, yes/no	65/128
Smoking status after surgery, yes/no	40/153
Disease location, n ^a	
L1 (ileal)	105
L2 (colonic)	36
L3 (ileocolonic)	52
L4 (upper disease)	13
Disease behavior, n ^a	
B1 (Non-stricturing, non-penetrating)	45
B2 (Stricturing)	87
B3 (Penetrating)	61
Perianal disease, yes/no	48/145
Extraintestinal disease, yes/no	13/180
Concomitant therapy at enrolment	
Mesalamine, n	91
Thiopurines, n	41
Corticosteroids, n	35
Anti-TNF, n	43
Follow up duration, median (range) – months	56 (6–158)

^a According to the Montreal classification [32].

time, free from recurrence, of the patients who had undergone ileal or colonic surgery. The incidence curves were compared with the log-rank test (Gehan-Breslow-Wilcoxon's test). P-values lower than 0.05 were considered statistically significant. All the statistical analyses were performed by computer software: SPSS (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, version 24.0. Armonk, NY: IBM Corp.) and GraphPad Prism release 6.0; (GraphPad Software Inc., La Jolla, CA, USA). The study protocol conformed to the ethical guidelines from WMA's Declaration of Helsinki (DoH).

3. Results

Overall, 557 patients underwent CD-related surgery between 2004 and 2016. Adequate follow-up data were available for 395 patients (71%). 164 patients (42%) were excluded as surgical intervention had been performed for perianal fistula (n=98), upper gastrointestinal disease (n=4), stoma creation (n=9) or bowel re-canalization (n=53). Moreover, 37 surgical interventions were excluded because of post-surgery complications (9.4%). Thus, 193 patients (86 females, mean age 52 ± 12 years) were totally included in the final analysis. The clinical baseline data of the operated patients have been detailed in Table 1, while the indication and technical data of surgical interventions are reported in Table 2.

Post-surgery CD recurrence was documented in 102 patients (53%), after a median 56-month (6–158) follow-up period. The recurrence was successfully treated by medical therapy adjustments in 72 patients (71%) and with a second surgical intervention in 30 patients (29%). Clinical characteristics of patients experiencing or not experiencing CD recurrence are detailed in Supplementary Table 1. In the majority of cases recurrence occurred in the same location of the first surgical intervention ($k=0.52$, $p<0.001$). Importantly, treatment escalation from initial post-surgical prophylaxis was recorded in 73% of patients with surgical relapse and in 67% in patients with medical relapse ($p=0.77$), excluding that observed differences in patients' outcomes could be related to a different therapeutic management. Twenty-four patients (23%) experienced a second recurrence after a median 28-month (8–85) follow-up period: of these 7 (30%) required a third surgical intervention and 5 (12%) had more than two recurrences.

Table 2
Surgical characteristics of the enrolled patients at baseline.

Surgical parameter	N = 193
Surgical indication	
Therapeutic failure	41
Symptomatic stricture	92
Penetrating disease (abscess/fistula)	56
Intestinal neoplasia	4
Surgical timing	
Urgency	8
Elective	185
Previous surgery, yes/no	119/74
Surgical technique	
Open	118
Laparoscopic	75
Surgical procedure	
Ileocaecal resection	83
Ileal resection	14
Colonic resection	52
Colectomy	7
Proctectomy	10
Strictureplasty	5
Mixed	22

At logistic regression analysis, active smoking following surgery and age ≤ 40 years at CD diagnosis were identified as independent risk factors for post-surgery CD relapse (Table 3). At Cox regression analysis, smokers were characterized by a reduced relapse-free survival as compared to non-smokers (Fig. 1). Specifically, the median time to recurrence for smokers was 45 months (95% CI 29–61) as compared with 82 months (95% CI 50–114) for non-smokers.

Table 3
Univariate and multivariate analysis of the variables associated with CD post-surgery recurrence.

Clinical parameters	N = 193	Univariate analysis		Multivariate analysis	
		HR (95% CI)	p	HR (95% CI)	p
Sex, n: male vs. female	107 vs. 86	1.2 (0.8–1.8)	0.33		
Age at diagnosis: <40 years vs. >40 years	138 vs. 50	1.6 (1.0–2.6)	0.05	2.1 (1.1–4.3)	0.03
Smoking status before surgery, yes vs. no	65/128	1.1 (0.7–1.6)	0.72		
Smoking status after surgery, yes vs. no	40/153	2.1 (1.2–3.9)	0.013	2.3 (1.3–4.2)	0.007
Disease location, n ^a : L2/L3 vs. L1	105 vs. 88	1.2 (0.8–1.8)	0.31		
Disease behavior, n ^a : B2/B3 vs. B1	45 vs. 148	0.9 (0.5–1.4)	0.54		
Perianal disease	48	0.9 (0.6–1.6)	0.93		
Extraintestinal manifestations	13	1.3 (0.5–2.9)	0.59		
Previous surgical resection, n: colonic/ileocolonic vs. ileal	75 vs. 118	1.3 (0.8–1.9)	0.26		
Surgical indication: active disease/neoplasia vs. complicated disease	148 vs. 45	0.9 (0.6–1.5)	0.82		
Post-surgical therapy, n: no-therapy/mesalazine vs. IMS/biological	88 vs. 97	1.0 (0.7–1.6)	0.86		

IMS: Immunosuppressive.

^a According to the Montreal classification [32].

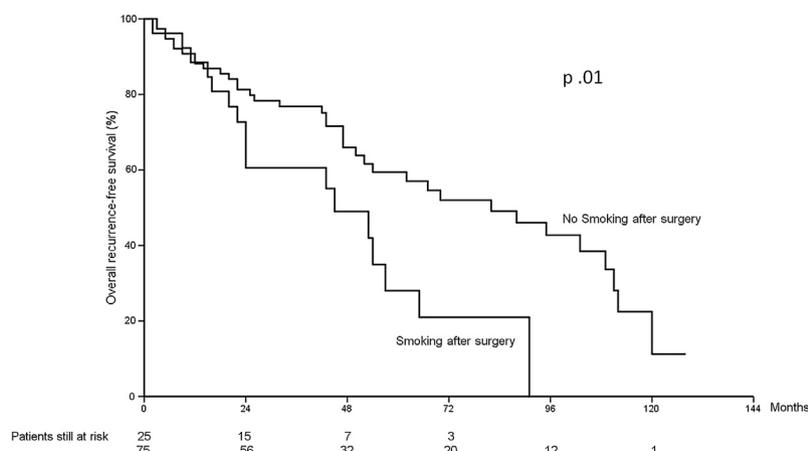


Fig. 1. Kaplan–Meier’s curve, showing the estimates (proportion) of patients free from post-surgery CD relapse over time and comparing smokers and non-smokers after surgical intervention.

Colonic or ileocolonic vs. ileal resection (HR = 3.0, 95% CI 1.4–6.2, $p = 0.004$) and lack of immunosuppressive or biological therapy following surgery (HR = 2.3, 95% CI 1.0–5.3, $p = 0.05$) were identified as significant risk factors for surgical CD relapse at univariate analysis. Of note, an increased risk of surgical CD recurrence following colonic/ileocolonic vs. ileal resection was still observed even when the patients receiving post-surgery prophylactic therapy with immunomodulators or biologics had been excluded from analysis (HR 3.2, 95% CI 1.1–8.9, $p = 0.03$). Conversely, no differences in surgical recurrence were found between patients with ileal vs. colonic/ileocolonic resection, when the patients receiving post-surgical immunosuppressants were separately analyzed ($p = 0.17$). Survival analysis confirmed that colonic or ileocolonic disease was associated with shorter survival time free from post-surgical relapse as compared with ileal disease (median time to surgical relapse 106 vs. 135 months, respectively (95% CI 91–122 vs. 127–143, $p = 0.002$) (Fig. 2). Moreover, patients undergoing isolated colonic resection (irrespective of colonic or ileocolonic localization) were characterized by a significantly reduced surgical recurrence-free time as compared with patients undergoing ileocaecal resection ($p = 0.006$) (irrespective of ileal or ileocolonic localization) (Supplementary Fig. 1).

The increased risk of surgical CD relapse for patients undergoing colonic or ileocolonic resection prompted us to perform the direct comparison of patients undergoing ileal (ISI) vs. colonic/ileocolonic (CSI) resection. One-hundred-eighteen (61%) and 75 (39%) patients had ISI and CSI, respectively, performed. As reported in Table 4, the two groups were similar as to sex, age at surgical intervention,

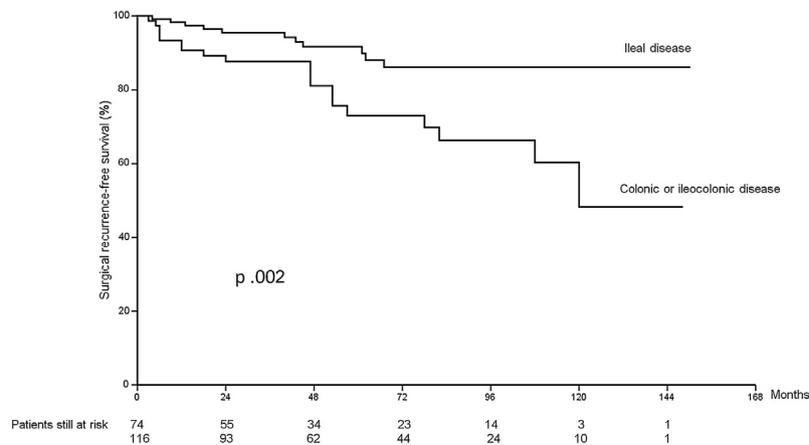


Fig. 2. Kaplan–Meier's curve, showing the estimates (proportion) of patients free from surgical CD relapse over time and comparing patients with colonic/ileocolonic vs. ileal disease.

Table 4

Clinical characteristics of the enrolled patients at baseline, as grouped according to the type of intervention, i.e.: into ileal surgery and colonic surgery.

Clinical parameters	ISI N = 118	CSI N = 75
Male/Female, n	64/54	43/32
Age at diagnosis		
≤40 years	77	61
>40 years	40	10
Age at enrolment, median (range) – years	49 (23–88)	50 (29–86)
Smoking status before surgery, yes/no	47/71	18/57
Smoking status after surgery, yes/no	32/86	8/57
Disease location, n ^a		
L1 (ileal)	105	–
L2 (colonic)	–	36
L3 (ileocolonic)	13	39
L4 (upper disease)	9	4
Disease behavior, n ^a		
B1 (Non-stricturing, non-penetrating)	12	33
B2 (Stricturing)	63	24
B3 (Penetrating)	43	18
Perianal disease, yes/no	19/99	29/46
Extraintestinal disease, yes/no	4/114	9/66
Concomitant therapy at enrolment		
Mesalamine, n	40	41
Corticosteroids, n	4	3
Thiopurines and anti-TNF, n	71	26
Follow up duration, median (range) – months	56 (6–158)	51 (6–148)
Relapse rate, yes/no	60/58	42/33
Relapse type		
Medical, n	49	23
Surgical, n	11	19*
Relapse site		
Ileum, n	33	13
Colon, n	7	29
Therapy after surgery		
Mesalamine, n	40	41
Corticosteroids, n	37	15
Thiopurines and anti-TNF, n	38	14*

ISI: Ileal surgical intervention.

CSI: Colonic surgical intervention.

^a According to the Montreal classification [32].

* p < 0.05.

disease duration, extra-intestinal manifestations, perianal involvement and therapy before surgery. Smoking habits post-surgery were similar in the two groups ($p = ns$) as was follow-up time. Prophylactic therapy with immunosuppressants or biologics after surgery was more frequent for the patients who underwent ISI than CSI (62% vs. 38% $p = 0.001$). Post-surgery CD recurrence was recorded in 60 (59%) patients with ISI and 42 (41%) with CSI, with no differences between the two groups ($p = ns$). Of note, the risk of surgical recurrence was significantly higher for patients with CSI than

those with ISI (25% vs. 9%, $p = 0.004$). A statistically significant difference with regard to the surgical recurrence risk persisted when comparing patients with ileal, ileocolonic and isolated colonic disease: ileal vs. colonic 9% vs. 25%, $p = 0.01$; ileal vs. ileocolonic 9% vs. 23%, $p = 0.01$; colonic vs. ileocolonic 25% vs. 23%, $p = 0.8$.

4. Discussion

Despite the advancements in medical therapies for Crohn's disease, surgical intervention is still required to control disease activity or CD-related complications in a large proportion of patients [11]. In a recent large cohort study the 5-year cumulative probability of first major surgery for CD was as high as 19.6% [12]. In the last decade a progressive decrease of CD surgical rates has been reported [12], paralleling the increasing use of thiopurines and TNF- α blockers, even if a causal relationship between increased exposure to immunosuppressants and reduced surgical rates is yet to be proved [11]. More conservative surgical indications and wider awareness of the international guidelines possibly account for this reduction in the number of CD-related surgeries. In our study cohort, indication for CD-related surgery was the failure of medical therapy in 21% of patients and CD-related complications in 77% of patients. Moreover, 2% of patients underwent surgery for gastrointestinal neoplasia. The current ECCO guidelines recommend surgery for symptomatic CD that is refractory to medical therapy and for CD-related complications, including symptomatic strictures or fistulizing disease [13]. Resective surgery is also an option for patients with severely active ileocaecal or colonic disease before starting immunomodulatory treatment or biological therapy [13].

The identification of the incidence and risk factors for post-surgical CD recurrence is key to the implementation of an effective prophylactic therapy, as well as the reduction of the risk of medical or surgical relapses, and the containment of CD-related disability. In our study cohort, a 53% post-surgical CD recurrence was observed after a median 56-month follow-up time: it mostly occurred in the same bowel tract of the first surgical intervention. The recurrence was successfully managed with medical therapy adjustments in 71% of patients, but it required a second surgical intervention in 29% of patients. Our results are comparable with data from the literature [14] as the reported rates of CD surgical recurrence vary from 18% to 38% and from 36% to 57% 5 and 10 years, respectively, from the first resection [15,16].

Logistic regression analysis pointed out smoking habit as an independent predictor of post-surgery recurrence. The role of cigarette smoking in increasing the risk of post-surgery relapse has been confirmed in most cohorts [17,18], and the current guidelines

recommend smoking be ceased after surgery for Crohn's disease [13]. Young age at diagnosis too has been identified as a predictor of post-surgery recurrence, reflecting the data from the literature, such as those from Yarur et al. [19], defining this anamnestic feature as suggestive of a more aggressive disease with a higher rate of recurrence. Importantly, univariate analysis could not highlight any association between post-operative immunosuppressants or biological agents and the risk of overall recurrence. The role of thiopurines or biologicals in reducing the risk for post-operative CD recurrence still remains controversial, as evidence both in favor of [18,20] and against [21,22] the effectiveness of these agents in preventing clinical relapse after surgery is available in the literature. On the contrary, there is more solid evidence to support the role of anti-TNF drugs in reducing the risk of endoscopic CD relapse [22,23].

As compared with ileal resection, previous colonic surgery was identified as a strong risk factor for a second surgical intervention. As to the risk of surgical recurrence, any role of CD localization remains controversial, and conflicting data are found in the literature. Several reports pointed to a higher incidence of a second surgical intervention in patients with colonic vs. ileocolonic disease or following segmental colectomy [24,25]. On the contrary, other studies have demonstrated that colonic localization is either protective [16,26–28] or not related to the risk of post-surgery recurrence [29]. In the present study, the higher rate of surgical recurrence in patients who underwent CSI compared with ISI comes with several possible explanations. As reported in a recent systematic review [30], colonic CD has its own genetics and clinical presentation, making the case for being considered as a separate condition from ileal/ileocaecal CD. In fact, in our cohort the patients undergoing CSI were younger, presenting more frequently with an inflammatory pattern and with higher prevalence of perianal involvement. These patients underwent surgical intervention mostly because of the failure of medical therapy rather than CD-related complications, and surgery was more frequently performed by open technique. As any differences in surgical recurrence rates following colonic vs. ileal resection persisted when the patients not receiving post-surgical immunosuppressants or biological therapies were separately analyzed, we could reasonably exclude that a less aggressive post-surgery medical approach, following colonic surgery, may be responsible for the observed results. Importantly, when only the patients receiving post-surgical immunosuppressants or biologics were considered, no differences in surgical recurrence rates between CSI and ISI were further observed, thus suggesting that an aggressive medical approach may reduce surgical recurrences in patients with colonic Crohn's disease. Finally, it could be argued that the higher rate of surgical recurrence may be associated with the surgical approach. Surgery in colonic CD represents one of the most debated issues and wide discrepancies are observed among expert surgeons, especially with regard to the extension of the resected specimen. Our results demonstrate a higher rate of colonic re-surgery in patients undergoing CSI, a possible indication for a more radical surgical approach in these patients. However, recent studies have demonstrated that partial resection in colonic CD is a safe technique with a reasonable recurrence rate [25,31] and that the extent of the resected specimen is not associated with the post-surgical outcome.

The main strength of our study resides in the opportunity to evaluate a large monocentric cohort with a long-term follow up. The collection of data from a single center reduces the possibility to incur in biases originating from loss of data or heterogeneity in medical and surgical approaches among different centers.

In conclusion, our study confirms that about half of the patients with CD experience clinical recurrence after surgery. Colonic surgical resection confers an increased risk for CD surgical recurrence. The excess risk of surgical relapse for CD patients undergoing CSI

can be reduced by post-operative immunosuppressants or biological therapy. These results suggest that aggressive postsurgical prophylaxis for CD patients undergoing colonic resection may be advisable.

Conflict of interests

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.dld.2018.07.035>.

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