




# Repeated surgery for recurrent Crohn's disease: does the outcome keep worsening operation after operation? A comparative study of 1224 consecutive procedures

Francesco Colombo<sup>1</sup> · Alice Frontali<sup>1</sup> · Caterina Baldi<sup>2</sup> · Maria Cigognini<sup>2</sup> · Giulia Lamperti<sup>1</sup> · Carlo A. Manzo<sup>2</sup> · Giovanni Maconi<sup>3</sup> · Sandro Ardizzone<sup>3</sup> · Diego Foschi<sup>4</sup> · Gianluca M. Sampietro<sup>2</sup> 

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## Abstract

Complicated Crohn's disease (CD) will require surgical treatment during patients' lifetime, with a considerable recurrence rate requiring additional surgery. The present study is a retrospective analysis of a prospectively maintained database in an IBD Tertiary Centre that included all the consecutive, unselected patients undergoing surgery for CD between 1993 and 2019. Patients treated with small bowel resections, colonic resections, conventional and non-conventional strictureplasties were considered. The aim was to evaluate morbidity and long-term recurrence of repeated surgery. Among the population included, the following procedures were performed: 713 (58.2%) primary surgery (group S1), 325 (26.5%) first recurrence (group S2), and 186 (15.3%) multiple recurrences (group S3). Patients undergoing repeat surgery were older ( $p < 0.0001$ ) and had a longer disease duration ( $p < 0.0001$ ), extended disease ( $p = 0.0001$ ), shorter time frame to first surgery ( $p < 0.0001$ ), nutritional impairment ( $p < 0.0001$ ), and a history of aggressive medical therapy ( $p = 0.04$ ). Patients undergoing surgery for recurrences required higher complexity level surgery, with more conservative approaches ( $p = 0.0004$ ) and a higher ostomy number ( $p = 0.06$ ). Recurrent patients had higher short bowel syndrome rate ( $p < 0.0001$ ), higher minor ( $p = 0.04$ ) but not major ( $p = 0.2$ ) postoperative complications rate. The 10-year surgical recurrence rate was 18% for group S1, 27% for S2, and 48% for S3, with significant differences at the log-rank test. Repeated surgery for complicated CD was associated with an increased rate of minor, but not major complications, requiring high-risk surgery, with a major ostomy rate and short bowel syndrome, and is associated with an increased long-term surgical recurrence, even on strictureplasty sites.

**Keywords** Crohn's disease · Surgery · Postoperative complications · Recurrence · Outcomes

## Abbreviations

IBD	Inflammatory bowel disease
CD	Crohn's disease
SP	Strictureplasty
NCSP	Non-conventional strictureplasty

## Introduction

Crohn's disease (CD) [1] is a chronic, pan-intestinal, inflammatory bowel disease (IBD) of unknown etiology, with a significant impact on patients' quality of life. Despite the encouraging results of biologics on the disease clinical history, the large majority of patients may undergo surgery at some point, and nearly 50% will recur within 10–20 years [2].

Several predictors of surgical recurrence have been identified, such as genetic predisposition, young age at diagnosis, surgery within one year of diagnosis, smoking habit, penetrating disease behavior, upper-GI location associated with stricturing behavior, perianal disease, mesentery characteristics, bowel wall thickening and endoscopic recurrence within one year after surgery [2–14]. Laparoscopy is nowadays the gold standard for primary surgery, and also in selected cases of recurrent disease, if adequate surgical expertise is

✉ Gianluca M. Sampietro  
gianluca.sampietro@unimi.it; gmsampietro@asst-rhodense.it

<sup>1</sup> Division of General Surgery, ASST Fatebenefratelli Sacco, Luigi Sacco University Hospital, Milan, Italy

<sup>2</sup> Division of General and HPB Surgery, ASST Rhodense, Rho Memorial Hospital, Corso Europa, 250, Rho, 20017 Milan, Italy

<sup>3</sup> Division of Gastroenterology, ASST Fatebenefratelli Sacco, Luigi Sacco University Hospital, Milan, Italy

<sup>4</sup> Second Unit of General Surgery, Multimedica IRCCS, S. Joseph Hospital, Milan, Italy

available [15, 16]. Regardless, primary surgery is performed by open or laparoscopic approach, in case of recurrence surgery is potentially associated with high postoperative complications rate due to altered anatomy, complex adhesions, and hidden perforating disease with abscesses and fistulas [17, 18]. Furthermore, repeated surgery has been reported to adversely affect long-term surgical recurrence [19, 20]. Few reports available in literature assess patients' outcome for iterative surgery and tend to be focused on ileocecal resections [21, 22]. No study has been reported considering the outcome in patients with multiple disease locations, involving the ileum and the colon, treated by resections and strictureplasties (SP), and undergoing repeated surgery.

Aim of the present study was to assess safety and efficacy of repeated surgery in a consecutive, unselected series of CD patients from a tertiary IBD Center.

## Materials and methods

### Study population

Patients operated for primary or recurrent CD between January 1993 and December 2019 were registered in the prospective Crohn's Disease Clinical Auditing and Research Database (CD-CARD) of the "Luigi Sacco" University Hospital, including demographic, clinical, surgical and follow-up data. Surgical decision-making process included formal Multi-Disciplinary Team meeting (MDT), involving gastroenterologists, pediatricians, surgeons, pathologists and radiologists, based on the complete preoperative work-up using CT scan or MRI, bowel ultrasonography, and endoscopy. All consecutive, unselected patients were considered eligible for the analysis and retrospectively reviewed, regardless of the number, location, and behavior of diseased segments, and the type and number of treatment adopted, such as small bowel and/or colonic resections, conventional (SP) and non-conventional (NCSP) strictureplasties. No exclusion criteria were applied. Patients were divided into three groups, according to the surgical history: primary surgery group (S1) including patients at first operation; patients at second operation due to surgical recurrence forming the secondary surgery group (S2); and patients undergoing three or more surgeries were included in the tertiary surgery group (S3).

### Surgical procedures

After an accurate intraoperative staging of all CD intestinal locations and characteristics, a "per-segment" approach was adopted for every single lesion [16, 23]. As previously reported, small bowel segments affected by penetrating disease were treated by minimal resection with mesentery removal. Absence of residual lumen, thick and retracted

mesentery and massive lymphadenopathy were further indications for small bowel resection. Intestinal continuity was restored by functional end-to-end anastomosis, either manual or stapled. Fibro-stenotic disease was treated by conventional strictureplasty (SP) in case of short lesions (Heineke-Mikulicz technique), and non-conventional strictureplasties (NCSP) in case of multiple and close strictures, or long diseased segment, or disease located to the terminal ileum or a previous ileo-colonostomy. Large bowel disease locations were always treated by resection, following colonic vascular anatomy, and with mesentery removal [3, 6, 7, 9, 23].

A planned temporary ostomy was performed in patients at high risk for post-operative septic complications, identified by the presence of two or three among preoperative high-dose steroid and/or anti-TNF treatment, intra-abdominal septic complications at time of surgery, and poor nutritional status.

### Outcome measures

The primary endpoint was to compare the peri-operative morbidity rate among the three groups (S1, S2 and S3). Post-operative complications were classified according to Clavien–Dindo classification in terms of maximum complication for patient developed during hospital stay or within 30 days from surgery [24]. Patients receiving total parenteral nutrition (TPN) or blood transfusion in the context of a scheduled perioperative optimization were not considered as Clavien–Dindo grade II. Severe postoperative morbidity was defined as any complication graded III or IV, and mortality as grade V. Secondary endpoints were to evaluate clinical and biochemical factors and long-term surgical recurrence rate, defined as the need for a new surgical procedure due to disease recurrence, associated to repeated surgery. Short bowel syndrome was defined as a reduction in gut function below the minimum necessary for absorption of macronutrients and/or water and electrolytes, requiring enteral or parenteral supplementation.

### Statistical analysis

Quantitative data were reported as mean and standard deviation ( $\pm$  SD). Continuous variables were compared using analysis of variance (ANOVA) or two-tailed, unpaired, Student's *t* test, and proportions were compared using two-tailed, Fisher's exact or Chi-square test, where appropriate. Time-to-event estimates for surgical recurrence were calculated using the Kaplan–Meier function, and compared using the log-rank test. The level of significance was set at  $p \leq 0.05$ . Statistical analysis was performed using STATISTICA 8 (data analysis software system), Stat Soft Inc. The CD-CARD database and the study were approved by

the ethics committee of our Institution (Approval Number 1247703013039, 12/12/2013).

### Ethical considerations

The study was conducted according to the ethical standards of the Declaration of Helsinki (2013 version) and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology [STROBE] guidelines [25, 26].

### Results

During the study period, 1224 consecutive patients were operated at “Luigi Sacco” University Hospital (Milano, Italia) for complicated CD: 713 (58.2%) for primary surgery (group S1), 325 patients at first surgical recurrence (26.6%), and 186 patients with multiple recurrences (group S3, 15.2%). Patients’ characteristics are reported in Table 1. Considering the Montreal Classification [11], the groups were similar in terms of gender, perianal disease, smoking habit, IBD family history, extra-intestinal manifestations,

**Table 1** Patients characteristics

	First surgery (S1) <i>n</i> = 713 (%)	Second surgery (S2) <i>n</i> = 325 (%)	3 or more surgeries (S3) <i>n</i> = 186 (%)	<i>p</i>
Age	39.9 ± 14.3	42.5 ± 12.9	46.1 ± 12.3	< 0.0001
Gender M/F	434/279 (61%, 9%)	186/139 (57%, 3%)	102/84 (55%, 45%)	0.2
Age A1, A2, A3	56, 473, 184 (8%, 66%, 26%)	51, 214, 60 (16%, 66%, 18%)	31, 133, 27 (17%, 72%, 15%)	0.0001
Location L1, L2, L3, L4	459, 96, 71, 87 (64%, 14%, 10%, 12%)	190, 29, 44, 63 (58%, 9%, 14%, 19%)	79, 6, 45, 57 (42%, 3%, 24%, 31%)	0.0001
Behavior B1, B2, B3	18, 286, 409 (3%, 40%, 57%)	8, 145, 172 (2%, 45%, 53%)	5, 75, 106 (3%, 40%, 57%)	0.7
Perianal disease Y/N	162/551 (23%, 77%)	80/245 (25%, 75%)	57/129 (31%, 69%)	0.08
Age at diagnosis	33.2 ± 14.3	30.6 ± 12.2	28.9 ± 10.6	0.0005
Disease duration	6.8 ± 7.3	12 ± 6.9	17.3 ± 8.6	< 0.0001
Time to 1st surgery	6.6 ± 7.3	3.4 ± 4.6	2.7 ± 3.9	< 0.0001
Smoking habit Y/N	281/432 (39%, 61%)	145/180 (45%, 55%)	88/98 (47%, 53%)	0.08
Family history Y/N	71/642 (10%, 90%)	30/295 (9%, 91%)	19/167 (10%, 90%)	0.9
Extra-intestinal man. Y/N	81/632 (11%, 89%)	43/282 (13%, 87%)	30/156 (16%, 84%)	0.1
Hemoglobin (g/L)	12.4 ± 1.9	12.3 ± 2	12 ± 1.9	0.04
WBC count (× 10 <sup>9</sup> /L)	8371 ± 3515	8126 ± 3301	8193 ± 3607	0.5
C-reactive protein (g/L)	3.8 ± 6.8	3.2 ± 5.8	4 ± 8.9	0.9
Albumin (g/L)	35.7 ± 9.4	35.2 ± 7.2	34.1 ± 7	0.03
Pre-albumin (g/L)	0.23 ± 0.06	0.22 ± 0.08	0.21 ± 0.1	< 0.0001
TPN Y/N	130/583 (18%, 82%)	73/252 (22%, 78%)	51/135 (27%, 73%)	0.01
INT Y/N	185/528 (26%, 74%)	87/238 (27%, 73%)	50/136 (27% 73%)	0.9
Preoperative therapy				
No, 5-ASA	345 (48%)	166 (51%)	82 (44%)	
Immunomodulators	79 (11%)	43 (13%)	35 (19%)	
Biologicals	66 (9%)	23 (7%)	24 (13%)	
Steroids	189 (27%)	76 (24%)	37 (20%)	
Combo	34 (5%)	17 (5%)	8 (4%)	0.04
Indication for surgery				
Stenosis	584 (82%)	274 (84%)	144 (77%)	
Fistula/abscess	102 (14%)	39 (12%)	35 (19%)	
Refractory	27 (4%)	12 (4%)	7 (4%)	0.3

Montreal Classification for CD: age at diagnosis A1 ≤ 16 years, A2 17–40 years, A3 > 40 years; disease location L1 terminal ileum, L2 colon, L3 ileocolonic, L4 jejunoleal; disease behavior: B1 non-stricturing non-penetrating, B2 stricturing, B3 penetrating; *p* = perianal disease; Preoperative therapy was considered within 12 weeks before surgery

TPN total parenteral nutrition, INT intraoperative transfusions

and disease behavior, but recurrent patients were more likely to have their diagnosis before the age of 16 (A1) and multiple disease locations (L3 and L4) ( $p < 0.0001$ ). The indication for surgery was similar among the three groups. However, patients in group S3 were significantly older ( $p < 0.0001$ ), with a longer disease duration ( $p < 0.0001$ ), younger age at diagnosis ( $p = 0.0005$ ) and shorter time frame between diagnosis and first surgical procedure in comparison with the other groups. In terms of preoperative optimization, S3 group patients also presented with lower hemoglobin, albumin and pre-albumin values, need for parenteral nutrition ( $p = 0.01$ ), and were more frequently treated with Anti TNF- $\alpha$  drugs in the last 12 weeks before surgery. Intraoperative findings are reported in Table 2. The shift of disease location, namely a recurrence on a different bowel district according to the Montreal Classification [11], was similar between S2 and S3 groups, but anastomotic recurrence was more common at first reoperation ( $p = 0.05$ ), while strictureplasty recurrence at further surgeries ( $p < 0.01$ ). The need for a colonic resection showed a downward trend in recurrences ( $p = 0.0004$ ), such as perforating disease at surgery ( $p = 0.0001$ ). Ostomies were more frequently performed after the second operation ( $p = 0.06$ ).

Intestinal resections gradually decreased from S1 to S3 (58% in S1, 51% in S2 and 46% in S3), while strictureplasties, both SP and NCSP, increased in all groups (42% in S1, 49% in S2 and 54% in S3).

Duration of surgery, an indirect but reliable parameter of complexity of surgical procedure, progressively increases among groups. In particular, those patients receiving their previous operation at “Luigi Sacco” IBD Unit had shorter operating time than those referred from other hospitals after the first or further recurrences. Overall postoperative mortality and morbidity occurred in 6/1124 (0.3%) and 353/1224 (28.8%) patients, respectively. Postoperative complications according to the Clavien–Dindo classification are summarized in Table 3. Overall complication rate significantly increases after repeated surgery (26.2%, 31.4%, 34.4%,  $p = 0.04$ ), but no differences were found among groups in terms of incidence of severe postoperative morbidity nor mortality (Clavien–Dindo III–V,  $p = 0.2$ ). An increased necessity of fecal diversion was present in the S3 group, with border-line statistical significance ( $p = 0.06$ ). Intestinal failure (SBS) was significantly more frequent after repeated surgical procedures ( $p < 0.0001$ ). In Fig. 1, the time-to-event estimates for surgical recurrence are reported. The cumulative proportions of recurrences at 10 years were 18% for S1, 27% for S2, and 48% for S3, with significant discrepancies at the log-rank test.

**Table 2** Intraoperative findings

	First surgery (S1) $n = 713$ (%)	Second surgery (S2) $n = 325$ (%)	3 or more surgeries (S3) $n = 186$ (%)	<i>p</i>
Shift of location Y/N	–	51/274 (16%, 84%)	21/165 (11%, 89%)	0.2
Anastomotic rec Y/N	–	197/128 (61%, 39%)	103/83 (55%, 45%)	0.05
Strictureplasty rec Y/N	–	19/306 (5%, 95%)	23/163 (12%, 88%)	0.01
Intraoperative procedures				
Small bowel resection	582 (44%)	241 (40%)	127 (38%)	
Colonic resection	177 (14%)	67 (11%)	25 (8%)	
SP	318 (24%)	153 (25%)	102 (30%)	
NCSP	243 (19%)	142 (24%)	76 (23%)	
Total	1311	603	330	0.0004
Duration of surgery				
General	158 ± 68	173 ± 69	183 ± 72	<0.0001
Previous domestic	158 ± 68 <sup>a</sup>	163 ± 60 <sup>a, b</sup> ( $n = 228$ )	172 ± 62 <sup>a, c</sup> ( $n = 126$ )	<sup>a</sup> 0.07, <sup>b</sup> 0.02
Previous foreign	–	180 ± 70 <sup>b, d</sup> ( $n = 97$ )	198 ± 74 <sup>c, d</sup> ( $n = 60$ )	<sup>c</sup> 0.01 <sup>d</sup> 0.12,
Fistula/abscess /N	270/132/311 (38%, 18%, 44%)	115/96/114 (35%, 29%, 36%)	48/36/102 (26%, 19%, 55%)	<0.0001
Ostomy Y/N	72/641 (10%, 90%)	35/290 (10%, 90%)	30/156 (16%, 84%)	0.06
Short bowel syndrome	1/710 (0.1%)	5/320 (1.5%)	12/174 (6.4%)	<0.0001

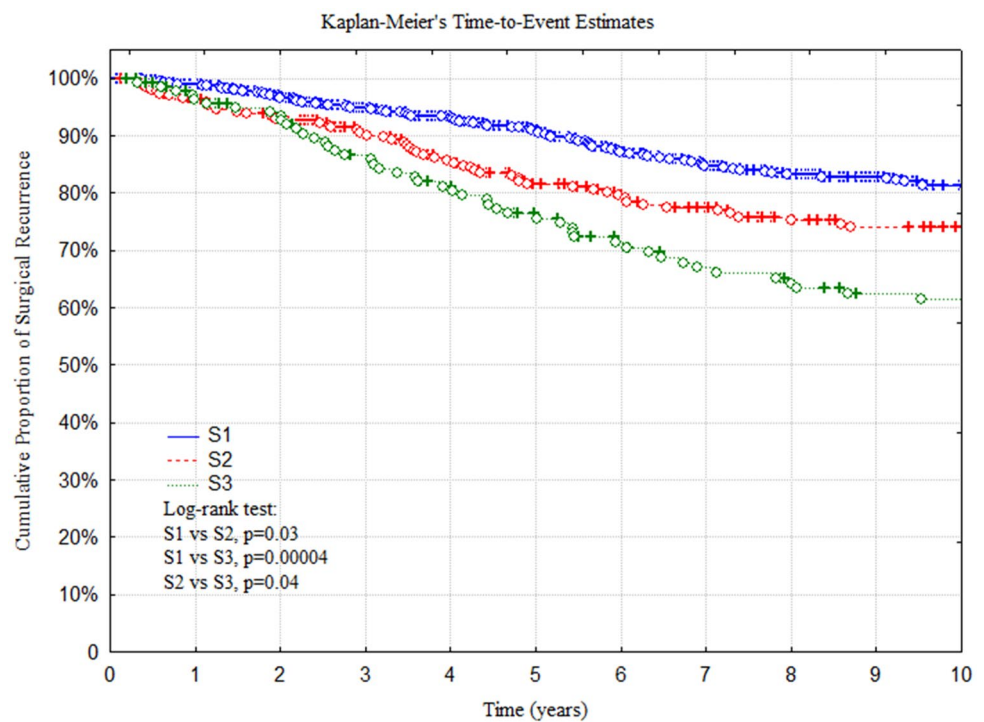
Surgical procedures are considered per segment, as more diseased segment could be comprised in one single resection or NCSP

Depending on whether their first operation was performed at domestic IBD Unit or in other hospitals the patients were compared as follows: a: S1 vs S2 vs S3; b: S2 domestic vs S2 foreign; c: S3 domestic vs S3 foreign; d: S2 vs S3 foreign

**Table 3** Postoperative complications

	First surgery (S1) <i>n</i> =713 (%)	Second surgery (S2) <i>n</i> =325 (%)	3 or more surgeries (S3) <i>n</i> =186 (%)	<i>p</i>
Clavien–Dindo				
I+II	118 (17%)	65 (20%)	40 (21%)	
III	60 (8.4%)	30 (9.2%)	19 (10.2%)	
IV	6 (0.8%)	5 (1.5%)	4 (2.1%)	
V	3 (0.4%)	2 (0.6%)	1 (0.5%)	
Total	187 (26.2%)	102 (31.4%)	64 (34.4%)	0.04
Major complications (III–V)	69 (9.6%)	37 (11.3%)	24 (12.9%)	0.2

**Fig. 1** Kaplan and Meier function showing the long-term surgical recurrence after each surgical procedure compared with the log-rank test



## Discussion

This is the first study comparing the postoperative outcomes of patients with primary or recurrent CD, comprising any intestinal location, and treated using a conservative strategy of minimal bowel resection and strictureplasties. Data regarding the outcome of surgery for single or multiple recurrent CD are limited in the literature and focused on ileocolic disease [17–19, 22, 27]. Since CD is a chronic, relapsing disease, it is reasonable that the younger the age at diagnosis and the longer the disease duration, the higher the frequency of multiple recurrences, as showed in Table 1. However, as previously reported, young age at diagnosis (Montreal Classification A1), extensive bowel involvement (Montreal Classification L4),

and short time-to-first surgery are definite factors involved in surgical disease recurrences [3, 9]. In fact, if perforating disease has to be considered a risk for recurrence in ileocecal and pure colonic locations, there is a well-defined sub-group of young patients, with extensive fibrostenotic disease, who are at high risk of repeated surgery and exhibit an indolent disease pattern difficult to control with current pharmacologic repertoire, as reported in the European Crohn's and Colitis Organisation—European Society of Coloproctology (ECCO-ESCP) 2018 guidelines [9, 15, 16]. This phenomenon is also evident in the long-term surgical recurrence rate which significantly increases after surgery for recurrent disease, suggesting that surgical recurrence is a definite risk for further recurrences, and adequate prophylactic therapies are still needed in this subgroup of patients [19].



More than half of the patients in S3 group (55%) presented with nutritional impairment, despite the use of preoperative optimization with parenteral nutrition. These patients are also less likely to suspend immunosuppressive and biological therapy when scheduled for surgery, with a potential additional risk factor for post-operative complications [16]. All these features have to be taken into account in terms of clinical workload when planning a surgical procedure, in particular during the complicated period of the COVID-19 pandemic [28, 29].

Recurrences of CD are generally localized in the anastomotic territory of a previous resection (>60%), but after a SP or a NCSP the specific recurrence rate by site is reported to be very low (<5%) [6, 9, 16, 30, 31]. In the present study, while the first recurrence occurred on a strictureplasty site in line with the reported 5% rate, the more the number of re-interventions, the more the recurrences on a strictureplasty site (12%), data were never reported in the literature before. Nevertheless, the need for bowel length preservation after repeated surgery pushed the use of strictureplasty and re-do strictureplasty over the 50% of bowel segments in the S3 group. On the contrary, colonic resections decreased from 14% in S1 to 8% in S3, suggesting that a bowel-sparing policy, together with adjuvant treatment, may positively impact on colonic disease recurrences [32, 33]. Furthermore, 16% of the patients in S2 and 11% in S3 groups experienced a shift in the disease location, by having the recurrence in a different bowel district than primary surgery. This shift in CD location at time of surgical recurrence still represents a poorly understood and neglected phenomenon.

There was a significant increasing trend of performing strictureplasties, reoperation after reoperation (42%—49%—54%) at the expense of bowel resections that conversely were less performed from S1 to S3 group (58%—51%—46%). These results suggest that a conservative approach, specifically represented by SP or NCSP, should be the operation of choice in recurrent CD patients, whenever possible, due to the low recurrence rate on a SP site and the associated lower rate of SBS.

Defining the degree of difficulty of a surgical intervention is a challenging issue in daily practice, since the countless different clinical, anatomical, and technical factors are involved. However, the duration of surgery turns out to be quite a reliable parameter (even though non-specific), especially because all the surgical procedures in this series have been performed by a small group of surgeons, with a standardized technique maintained over the years. Duration of surgery had an increasing trend at repeated surgeries, but it was not statistically significant for those patients operated at “Luigi Sacco” IBD Unit since the first operation. On the other side, those patients referred to the IBD Unit after the first surgery was performed in other hospitals required longer operating time for both first and further recurrences.

Also, the incidence of short bowel syndrome (SBS) is related to the number of surgical procedures received from the patients. In the literature, SBS cumulative risk is reported to be of 0.8% at 5 years, 3.6% at 10 years, and 8.5% at 20 years [34–36]. In this series, probably due to the highly conservative approach of minimal bowel re-resections and strictureplasties, the SBS incidence in S1 group was 0.1%, with a disease duration of  $6.8 \pm 7$  years; in S2 group 1.5%, with a disease duration of  $12 \pm 6.9$  years; and in S3 group was 6.4%, with a disease duration of  $17.3 \pm 8.6$  years ( $p < 0.0001$ ). However, only 2 out of 12 patients (16%) were operated at the “Luigi Sacco” IBD Unit for the first and second surgical procedure, while the remaining 10 patients (83%) were referred after previous extensive small bowel resections performed in other hospitals. The lower frequency of SBS and the shorter operating time in those patients treated and followed up from the very beginning at “Luigi Sacco” IBD Unit suggest the importance of referring IBD patients to dedicated surgeons [23].

All the authors that examined the outcome of CD patients undergone to multiple surgeries agreed that recurrences are technically demanding due to postoperative adhesions, modified anatomy, and complex perforating disease, but without a significant increase in severe post-operative complications. In this series, the overall postoperative complication rate was 28% and major complication rate 10%, with a difference in minor ( $p = 0.04$ ) but not major ( $p = 0.2$ ) Clavien–Dindo complication rate among all groups. A result similar to that reported in the series focused on terminal ileum disease [17–19, 21, 22, 27]. Heimann et al. reported that a disease requiring multiple re-operations is more aggressive and is more likely to result in complex resections and permanent ileostomy, in line with the results of the present series [20].

Some limitations have to be considered in the interpretation of the study results: this is a retrospective analysis of a prospective database, from a single tertiary center, covering a long-term period of 25 years. If the surgical strategy has been maintained almost unchanged over the years, the surgical approach has been shifted from open to laparoscopic surgery, and the adjuvant medical therapy has been enriched with the addition of novel biological therapies [3–6, 9, 37–39]. However, laparoscopy was adopted for CD by the “Luigi Sacco” IBD Unit since 2007, but it was offered only to the patients at their first operation or those presenting with a recurrence after a previous laparoscopic surgery. Those patients treated by previous open surgery were not candidate to laparoscopy. This approach would minimize and equalize the effect of laparoscopy among the different groups [38–40]. The effect of adjuvant therapy on postoperative recurrence is not in the aims of the present study. On the one hand, surgical recurrence is a long-term event and during the years, several therapeutic changes could be made in every single patient, making it almost impossible to evaluate

the potential effect of each drug in a very long period. On the other hand, the use of therapies over the years, following the updated guidelines, has probably had a uniform distribution in the series.

## Conclusion

Repeated surgery for complicated CD is associated with an increase in minor, but not major Clavien–Dindo complications rate. It requires a longer operating time, with a potential for augmented ostomies and SBS. Patients operated from the first operation in a referral center, with a dedicated IBD team, are less likely to undergo complex procedures with extensive resections in the following surgery for recurrence. Long-term surgical recurrence rate after repeated surgery remains high and a bowel-sparing strategy appears to be more favorable in terms of further recurrences and SBS risk.

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## Declarations

**Conflict of interest** None of the authors have conflicts to declare.

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