Post-operative recurrence of Crohn’s disease: a prospective study at 5 years

Sara Onali, M.D., Ph.D., Emma Calabrese, M.D., Ph.D., Carmelina Petruzzello, M.D., Ph.D., Elisabetta Lolli, M.D., Marta Ascolani, M.D., Alessandra Ruffa, M.D., Giuseppe Sica, M.D., Alessandra Rossi, Carlo Chiaramonte, M.D., Francesco Pallone, M.D., Livia Biancone, M.D., Ph.D.

1 GI Unit, Department of Systems Medicine, 2 Surgical Unit, Department of Surgery, 3 Department of Statistic, University of Rome “Tor Vergata”, Italy

Abbreviations: CD=Crohn’s Disease; Postoperative Recurrence=POR; Inflammatory Bowel Disease=IBD; Small Intestine Contrast Ultrasonography=SICUS; PEG=Polyethylene Glycol; BWT=Bowel Wall Thickness; Crohn’s Disease Activity Index=CDAI; OR=Odds Ratio; CI=Confidence Interval; BMI=Body Mass Index; Anti-TNFα=Anti-Tumor Necrosis Factor-α

Conflict of interest: None declared.

Funding: The study was supported by the Fondazione “Umberto Di Mario”, Largo Marchiafava, Rome, Italy; Center of Excellence for the Study of the Genomic Risk of Complex Multifactoral Diseases, Universita’ di Roma “Tor Vergata,” Rome, Italy

Corresponding Author
Livia Biancone, M.D., Ph.D.
GI Unit
Department of Systems Medicine
University of Rome “Tor Vergata”
Via Montpellier, 1
00133 Rome, Italy
Tel. +39.06.20903737; +39.06.20908390;
Fax +39.06.20903738
E-mail:biancone@med.uniroma2.it
ABSTRACT

Background. We aimed to prospectively assess whether endoscopic recurrence severity at 1 year in Crohn’s disease is predictive of clinical recurrence within 5 years.

Methods. Clinical recurrence (Crohn’s Disease Activity Index>150) was assessed yearly for 5 years in Crohn’s disease patients undergoing ileo-colonic resection. At 1 year, recurrence was assessed by colonoscopy (Rutgeerts’ score ≥i1 or ≥2i) and small intestine contrast ultrasonography.

Results. 40 patients were included (23 males, median age 39 [16-69] years). Clinical recurrence occurred within 5 years in 16 (40%) patients (years 1, 2, 3, 4, 5: 2 [5%];10 [25%];4 [10%];2 [5%];4 [10%], respectively). At 1 year, endoscopic recurrence (score≥i1) occurred in 39 (97.5%) patients (score≥i2:33 [82.5%]). Ultrasound detected lesions compatible with recurrence in 39/40 (97.5%) patients. Endoscopic score at 1 year was correlated with clinical score at 2 years (p=0.007; r=0.41). Endoscopic score at 1 year was higher in patients with (n=10) vs without (n=30) clinical recurrence at 2 years (3 [2-4] vs 2 [0-4]; p=0.003). Higher endoscopic score (>i2) at 1 year was a risk factor for clinical recurrence within 5 years (OR=0.18; 95%CI 0.04-0.71; p=0.008).

Conclusions. In Crohn’s disease, severity of endoscopic recurrence at 1 year remains a predictive marker of clinical recurrence within 5 years. Small intestine contrast ultrasonography is useful for assessing 1-year recurrence.

Key Words: Crohn’s Disease; Postoperative Recurrence; Ileocolonoscopy; Small Intestine Contrast Ultrasonography; endoscopic recurrence
INTRODUCTION

Postoperative recurrence after ileo-colonic resection is a feature of Crohn's disease (CD) (1-7). A variable frequency of recurrence has been reported in different study populations (1-9) bearing different risk factors (6,10-14). More recently, early colonoscopy and immunosuppressive treatments, including tumour necrosis factor (TNF)-α antagonists, have been shown to reduce the risk of endoscopic and clinical recurrence (15-19).

Ileocolonoscopy still represents the gold standard for assessing the postoperative recurrence of CD after ileo-colonic resection (6,15-19). The endoscopic degree of recurrence at 1 year has consistently been shown to predict the clinical recurrence of CD within 3 years after surgery (1,2,6-9). Beside the severity of endoscopic recurrence, additional risk factors for early recurrence have been reported in CD (6,10-14). Identification of the subgroup of patients at risk for early clinical recurrence may be useful for timely immunomodulatory treatments and for possible relapse prevention. Early colonoscopy after surgery was recently shown to be useful for this purpose (15-19).

Alternative non-invasive techniques for assessing CD recurrence have been proposed (20-25). In a cohort of CD patients with ileo-colonic resection followed up for 3 years we reported that, in experienced hands, small intestine contrast ultrasonography (SICUS) provides findings compatible with endoscopic recurrence at 1 year (24). The endoscopic score at 1 year was higher in patients developing relapse than in patients maintaining remission at 2 years (24). Whether ileocolonoscopy and SICUS may be used as predictors of clinical recurrence in the longer follow up was not investigated.

We therefore aimed to investigate the role of endoscopic recurrence at 1 year as predictor of clinical outcome at 5 years when correcting for confounding factors (6,10-14) in an homogeneous cohort of patients undergoing ileo-colonic resection for CD. The usefulness of SICUS at 1 year for predicting clinical recurrence was also investigated in a 5-year follow-up.

MATERIAL AND METHODS

Study population

All patients undergoing elective ileo-colonic resection for CD from July 2003 to February 2007 in our tertiary centre were considered eligible for the study. The diagnosis of CD and indication for surgery were made according to conventional criteria (6,20) and clinical characteristics of CD prospectively reported. Inclusion
criteria were: diagnosis of CD according to current guidelines (20); age from 16 to 70 years; compliance with follow-up; indication for elective ileo-colonic resection; intestinal resection performed by the same surgical unit, surgical removal of all the involved tissue, as confirmed by histological analysis of the sample; written informed consent. Exclusion criteria were: relevant comorbidities contraindicating elective resection or colonoscopy; body mass index (BMI) >30 (not allowing SICUS assessment); low compliance to follow-up visits; early postoperative complications (i.e. ≤1 month from surgical discharge).

CD behaviour was classified according to current guidelines: B1=non-stricturing non-penetrating, B2=stricturing, B3=penetrating (26).

Study protocol

From July 2003 to February 2007, all eligible CD patients fulfilling the inclusion criteria were prospectively enrolled and followed for 5 years. In each patient, demographic and clinical characteristics of patients, (CD site, extent, behaviour, age at diagnosis of CD, CD duration) and risk factors for recurrence (prior intestinal surgery, penetrating behaviour, perianal location, extensive small bowel resection >50 cm, smoking) (6,10-14) were recorded. After surgery, all patients were treated with mesalamine (2.4 gr/day) within 14 days. Additional treatment strategies during follow-up were used according to current guidelines (6). The study protocol included ileocolonoscopy and SICUS at 1 year and clinical assessment (Crohn’s Disease Activity Index, CDAI)(27) every year for 5 years. At 1 year, recurrence was assessed by ileocolonoscopy according to Rutgeerts et al. (1,2), as gold standard (score ≥1). In a subgroup analysis, according to recent clinical trials (15-19), an endoscopic score ≥i2 was also considered for this purpose. At 1 year, findings compatible with recurrence were also assessed by SICUS, using ileocolonoscopy as gold standard. The two procedures were performed by 2 independent gastroenterologists, unaware of previous findings. During clinical assessments, CD treatments were recorded and related to recurrence. Risk factors for postoperative recurrence (6,10-14) were also recorded during follow-up. The Tor Vergata University Ethics committee approved the study protocol, allowing inclusion of patients younger than 18 years (protocol number 41/02). All patients and legal guardians (for patients younger than 18 years of age) provided written informed consent to participate. Clinical recurrence (CDAI>150) was assessed every year for 5 years (27).

Ileocolonoscopy

Endoscopic assessment with visualization of the neo-terminal ileum was performed at 1 year follow-up, and the severity of recurrence graded according to the Rutgeerts’ score (i.e.: 0–i4)(1,2).
The severity of recurrence at the peri-anastomotic area was also supported by a photographic documentation, thus allowing a second revision performed at the end of each colonoscopy by the same dedicated endoscopist. The degree of endoscopic recurrence was assessed once by the same endoscopist, according to both the endoscopic view and to the photographic documentation of the peri-anastomotic area evaluated at the end of each examination. Ileocolonoscopy was performed with or without sedation (i.v. midazolam), according to patient request. Biopsies were taken from the involved and uninvolved areas, for routine histologic assessment.

**SICUS**

SICUS was performed by the same independent experienced gastroenterologist at 1-year follow-up. Patients were examined in the fasting state, without any specific preparation the day before SICUS. The day of SICUS, the examination was performed as previously described (22-25) after the ingestion of 375 mL (range, 250–500 mL) of polyethylene glycol (PEG), using a convex transducer (1–8 MHz) and a high-frequency linear-array transducer for details (3–11 MHz) (Esaote; My Lab Twice, Genoa, Italy). Technically adequate scans were obtained in all patients. Findings compatible with small bowel CD recurrence, including bowel wall thickness (BWT ≥3 mm) were defined as previously described (22-25).

**Histological assessment**

Biopsies were taken from the peri-anastomotic area for histological assessment. Histologic assessment of biopsies taken from the peri-anastomotic area was performed to confirm the presence of lesions compatible with CD and to exclude the presence of dysplastic/neoplastic lesions. Histological analysis was not performed to assess CD recurrence. Surgical samples were also evaluated to confirm the diagnosis of CD and to exclude residual lesions in the resected margins.

**Statistical analysis**

Data collected in a common database were evaluated by two experts in the field (CG, AR). Results were expressed as median and range. Differences between groups were assessed by the Students’ T test (CDAI values in patients with vs without endoscopic recurrence) or by the Chi square test (for comparing frequencies). At the end of the study, the analysis included the possible relation between presence and severity of endoscopic recurrence at 1 year and development of clinical recurrence (CDAI>150) within the 5 years follow-up. Endoscopic recurrence was defined according to an endoscopic degree ≥i1 or, in a separate analysis, ≥i2. This analysis was performed when considering the frequency of clinical recurrence either separately during each of the 5 years, or globally as overall frequency of recurrence developing within 5 years after ileo-colonic resection.
For this analysis, recurrence was defined by an endoscopic degree ≥i2. This analysis was assessed by using the Odds Ratio (OR). Correlation between the occurrence of endoscopic recurrence and any first clinical recurrence during the 5 years follow-up was analysed by the Chi square test, for assessing the effect of possible confounding variables (6,10-14). Correlations between each variable and either endoscopic recurrence or first clinical recurrence were assessed by the Students’ T test, Wilcoxon test, Chi square test and Fisher test, when appropriate. The incidence rate (1000 person-year) of the first clinical recurrence and the median survival time to first clinical recurrence in patients with or without endoscopic recurrence were calculated. Kaplan-Meier survival curve and log Rank test were used to evaluate the role of endoscopic recurrence on the occurrence of the first clinical recurrence. The effect of possible confounding variables was determined by Cox regression model (Hazard Ratio, HR). Cox model with the endoscopic recurrence (unadjusted HR) was compared with the same model adjusted for confounding variables (adjusted HR).

RESULTS

Study Population

During the study period, 54 CD patients underwent ileo-colonic resection in our centre. Among these 54 patients, 11 (20.3%) did not fulfil the inclusion criteria and were not enrolled. In these 11 patients, exclusion criteria were: non-compliance to follow-up visits (n=1) and non-compliance to undergo follow-up colonoscopy (n=10), as stated by each patient before enrolment. Therefore, 43 CD patients (23 males, median age 39 years, range 16-69) undergoing ileo-colonic resection were enrolled and prospectively followed. Among these 43 patients, 40 completed the study protocol at 5 years with ultrasonographic and endoscopic evaluation at 1 year and yearly clinical assessment for 5 years. The remaining 3 patients were lost to follow-up in the early postoperative period. The median follow-up evaluated when considering all 43 patients enrolled was 5.5 years (range 0.04-9.7). Clinical characteristics of the 40 patients completing the follow-up at 5 years are summarized in Table 1. The median age at diagnosis of CD was 28 years (range 15–49) and the median CD duration was 6 years (range 0.5–29).

Before surgery (≤12 months), 6/40 patients had been treated with TNF-α antagonists and 11/40 with thiopurines (all azathioprine), including 5 patients who received combined treatment.
After surgery, all 40 patients were treated with mesalamine (2.4 gr/day) within 14 days to prevent recurrence, and continued for 5 years. Overall, during the 5 years follow-up, 4 patients were treated with anti-TNF-α and 1 patient with azathioprine.

**Clinical and endoscopic recurrence at 1 year**

Forty patients who completed the clinical, endoscopic and sonographic assessments at 1 year were followed clinically for 5 years.

Clinical recurrence (CDAI>150) at 1 year was observed in 2/40 patients (5%, CDAI 155 and 220, respectively, median 176; Figure 1). In these 2 patients, clinical remission was induced by: budesonide in one patient (9 mg/day tapered 3 mg/4 weeks), and by prednisone (1 mg/kg tapered 5 mg/week), followed by TNFα antagonists (adalimumab induction and maintenance for 24 months) in the second patient.

Endoscopic recurrence at 1 year was detected in 39/40 patients (97.5%, Rutgeerts’ score ≥i1; Figure 2) and in 33/40 patients (82.5%, Rutgeerts’ score ≥i2). At 1 year, the severity of endoscopic recurrence was grade 0 in 1 (2.5%), grade 1 in 6 (15%), grade 2 in 12 (30%), grade 3 in 11 (27.5%), and grade 4 in 10 (25%, stenosis not passed by the endoscope in 1; Figure 2). At 1 year, the small number of patients developing clinical recurrence (n=2), did not allow to compare the endoscopic score in the subgroups of patients with or without clinical recurrence. When endoscopic recurrence was defined as a degree ≥i2 rather than ≥i1, recurrence occurred in 33/40 patients (82.5%).

At 1 year, SICUS detected lesions compatible with recurrence in 39/40 patients (97.5%), in agreement with endoscopic findings. In all 39 patients, an increased BWT (median 4.75 mm; range 3–7) was the only finding. The median SICUS examination duration was 40 minutes (range, 35–90 min).

**Clinical recurrence at 2, 3 and 4 years**

At 2 years, clinical recurrence occurred in 10/40 patients (25%, CDAI 180, range 155-200; Figure 1). Clinical remission was induced in all patients by budesonide (n=4) or prednisone (n=6). Among these 10 patients, 2 had already shown clinical recurrence at 1 year, and all patients showed endoscopic recurrence of grade >i1 (grade 2, n=2; grade 3, n=5; grade 4, n=3). The median endoscopic score at 1 year was significantly higher in the 10 patients with clinical recurrence (n=10) than in the 30 patients maintaining remission at 2 years (median, range: 3 [2-4] vs 2 [0-4]; p=0.003).

At 3 years, clinical recurrence developed in 4/40 patients (10%, CDAI 200, range 150-248; Figure 1). Remission was induced by budesonide 9 mg (n=2) or prednisone (1 mg/kg)(n=2), followed by anti-TNFα
(adalimumab 160, 80, 40 mg eow for 36 months) in one patient, or by azathioprine (2 mg/kg for 24 months) in the second patient. In 1 of these 2 patients, clinical recurrence had already occurred at 1 and 2 years. At 1 year, recurrence in these 4 patients had been grade 2 (n=2) or 4 (n=2). The small number of patients with clinical recurrence (n=4, Figure 1) did not allow to compare endoscopic score between patients with or without clinical recurrence.

At 4 years, clinical recurrence occurred in 2/40 patients (5%, CDAI 202, range 160-244; Figure 1). Clinical remission in these 2 patients was induced by budesonide (n=1) or prednisone (n=1), followed by adalimumab (160, 80, 40 mg eow for 24 months) in one patient. In both patients, clinical recurrence occurred only at 4 years, and endoscopic recurrence at 1 year was grade 4. The few cases of clinical recurrence (n=2), did not allow to compare the endoscopic score between patients with or without clinical recurrence.

At 4 years, CRP seropositivity was observed in 7/40 patients (17.5%). At 1 year, endoscopic score in these 7 patients had been grade 4 (n=3), grade 2 (n=1), and grade 3 (n=3); median BWT at SICUS had been 5.5 mm (range 3.5-7).

**Clinical recurrence at 5 years**

At 5 years, clinical recurrence occurred in 4/40 patients (10%, CDAI: 167, range 150-224; Figure.1), and 3 of them already had clinical recurrence at 3 years. Remission was induced by budesonide (9 mg/ day; n=1) or prednisone (1 mg/Kg; n=3), followed by anti-TNFα (adalimumab 160,80,40 mg eow for 12 months; n=1). At 1 year, the endoscopic degree of recurrence in these 4 patients had been grade 0 (n=1) or 4 (n=3). At 5 years, the limited cases of clinical recurrence (n=4) did not allow to compare the endoscopic score between patients with or without clinical recurrence.

At 5 years, CRP seropositivity was observed in 3/40 patients (7.5%). At 1 year, the endoscopic score in these 3 patients had been grade 0 (n=1), grade 2 (n=1), or grade 3 (n=1); BWT at SICUS had been 3.5, 3.5 and 5 mm, respectively (normal ≤3).

**Endoscopic recurrence grade at 1 year as a risk factor for clinical recurrence 5 years after ileo-colonic resection**

The overall incidence rate of first clinical recurrence was 102.6/1000 patient/years. Clinical recurrence (CDAI>150) within 5 years was observed in 16/40 patients (40%). Although the cumulative number of relapses during the 5 years’ follow-up was 22, 6 patients indeed showed recurrent clinical relapses. Kaplan-Meier curves showed that the probability to survive free of first clinical recurrence over 5 years was significantly higher in the
subgroup of patients with an endoscopic score ≤2 vs ≥3 (p=0.0178; Figure 3). The subgroup of patients showing an endoscopic score ≥3 at 1 year had a significantly higher risk of clinical recurrence during the 5-year follow-up when compared with patients with endoscopic score ≤2 (HR 3.4 p=0.0018). Histograms in Figure 4 show the number of patients with clinical recurrence within 5 years of surgery, subgrouped according to the degree of endoscopic recurrence (≤i2 vs >i2) at 1 year. As shown, in these 40 patients a higher degree of endoscopic recurrence (>i2) at 1 year was a significant risk factor for clinical recurrence within 5 years (OR=0.18; 95% CI 0.04-0.71; p=0.008).

When considering known risk factors for early CD recurrence, among the 16 patients who developed clinical recurrence over 5 years there were: 5 active smokers (31%), 7 younger than 40 years (44%), 5 with penetrating CD (31%), 5 with a history of perianal disease (31%), 2 with previous surgery for CD (12.5%), 5 with past/present immunosuppressant use (31%), and 4 with a history of anti-TNFα use (25%). Cox model showed that the risk of a first clinical recurrence was significantly higher in patients with endoscopic recurrence of grade ≥3 vs ≤2 (HR=3.589; 95% CI 1.152-11.182). The role of endoscopic recurrence at 1 year as a predictor of clinical recurrence was corrected for confounding factors (i.e. smoking, prior intestinal surgery, penetrating disease behaviour and perianal location, extensive small bowel resection, [>50 cm]) (6,10-14). When separately considering each of these risk factors, endoscopic recurrence was significantly correlated only with prior surgery (p=0.0486). Overall, the analysis showed that pooled confounding factors did not significantly influence the risk of clinical recurrence in relation to the degree of endoscopic recurrence at 1 year (pooled HR [95% CI] 2.846 [0.84-9.64]; p=0.09 and 3.24 [0.95-11]; p=0.06 when considering smokers and ex-smokers vs no-smokers or, separately, smokers, ex-smokers, non-smokers, respectively). The influence of tobacco status was also separately evaluated, showing that smoking was significantly correlated with the occurrence of a second but not of a first clinical recurrence (p=0.03 and p=0.64, respectively). In contrast, previous surgery did not significantly influence clinical relapse (p=0.13 and p=0.10 for the first and second relapse). A Cox model was applied to address whether anti-TNFα treatments and, separately, thiopurines before surgery affected the rate of clinical recurrence. Although the limited number of treated patients limited this analysis, these treatments before surgery were not identified as confounding factors significantly affecting the rate of clinical recurrence adjusted for the endoscopic findings at 1 year (HR [95% CI]: AZA 1.19 [0.41-3.44]; p=0.74; Anti-TNFα 1.74 [56-5.41]; p=0.34). Moreover, after the first clinical recurrence, the use of azathioprine or anti-TNFα before surgery was not significantly correlated with the occurrence of a second or third clinical relapse within 5 years (AZA: p=0.72
and \( p=0.61; \text{anti-TNF}\alpha: p=0.31 \) and \( p=0.21 \), respectively). When the severity of endoscopic recurrence at 1 year was correlated with the CDAI score, a significant correlation was observed with the CDAI score at 2 years (\( p=0.007; r=0.41 \)), but not at 1, 3, 4 and 5 years.

**DISCUSSION**

Ileocolonoscopy is the gold standard for assessing postoperative recurrence after ileo-colonic resection for CD \( 6,15-19 \). Entero-magnetic resonance imaging/computed tomography and ultrasonography in experienced hands represent complementary tools for visualizing extramural lesions related to recurrence \( 6,21-25 \). The natural history of CD recurrence has been extensively described by Rutgeerts et al. \( 1,2,28,29 \), consistently showing that the severity of endoscopic recurrence at 1 year is predictive of earlier clinical relapse. In a prospective study including a small number of patients followed up for 3 years after ileo-colonic resection, we reported that the endoscopic score at 1 year was higher in patients with clinical recurrence at 2 years \( (p=0.003)(24) \). These findings prompted us to assess the role of ileocolonoscopy and SICUS performed 1 year after surgery, in clinical management of CD patients followed for 5 additional years.

The neo-terminal ileum was evaluated in all the 40 patients enrolled, thus allowing a proper assessment of the role of colonoscopy for predicting clinical recurrence. Surgical resection, endoscopy and SICUS were independently assessed by the same referral surgical unit or dedicated gastroenterologists experts in the field. These observations support the reliability and reproducibility of the findings. A high frequency of endoscopic recurrence, as defined by a score \( \geq 1 \) \( (1,2) \) was detected at 1 year \( (97.5\%) \). In contrast, the frequency of clinical recurrence at 1 year was quite low \( (5\%) \). The observed frequencies are in agreement with our previous studies \( (22-25) \). The observed high rate of endoscopic recurrence at 1 year is within the upper limit \( (93\%) \) reported by independent studies including different risk factors for recurrence \( (6,10-14) \). In our population, a relatively young median age at both surgery \( (39 \text{ years}) \) and at CD diagnosis \( (28 \text{ years}, \text{oldest patient aged 49}) \), was observed. Moreover, one fourth of patients had a previous resection and 60% had present or past history of tobacco smoking. Differences in terms of study design and risk factors for recurrence \( (3-14) \) among tested CD populations may well account for the observed discrepancies. The degree of endoscopic recurrence \( (1,2) \) may show wide interobserver variations even when assessed by experienced gastroenterologists \( (30) \). A different rate of clinical and endoscopic recurrence at 1 year has been shown when considering randomized controlled trials or studies from referral centres. Data from referral centres showed a clinical recurrence rate at 1 and 5
years ranging from 20% to 37%, and from 34% to 47%, respectively (1-19,22-25). In referral centres, endoscopic recurrence at 1 and 3 years was observed in 48% to 93% and in 85% to 100% of patients, respectively (1-19,22-25). Conversely, in randomized clinical trials, clinical recurrence occurred in one fourth of patients and endoscopic recurrence in more than half of patients at 1 year (6,31).

In the present study, all colonoscopies were performed by the same experienced endoscopist, assessing the severity of recurrence at the end of each examination, when considering both the endoscopic and the photographic documentation of the peri-anastomotic area. No inter- or intraobserver agreement was therefore evaluated. A fair inter-observer agreement for the Rutgeerts’ score assessed by experts has been reported (kappa 0.57 [0.51–0.65]), nevertheless, the reproducibility of endoscopic scores in inflammatory bowel disease remains suboptimal (30). This issue needs to be considered among variables contributing to the discrepant findings in terms of rate of endoscopic recurrence. The Rutgeerts’ score has not been formally validated, although it is widely used in both clinical practice and trials (32). When recurrence was defined by an endoscopic score >i2 (rather than ≥i1) as recently suggested (15-19), a lower frequency of recurrence was observed (50%) at 1 year. A grade 1 recurrence is defined by <5 apthoid ulcers in the neo-terminal ileum (1,2). The number of aphtoid ulcers may increase proportionally to the extent of the neo-terminal ileum visualized. This bias is not observed when using a score >i2 (rather than ≥i1) for defining recurrence. Nevertheless, wide interobserver variations are still observed when grading the severity of endoscopic recurrence (30). Due to these observations, central reading is currently used in clinical trials, but not in the present single centre study.

Present findings also provide additional data regarding the role of SICUS in detecting lesions compatible with small bowel CD recurrence (22-25). On the basis of our previous study at 3 years (24.), the role of this technique for predicting clinical recurrence was investigated yearly for 5 years. The recurrence rate at 1 year was comparable as assessed by endoscopy or by ultrasonography, although SICUS findings were not predictive of clinical recurrence at 4 and 5 years. The low frequency of clinical relapse in our CD population limited this analysis. The high frequency of positive findings by SICUS was in agreement with endoscopic findings. Conversely, discrepancies between colonoscopy and SICUS as predictors of clinical recurrence may well be explained by the different view of the bowel wall provided by these 2 techniques. (i.e., luminal vs extra luminal)(22,24,25).

The median endoscopic score of recurrence at 1 year was higher in patients developing clinical recurrence at 2 years, than in patients maintaining remission (p=0.003), in agreement with previous studies.
(1,2). The same finding was not observed for patients developing clinical recurrence at 3, 4 or 5 years, in agreement with our previous study, including patients followed for 3 years (24). The CDAI score has not been validated for assessing CD recurrence after surgery, thus representing a limit of the present study (6,32). Moreover, some of the parameters included in the CDAI (i.e. diarrhoea) are highly affected not only by recurrence but also by resection itself (6,32). However, the CDAI still represents the most valuable tool for assessing clinical recurrence in CD, showing a low sensitivity and but high specificity. (6,32). As additional morphological and biological assessments, SICUS and CRP were also investigated, while faecal calprotectin and lactoferrin were not tested (6). In agreement with present findings, Yamamoto et al. (33) also reported a positive correlation only between the severity of endoscopic recurrence and the clinical recurrence rate during the following 5 years. In contrast to the present study, ileocolonoscopy was performed early after surgery (6 months) and no additional techniques, such as SICUS were performed (34).

The present study includes findings from a cohort of 40 CD patients enrolled 35 years after the first evidence indicating the severity of endoscopic recurrence at 1 year as a risk factor for clinical recurrence (1,2). Since the 1980s, the spectrum of treatment strategies, including biologics, has markedly increased. TNF-α antagonists only recently have been proposed for preventing or treating the early post-operative recurrence (15-19,34,35). Their use early after surgery might influence the role of endoscopic recurrence grade at 1 year as a predictor of clinical recurrence. In our study, the number of patients and events were too small to draw conclusions on smoking, previous treatments, correlations between CDAI and endoscopic recurrence. This is particularly true when considering the number of patients treated with thiopurines and/or anti-TNFα after surgery. With this limitation, a Cox model suggested that biologics and thiopurines did not represent confounding factors affecting the rate of clinical recurrence adjusted for the endoscopic findings at 1 year. To the best of our knowledge, data regarding the role of endoscopy and SICUS for predicting clinical recurrence of CD in patients prospectively followed for 5 years are currently lacking. In the tested cohort, the endoscopic degree of recurrence 1 year after ileocolonic resection was a predictive marker of clinical recurrence at both at 2 years and within the following 5 years. Present observations further support the role of SICUS in experienced hands as a useful non-invasive tool for detecting small bowel lesions compatible with CD recurrence. Whether the use of thiopurines and/or TNFα antagonists early after surgery may influence the role of endoscopic findings at 1 year as a predictor of subsequent clinical recurrence of CD requires further investigation.
Conflict of interest: None declared.

Funding: The study was supported by the Fondazione “Umberto Di Mario”, Largo Marchiafava, Rome, Italy; Center of Excellence for the Study of the Genomic Risk of Complex Multifactoral Diseases, Universita’ di Roma “Tor Vergata,” Rome, Italy
REFERENCES


**Acknowledgement** The authors are grateful to Ms. Danila Giampaolo for her assistance in collecting medical records of patients.
FIGURES LEGENDS

FIGURE 1
Histograms showing the frequency of clinical recurrence (CDAI>150) at 1,2,3,4, and 5 years in the 40 Crohn’s disease patients followed for 5 years after ileo-colonic resection.
CDAI, Crohn’s disease activity index

FIGURE 2
Frequency of endoscopic recurrence at 1 year in 40 Crohn’s disease patients followed for 5 years after ileo-colonic resection. The recurrence score is based on Rutgeerts’ et al.(3,4).

FIGURE 3
Kaplan-Meier curves showing that the probability to survive first clinical recurrence over 5 years was significantly higher in the subgroup of patients with an endoscopic score of recurrence ≤2 vs ≥ 3 (p=0.0178).

FIGURE 4
Histograms showing the number of Crohn’s disease patients developing clinical recurrence (Crohn’s disease activity index >150) within 5 years after surgery, subgrouped according to the degree of endoscopic recurrence (≤2 vs >2). A higher degree of endoscopic recurrence (≥2) at 1 year was a risk factor for clinical recurrence within 5 years after surgery (OR=0.18; 95% CI 0.04-0.71; p=0.008).
Table 1. Demographic and clinical characteristics of 40 patients with Crohn’s disease followed for 5 years after ileo-colonic resection

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CD patients (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>23 (57.5%)</td>
</tr>
<tr>
<td>CD type</td>
<td></td>
</tr>
<tr>
<td>B1</td>
<td>1 (2.5%)</td>
</tr>
<tr>
<td>B2</td>
<td>25 (62.5%)</td>
</tr>
<tr>
<td>B3</td>
<td>14 (35%)</td>
</tr>
<tr>
<td>Smoking habit</td>
<td></td>
</tr>
<tr>
<td>Active smokers</td>
<td>15 (37.5%)</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>9 (22.5%)</td>
</tr>
<tr>
<td>Non smokers</td>
<td>16 (40%)</td>
</tr>
<tr>
<td>Median Age at time of surgery (years)</td>
<td>39 (16-69)</td>
</tr>
<tr>
<td>Previous appendectomy</td>
<td>17 (42.5%)</td>
</tr>
<tr>
<td>Family History of IBD</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>Perianal disease</td>
<td>9 (22.5%)</td>
</tr>
<tr>
<td>Indication for ileo-colonic resection</td>
<td></td>
</tr>
<tr>
<td>Abscess/fistulae</td>
<td>7 (17.5%)</td>
</tr>
<tr>
<td>Sub/obstructions</td>
<td>33 (82.5%)</td>
</tr>
<tr>
<td>Previous intestinal resections</td>
<td>5 (12.5%)</td>
</tr>
<tr>
<td>Median BMI before surgery</td>
<td>23 (18-38)</td>
</tr>
</tbody>
</table>

CD, Crohn’s disease; IBD, inflammatory bowel disease; BMI, body mass index
FREQUENCY OF ENDOSCOPIC RECURRENCE AT 1 YEAR

GRADIENT 0 (2.5%)  
n=1

GRADIENT 4 (25%)  
n=10

GRADIENT 3 (27.5%)  
n=11

GRADIENT 1 (15%)  
n=6

GRADIENT 2 (30%)  
n=12

FIGURE 2
Endoscopic degree of recurrence (0-4) at 1 year

Comparing the number of patients with different grades of recurrence shows a significant difference

No clinical recurrence ≤ 5 yrs
Clinical recurrence ≤ 5 yrs

GRADE ≤ 2
GRADE > 2

P=0.008

FIGURE 4