Title page

AntiTNF α: Risk factor of major complications following ileocolic resection for Crohn's disease.

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Abstract

Introduction: The aim of this study was to determine the risk factors of complications in the era of anti-tumor necrosis factor.

Methods: This was a single-center retrospective study covering the period 1999 to 2015 of patients who underwent a first ileocolic resection for Crohn's disease. We evaluated the impact of preoperative characteristics and operative data on serious complications within 90 days after surgery.

Results: 146 patients were included. Post-operative morbidity was 43.8 % with 21 serious complications (14.4%). A univariate analysis, anti TNF in the 3 months before surgery (p= 0.0007), anti TNF and corticosteroid combination (p = 0.006), and operating time upper than 150 minutes (p= 0.01),were associated with the occurrence of a serious complication. In multivariate analysis, anti TNF (OR = 4.21; 95% CI 1.23 to 16.87; p= 0.02) and conversion (OR = 7.95; 95% CI = 1,68- 44.89; p= 0.009) were risk factors of serious complications.

Conclusion: The use of anti-TNF within 3 months before surgery and conversion during laparoscopy are risk factors of serious complications after ileocolic resection for Crohn's disease.

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Introduction

Crohn's disease is a chronic inflammatory disease affecting all segments of the digestive tract. About two-thirds of patients have ileal or ileocolic localisation (1-3) and 70% of cases have a lesion of the last ileal loop (4). The surgery rate is about 5% per year (5). It is estimated that 30% of patients were operated on five years after diagnosis and 50% after 10 years (6).

The use of anti TNF alpha is increasing but the impact on the bowel resection rate is uncertain (7-11). This raises the question of whether it reduces or delays the need for surgery.

Although post-operative mortality is very low (<0.5%) in Crohn's disease (12,13), the overall morbidity varies from 23 to 49% (14-16). The rate of intra-abdominal infectious complications is estimated between 10 to 13% (17-19) with a rate of anastomotic leakage from 5 to 11% (20,21). These complications increase the risk of anastomotic recurrence (22).

Identifying all risk factors of post-operative complications in Crohn's disease is essential prior to surgery to help determine the achievement of a temporary stoma (19,21). Several risk factors have been mentioned in the literature (23). Malnutrition must be assessed using serum albumin (less than 30g / l) and determining the percentage of body weight loss (5% in 1 month or 10% over 6 months) (19,22). The use of systemic corticosteroids within 3 months prior to surgery increases the risk of post-operative septic complications (12,19,24). An operative time exceeding 180 minutes (25) and a history of bowel resection (24) are also risk factors of post-operative complications.

The presence of fistulas or intra-abdominal abscesses are more important risk factors than the phenotype (19). However, this risk is reduced if the abscess is drained before surgery

(26). In such situations, it is recommended to prepare the patient for surgery (drainage, antibiotics, nutrition) (27).

The fistula rate seems to increase with end to end anastomosis (28). However, there is no difference between mechanical and manual anastomosis in terms of post-operative fistulas (19,24). The ECCO consensus of 2010 recommended a wide lumen stapled side to side ileocolic anastomosis (27).

Thiopurines, aminosalicylates, methotrexate (24), duration of disease, margins of resection, extent of resection, and number of anastomoses are not considered to be risk factors for post-operative complications (13,25,29).

Anti TNF alpha are directed against the cytokine of the same name, which is involved in the pathogenesis of Crohn's disease, and is a key component of the immune response. Inactivation could lead to severe post-operative complications, particularly infectious ones. The use of anti-TNF alpha has increased, with a controversial impact on post-operative morbidity (27). Several studies and meta-analyzes did not find an increased risk in post-operative complications (14-16,18, 20, 30-33), while others found an increased risk in patients treated with anti TNF alpha within 3 months (17,21,34-38).

Yamamoto et al. (19) and Alves et al. (12) identified several risk factors: use of systemic steroids before surgery, denutrition, abcess or fistula at the time of surgery, and recurrent clinical episodes. The former study showed a 5% risk of intra-abdominal septic complications without a risk factor, but 14%, 16%, 29% and 50% for one, two, three or four risk factors, respectively. The latter recommended a temporary stoma in high-risk patients, (at least three risk factors).

The aim of this study was to determine the risk factors of major complications following ileocolic resection for Crohn's disease in the era of anti TNF alpha.

Methods

Data on patients older than 16 years old who underwent ileocecal or ileocolic resection for Crohn's disease in the General Surgery Department of the University of Nice (France) were collected for the period January 1999 to December 2015. Cases were excluded where the diagnosis of Crohn's disease was uncertain or could not be confirmed after histological analysis and iterative ileocolic resection.

Patients with intra-abdominal or retroperitoneal abscess were treated by percutaneous or surgical drainage, antibiotics and enteral or parenteral nutrition. Surgery was delayed, if possible. The percutaneous drainage was preferred if accessible and available.

The surgical procedure consisted of a right colectomy or an ileocaecale resection according to the location of the lesions and performed by laparoscopy or laparotomy. The decision to make a temporary stomy was based on preoperative data (corticosteroids treatment, malnutrition) and intraoperative findings (abscess, fistulas). Otherwise, a stapled or manual side to side ileocolic anastomosis was performed.

The following data were collected for each patient: age, gender, ASA score, smoker status, malnutrition, disease duration since diagnosis, treatments before surgery, indication for surgery (stenosis, penetrating, tumor), and the presence of preoperative abscesses and drainage. In addition, data were collected on the surgical approach (laparotomy, laparoscopic), conversion to laparotomy, the type of anastomosis (manual, stapled), the operative time, the creation of a temporary stomy, digestive suture. Post-operative outcomes were also obtained.

Malnutrition was defined by one of the following criteria at the time of surgery: weight loss less than 5% in 1 month or 10% within 6 months, a serum albumin level less than 30 g/l, or a BMI below 18.5 kg/m2.

Concerning preoperative medical treatments, data were recorded for patients treated

with (a) systemic steroids for at least one week in the 3 months prior to surgery, (b) anti-TNF administration (infliximab, adalimumab, certolizumab pegol) in the 3 months prior to surgery, and (c) a treatment by aminosialycilé thiopurine, methotrexate or budesonide at the time of surgery.

The primary endpoint was the occurrence of a major complication during hospitalization or within 90 days following surgery. Complications were divided according to the classification of Clavien-Dindo using five grades (39). These complications were defined as major for grades III and IV. Post-operative complications were divided into medical and surgical complications. Intra-abdominal sepsis was determined by the presence of an intra-abdominal abscess and/or an anastomotic leakage.

Statistical analysis

Continuous variables were expressed as the mean plus or minus the standard deviation. Patients were divided into two groups according to the occurrence of major complications. A Wilcoxon test was performed to determine differences between the two groups for qualitative variables and Chi-squared for quantitative data. All variables with a probability <0.20 in the univariate analysis were included in the multivariate analysis so as to identify independent risk factors for post-operative major complications. These variables were included in a logistic regression model. A p value <0.05 was defined as statistically significant. Statistical analyzes were performed using JMP 12.1.0 software (SAS Institute, Cary, NC, USA).

Results

This study included 153 patients, of which 7 patients were excluded because of an iterative ileocolic resection, uncertain diagnosis of Crohn's disease after histological analysis or insufficient postoperative data.

Post-operative data are contained in **Table 1**. No deaths occurred, although 43.8% of patients had one or more complications. Minor complications (Grade I-II) occurred in 43.1 % including post-operative ileus (8.2%), wounds infections (7.5%), complications of stomy (4.8%) and intra-abdominal sepsis (8.2%).

Major complications (Grade III-IV) occurred in 21 patients (14.4%). One post-operative occlusion required surgery for adhesiolysis and one patient had a wound infection that required surgery. One patient presented a post-operative clinical peritonitis with a diffuse pneumoperitoneum on a CT scan. Surgical exploration did not find anastomotic leakage and allowed the emptying of the pnemoperitoneum. One patient had surgery to fix a prolapsed stoma.

An intra-abdominal sepsis occurred in 28 (19.2%) patients, 16 (11%) were anastomotic leaks, 12 (8,2%) were intra-abdominal abscess, and 16 (11%) had been classified as major complications. Thirteen patients with intra-abdominal sepsis required a radiological drainage and 2 required surgical drainage. Three patients with an anastomotic fistula required surgery for resection of the anastomosis and creation of a stoma.

The mean hospital stay was 11.2 days +/- 6.7 days and 26 (17.8%) patients were readmitted.

The pre-operative characteristics of the patients are summarized in **Table 2**. There was no significant difference between patients with major post-operative complication and the others.

The mean extent of ileocolic resection was 28.9 +/- 12.6 cm, with an average of 21.9

+/- 12.5 for the ileum and 6.6 cm +/- 4.7 cm for the colon. There were no differences between the groups.

Concerning pre-operative treatment, **Table 3**, there were serious complications in patients treated with anti TNF alpha (p = 0.0007) or combination of corticosteroids and anti TNF alpha (p = 0.006) in the three months prior to surgery. The difference was not significant for patients treated with corticosteroids alone.

The stoma rate was higher in the corticosteroid group (38.7% vs 23.8%; p = 0.018), in patients with malnutrition and pre-operative abcess (44% vs 23%; p = 0.0045 and 54% vs 17% ; p = 0.0001). There were no differences in stoma creation between patients treated by anti TNF alpha as compared to the others (29.17% vs 34%; p = 0.53).

Operative data are summarized in **Table 4**. Laparoscopy was performed in 66.4% of patients and a conversion was necessary in 17.1% of cases. Anastomosis were manual in half of the cases, stapled in 21.2%, and a stoma was realized in 30.1% of the patients. In 3 patients, a loop ileostomy was created above the ileocolic anastomosis. In univariate analysis, there were more post-operative severe complications when the operative time was greater than 150 minutes (80% vs 50%; p = 0.01).

In multivariate analysis (**Table 5**), the conversion from laparoscopy to laparotomy was a risk factor with serious complications (OR = 7.95; 95% CI 1.68 to 44.89; p = 0.009). Anti TNF alpha treatment during the 3 months before the surgery was also a risk factor (OR = 4.21; 95% CI 1.23 to 16.87; p = 0.02).

Discussion

In this study the rate of anastomotic leak was 11%, which is similar to the literature. However we found 19% of intra-abdominal infectious complications, which is higher as compared to other studies (10-13%) (17-19).

Anti-TNF alpha is widely used in the treatment of Crohn's disease. The use of anti-TNF alpha in the 3 months prior to surgery is estimated to be between 20 and 46% depending (16,20,31,40). In this study the average use was 34.3% but between 1998 and 2007 the rate was 14% and 47% between 2008 and 2015, reflecting the increasing use of this therapeutic class.

The impact of anti-TNF α on post-operative morbidity remains controversial, in particularly infectious ones (27). Some studies and meta-analyzes did not find an increased risk of post-operative morbidity, overall infections or intra-abdominal infections (14-16,18,20,24,30,32,41). These studies are heterogeneous including all types of digestive resections and patients with Crohn's disease and others with ulcerative colitis (32, 41). Moreover, some of these studies included all immunosuppressive treatments (thiopurine, methotrexate, anti-TNF α) (16,18), introducing an obvious bias. Other studies have shown an increased risk of post-operative complications with anti TNF, especially infections and intra abdominal sepsis (34-38, 40).

In order to have a homogeneous group we, limited our investigation to ileocolic resection. Two previous studies focused only on ileocolic resections. Appau et al. (21) found the use of anti TNF α within 3 months as a risk factor for intraabdominal sepsis and Serradori et al. (17) excluded patients with stoma and demonstrated that the combination corticosteroid / anti TNF α was also a risk factor for post-operative intra-abdominal infection. We excluded iterative resections because it was previously shown to be an independent risk factor for post-operative morbidity (24).

There are variability's in studies on the primary endpoint that can be characterized by the rate of post-operative morbidity, infectious complications, intra-abdominal sepsis or anastomotic leakage.

We choose major complications as a primary endpoint (more than grade II of the Clavien Dindo classification (39)). These are serious complications that require radiological, surgical intervention or intensive care unit management. It appeared to be the most relevant criteria because it has an impact on post-operative management of patients.

According to the pharmacokinetics, the anti TNF alpha remains in the blood for 3 months following administration. The majority of studies such as ours included in the anti-TNF α group all patients with an injection in the three months before surgery. (17,21,34-38)

One study examined the relationship between the dosage of anti TNF α in serum within seven days before surgical resection and post-operative outcomes. For Crohn's disease, the rate of overall infectious complications was statistically superior when the dosage of anti TNF α was higher than 3 mg / ml (42). Currently, such blood tests are not routinely performed before surgery.

For patients with high risk of recurrence, some studies recommend a post-operative anti TNF α treatment (43,44). A randomized controlled study placebo versus infliximab showed no increased risk of post-operative complications in patients with infliximab treatment between 2 to 4 weeks after surgery (45).

The rate of conversion of patients undergoing laparoscopic was 17%, which is acceptable according others studies (6.8 to 17%) (46-50). The main causes of conversion were local inflammation, intra-abdominal abscess and adhesions. Conversion during laparoscopy was previously shown as a risk factor of post-operative morbidity in colorectal surgery (51,52). However, the present study is the first to demonstrate it in surgery for Crohn's Disease.

Regarding other risk factors, steroids, malnutrition and pre-operative abscess were not found in our study. This is explained by a statistically higher rate of stoma in these patients.

Our study had several limitations. Since it is retrospective, some data were missing and post-operative care was not standardized. Therefore there is a risk that the results could be under or over-estimated. In addition, over the course of the 17 years there was an evolution of techniques and management.

In conclusion, our study confirms that the use of anti TNF α in the three months before surgery is a risk factor of major post-operative complications after ileocolic resection for Crohn's disease. An interval of at least 3 months before the surgery is necessary. Otherwise, the creation of a stoma should be considered. In addition, we have shown that the conversion of laparoscopy to laparotomy was also a risk factor.

Finally, conducting a prospective study by correlating the number of risk factors and the rate of post-operative complications could be relevant. This could lead to a nomogram portraying high-risk post-operative complications and situations justifying a stoma.

Reference

1. Gollop JH, Phillips SF, Melton LJ, Zinsmeister AR. Epidemiologic aspects of Crohn's disease: a population based study in Olmsted County, Minnesota, 1943-1982. *Gut*. 1988;29(1):49-56.

2. Henriksen M, Jahnsen J, Lygren I, Ibsen Study Group. Clinical course in Crohn's disease: results of a five-year population-based follow-up study (the IBSEN Study). *Scandinavian Journal of Gastroenterology*. 2007;42(5):602-10.

3. Wolters FL, Russel MG, Sijbrandij J, et al. Phenotype at diagnosis predicts recurrence rates in Crohn's disease. *Gut*. 2006;55(8):1124-30.

4. Baumgart DC, Sandborn WJ. Inflammatory bowel disease: clinical aspects and established and evolving therapies. *Lancet*. 2007;369(9573):1641-57.

5. Cosnes J, Nion-Larmurier I, Beaugerie L, et al. Impact of the increasing use of immunosuppressants in Crohn's disease on the need for intestinal surgery. *Gut*. 2005;54(2):237-41.

6. Peyrin-Biroulet L, Loftus EV, Colombel JF, Sandborn WJ. The natural history of adult Crohn's disease in population-based cohorts. *The American Journal of Gastroenterology*. 2010;105(2):289-97.

7. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet*. 2002;359(9317):1541-49.

8. Colombel JF, Sandborn WF, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology*. 2007;132(1):52-65.

9. Burke JP, Velupillai Y, O'Connell PR, Coffey JC. National trends in intestinal resection for Crohn's disease in the post-biologic era. *International Journal of Colorectal Disease*. 2013;28(10):1401-6.

10. Slattery E, Keegan D, Hyland J, et al. Surgery, Crohn's disease, and the biological era: has there been an impact? *Journal of Clinical Gastroenterology*. 2011;45(8):691-93.

11. Jones DW, Finlayson SRG. Trends in surgery for Crohn's disease in the era of infliximab. *Annals of Surgery*. 2010;252(2):307-12.

12. Alves A, Panis Y, Bouhnik Y, et al. Risk factors for intra-abdominal septic complications after a first ileocecal resection for Crohn's disease: a multivariate analysis in 161 consecutive patients. *Diseases of the Colon and Rectum*. 2007;50(3):331-36.

13. Post S, Betzler M, Von Ditfurth B, Schürmann G, Küppers P, Herfarth C. Risks of intestinal anastomoses in Crohn's disease. *Annals of Surgery*. 1991;213(1): 37-42.

14. Nasir BS, Dozois EJ, Cima RR, et al. Perioperative anti-tumor necrosis factor therapy does not increase the rate of early postoperative complications in Crohn's disease. *Journal of Gastrointestinal Surgery*. 2010;14:1859-65; discussion 1865-66.

15. Kasparek MS, Bruckmeier A, Beigel F, et al. Infliximab does not affect postoperative complication rates in Crohn's patients undergoing abdominal surgery. *Inflammatory Bowel Diseases*. 2012;18(7):1207-13.

16. Colombel JF, Loftus EV, Tremaine WJ, et al. Early postoperative complications are not increased in patients with Crohn's disease treated perioperatively with infliximab or immunosuppressive therapy. *The American Journal of Gastroenterology*. 2004;99(5):878-83.

17. Serradori T, Germain A, Scherrer ML, et al. The effect of immune therapy on surgical site infection following Crohn's disease resection. *The British Journal of Surgery*. 2013;100(8):1089-93.

18. Bafford AC, Powers S, Ha C, et al. Immunosuppressive therapy does not increase operative morbidity in patients with Crohn's disease. *Journal of Clinical Gastroenterology*. 2013;47(6):491-95.

19. Yamamoto T, Allan RN, Keighley MR. Risk factors for intra-abdominal sepsis after surgery in Crohn's disease. *Diseases of the Colon and Rectum*. 2000;43(8):1141-45

20. Myrelid P, Marti-Gallostra M, Ashraf S, et al. Complications in surgery for Crohn's disease after preoperative antitumour necrosis factor therapy. *The British Journal of Surgery*. 2014;101(5):539-45.

21. Appau KA, Fazio VW, Shen B, et al. Use of infliximab within 3 months of ileocolonic resection is associated with adverse postoperative outcomes in Crohn's patients. *Journal of Gastrointestinal Surgery*. 2008; 12:1738-44.

22. Lesalnieks I, Kilger A, Glass H, et al. Intraabdominal septic complications following bowel resection for Crohn's disease: detrimental influence on long-term outcome. *International Journal of Colorectal Disease*. 2008;23(12):1167-74.

23. Crowell KT, Messaris E. Risk factors and implications of anastomotic complications after surgery for Crohn's disease. *World Journal of Gastrointestinal Surgery*. 2015 Oct 27;7(10):237-42

24. Huang W, Tang Y, Nong L, Sun Y. Risk factors for postoperative intra-abdominal septic complications after surgery in Crohn's disease: a meta-analysis of observational studies. *Journal of Crohn's & Colitis*. 2015;9(3):293-301.

25. Kanazawa A, Yamana T, Okamoto K, Sahara R. Risk factors for postoperative intra-abdominal septic complications after bowel resection in patients with Crohn's disease. *Diseases of the Colon and Rectum*. 2012;55(9):957-62.

26. Müller-Wille R, Iesalnieks I, Dornia C, et al. Influence of percutaneous abscess drainage on severe postoperative septic complications in patients with Crohn's disease. *International Journal of Colorectal Disease*. 2011;26(6):769-74.

27. Dignass A, Van Assche G, Lindsay JO, et al. The second european evidence-based consensus on the diagnosis and management of Crohn's disease: current management. *Journal of Crohn's & Colitis*. 2010;4(1):28-62.

28. Simillis C, Purkayastha S, Yamamoto T, et al. A meta-analysis comparing conventional end-to-end anastomosis vs. other anastomotic configurations after resection in Crohn's disease. *Diseases of the Colon and Rectum*. 2007;50(10):1674-87.

29. Heimann TM, Greenstein AJ, Mechanic L, Aufses AH. Early complications following surgical treatment for Crohn's disease. *Annals of Surgery*. 1985;201(4):494-98.

30. Rosenfeld G, Qian H, Bressler B. The risks of post-operative complications following pre-operative infliximab therapy for Crohn's disease in patients undergoing abdominal surgery: a systematic review and meta-analysis. *Journal of Crohn's & Colitis*. 2013;7(11):868-77.

31. Canedo J, Lee SH, Pinto R, et al. Surgical resection in Crohn's disease: is immunosuppressive medication associated with higher postoperative infection rates? *Colorectal Disease*. 2011;13(11):1294-98.

32. Kunitake H, Hodin R, Shellito PC, et al. Perioperative treatment with infliximab in patients with Crohn's disease and ulcerative colitis is not associated with an increased rate of postoperative complications. *Journal of Gastrointestinal Surgery*. 2008;12(10):1730-37.

33. Marchal L, D'Haens G, Van Assche G,et al. The risk of post-operative complications associated with infliximab therapy for Crohn's disease: a controlled cohort study. *Alimentary Pharmacology & Therapeutics*. 2004;19(7):749-54.

34. Ahmed Ali U, Martin ST, Rao AD, Kiran RP. Impact of preoperative immunosuppressive agents on postoperative outcomes in Crohn's disease. *Diseases of the Colon and Rectum*. 2014;57(5):663-74.

35. El-Hussuna A, Krag A, Olaison G, et al. The effect of anti-tumor necrosis factor alpha agents on postoperative anastomotic complications in Crohn's disease: a systematic review. *Diseases of the Colon and Rectum*. 2013;56(12):1423-33
.

36. Billioud V, Ford AC, Del Tedesco E, et al. Preoperative use of anti-TNF therapy and postoperative complications in inflammatory bowel diseases: a meta-analysis. *Journal of Crohn's & Colitis*. 2013;7(11):853-67.

37. Kopylov U, Ben-Horin S, Zmora O, et al. Anti-tumor necrosis factor and postoperative complications in crohn's disease: systematic review and meta-analysis. *Inflammatory Bowel Diseases*. 2012;18(12):2404-13.

38. Brouquet A, Maggiori L, Zerbib P, et al. Anti-TNF therapy is associated with an increased risk of postoperative morbidity after surgery for ileocolonic Crohn disease. Ann Surg 2017, Epub ahead of print.

39. Dindo D, Demartine N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Annals of Surgery*. 2004; 240:205-13.

40. Syed A, Cross RK, Flasar MH. Anti-tumor necrosis factor therapy is associated with infections after abdominal surgery in Crohn's disease patients. *The American Journal of Gastroenterology*. 2013;108(4):583-93.

41. Krane MK, Allaix ME, Zoccali M, et al. Preoperative infliximab therapy does not increase morbidity and mortality after laparoscopic resection for inflammatory bowel disease. *Diseases of the Colon and Rectum*. 2013;56(4):449-57.

42. Lau C, Dubinsky M, Melmed G, et al. « The Impact of Preoperative Serum Anti-TNFα Therapy Levels on Early Postoperative Outcomes in Inflammatory Bowel Disease Surgery ». *Annals of Surgery* 261, 2015: 487-96.

43. Papamichael K, Archavlis E, Lariou C, Mantzaris GJ. Adalimumab for the prevention and/or treatment of postoperative recurrence of Crohn's disease: A prospective, two-year, single center, pilot study. Journal of Crohn's and Colitis. 2012: 924-31.

44. De Cruz P, Kamm M, Hamilton AL, et al. Adalimumab prevents postoperative Crohn's disease recurrence, and is superior to thiopurines: Early results from the prospective POCER study. ECCO Barcelona February 2012. Abstract P342.

45. Regueiro M, El-Hachem S, Kip KE, et al. Postoperative infliximab is not associated with an increase in adverse events in Crohn's disease. *Digestive Diseases and Sciences*. 2011;56(12):3610-15.

46. Tavernier M, Lebreton G, Alves A. Laparoscopic surgery for complex Crohn's disease. *Journal of Visceral Surgery*. 2013;150(6):389-93.

47. Tan JJY, Tjandra JJ. Laparoscopic surgery for Crohn's disease: a meta-analysis. *Diseases of the Colon and Rectum*. 2007;50(5):576-85.

48. Milsom JW, Hammerhofer KA, Böhm B, et al. Prospective, randomized trial comparing laparoscopic vs. conventional surgery for refractory ileocolic Crohn's disease. *Diseases of the Colon and Rectum*. 2001;44(1)1-8.

49. Maartense S, Dunker MS, Slors JF, et al. Laparoscopic-assisted versus open ileocolic resection for Crohn's disease: a randomized trial. *Annals of Surgery*. 2006;243(2)143-49.

50. Msika S, Iannelli A, Deroide G, et al. Can laparoscopy reduce hospital stay in the treatment of Crohn's disease?. *Diseases of the Colon and Rectum*. 2001;44(11):1661-66.

51. Masoomi H, Moghadamyeghaneh Z, Mills S, et al. Risk factors for conversion of laparoscopic colorectal surgery to open surgery: does conversion worsen outcome? *World Journal of Surgery*. 2015;39(5):1240-47.

52. Moghadamyeghaneh Z, Masoomi H, Mills SD, et al. Outcomes of conversion of laparoscopic colorectal surgery to open surgery. *Journal of the Society of Laparoendoscopic Surgeons*. 2014;18(4):e2014.00230.

Table

	N (%)
Morbidity	**64 (43.8%)**
Clavien Dindo	
I	22
II	21
III	20
IV	1
V	0
Complications grade I-II	**63**
Medical	21
Urinary infection	6
Acute urinary retention	2
Renal complication	4
Pericarditis	1
Pulmonary complication	2
VTE	2
Catheter infection	2
Acute pancreatitis	1
Claude Bernard Horner syndrome	1
Surgical	42
Occlusion	12
Wound infection	11
Stomal complication	7
Too productive	6
Bleeding	1
Intra abdominal infection	12
Anastomotic fistula	6
Intra abdominal abscess	6
Complications grade III-IV	**21**
Medical	1
Pulmonary complication	1
Surgical	20
Occlusion	1
Wound infection	1
Stomial prolapse	1
Compressive pneumoperitoneum	1
Intra-abdominal infection	16
Anastomotic fistula	10
Intra-abdominal abscess	6
Re-surgery	**9 (6.2%)**
Hospital stay, days (mean +/- SD)	**11.2 +/- 6.7**

VTE = venous thromboembolism ; SD = standard deviation : N = number of patients

Table 1 : Post-operative outcomes.

	Total	Others	Complications Grade III-IV	*P*
	N = 146 (%)	N = 125	N = 21	
Age, years (mean +/- SD)	35.8 +/- 13	36.4 +/- 13.5	32.7 +/- 8.5	*0.38*
Gender (n)				*0.32*
F	76 (52.1)	63 (50.4)	13 (61.9)	
M	70 (47.9)	62 (49.6)	8 (38.1)	
ASA score (n)				*0.33*
1	26 (17.8)	21 (16.8)	5 (23.8)	
2	111 (76)	96 (76.8)	15 (71.4)	
3	5 (3.4)	5 (4)	0	
4	2 (1.4)	1 (0.8)	1 (4.8)	
Not available	2 (1.4)	2 (1.6)	0	
Smoking (n)	56 (38.4)	46 (36.8)	10 (47.6)	*0.35*
BMI, Kg/m^2 (mean +/-	21 +/- 3.9	21 +/- 4	21 +/- 3.3	*0.8*
Malnutrition (n)	50 (34.2)	45 (36)	5 (23.8)	*0.26*
Disease duration, months (mean +/- SD)	85.3 +/- 87.5	87.2 +/- 90.8	74.43 +/- 65.1	*0.88*
Indication for surgery (n)				*0.89*
Stenosis	82 (56.1)	69 (55.2)	13 (61.9)	
Penetrating	62 (42.5)	54 (43.2)	8 (38.1)	
Tumor	2 (1.4)	2 (1.6)	0	
Preoperative abscess (n)	50 (34.2)	42 (33.6)	8 (38.1)	*0.69*
Preoperative drainage (n)	20 (13.7)	16 (12.8)	4 (19)	*0.44*

BMI = Body Mass Index ; ASA = American Society of Anesthesiologists ;
SD = standard deviation ; n = number of patients

Table 2 : Pre-operative patient characteristics.

	Total	Others	Complications Grade III-IV	*p*
	N = 146 (%)	N = 125	N = 21 (14.4%)	
Anti TNF α in the 3 months (n)	50 (34.2)	36 (28.8)	14 (66.7)	*0.0007*
Corticosteroid in the 3 months (n)	62 (42.5)	50 (40)	12 (57.1)	*0.14*
Association (n)	25 (17.1)	17 (13.6)	8 (38.1)	*0.006*
Other treatments (n)				
Thiopurine	41 (28.1)	38 (30.4)	3 (14.3)	*0.12*
Methotrexate	4 (2.7)	4 (3.2)	0	*0.40*
Budesonide	24 (16.4)	21 (16.8)	3 (14.3)	*0.75*
Aminosialycile	38 (26)	35 (28)	3 (14.3)	*0.17*

Association = Association anti TNF α - systemic corticosteroid in the 3 months before surgery ; n =number of patients

Table 3: Pre-operative treatments.

	Total	Others	Complications Grade III-IV	*p*
	N = 146 (%)	N = 125	N = 21 (14.4%)	
Surgical approch (n)				*0.31*
Laparotomy	49 (33,6)	44 (35.2)	5 (23.88)	
Laparoscopy	97 (66.4)	81 (64.8)	16 (76.2)	
Conversion (n)	25 (17.1)	19 (15.2)	6 (28.6)	*0.13*
Digestive suture associated (n)	24 (16.4)	21 (16.8)	3 (14.3)	*0.78*
Anastomosis (n)				
Stapled	31 (21.2)	26 (20.8)	5 (23.8)	*0.76*
Manual	73 (50)	65 (52)	8 (31.1)	*0.24*
Stomy (n)	45 (30.8)	37 (29.6)	8 (38.1)	*0.73*
Operative time > 150 mn (n)	73 (50)	57 (50)	16 (80)	*0.01*
n = number of patients				

Table 4 : Data on surgery.

	OR	*p*
Conversion	7.95 IC 95% (1.68-44.89)	*0.009*
Anti TNF α in the 3 months	4.21 IC 95% (1.23-16.87)	*0.02*

Table 5 : Multivariate analysis of risk factors for severe post-operative complications.