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Positive histologic margins is a risk factor of recurrence after ileocaecal resection in Crohn's disease

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Key words : Crohn's disease, margins, postoperative recurrence

Abstract

Introduction: Surgical resection is not curative in Crohn's disease (CD) and, recurrence after surgery is a common situation. The identification of patients at high risk of recurrence remains disappointing in clinical practice.

Objective: To evaluate the impact of residual microscopic disease on margins on the risk of recurrence after ileocaecal resection in CD.

Patients and methods: All patients who underwent ileocaecal resection between January 1992 and December 2016 were prospectively identified. Demographic data, clinical, surgical and histological variables were retrospectively collected. Positive histologic margin was assessed prospectively and defined by the presence of acute inflammatory lesions on margins: erosion, ulceration, chorion infiltration by neutrophils, cryptic abscesses or cryptitis.

Results: One hundred twenty five patients were included, with a median follow-up of 8 years (Interquartile Range (IQR), 4.3 - 15.2). Half (49.6%, n=62) were women, and the median age at surgery was 33 years (IQR, 24 - 42). Fifty-six (44.8%) had positive inflammatory margins. Five years after surgery, respectively 29 (51%) and 23 (34%) patients with positive and negative margins had clinical recurrence ($p=0.034$). At the end of the follow-up, respectively 60% (n=34) and 47% (n=33) patients had clinical recurrence ($p=0.07$). CD-related hospitalizations were observed in respectively 37.5% (n=21) and 18.8% (n=13) with positive and negative margins ($p=0.02$). Fourteen patients (25%) with positive intestinal margins had surgical recurrence at the end of the follow-up compared to 5 patients (7%) with negative margins ($p=0.04$). Multivariate analysis confirmed that positive intestinal margin was independently associated with surgical recurrence (OR, 4.7 (CI95%, 1.4-15.3), $p=0.01$).

Conclusion: Positive histologic margin was associated with an increased risk of clinical and surgical recurrence after ileocaecal resection for Crohn's disease.

INTRODUCTION

Crohn's disease (CD) is a chronic and progressive condition that can lead to irreversible bowel damage as strictures, abscesses or fistulas (1). The management of CD has been profoundly modified by the emergence of anti-TNFs. Nevertheless, a quarter of patients still require surgery within five years of diagnosis and 70-80% of patients undergo surgery during their lifetime (2-9). The most common surgery in CD is ileocaecal resection. This surgery is not curative - 5 years after surgery, 70% of patients present an endoscopic recurrence, 60% a clinical recurrence and 20% require a second surgery (3,10-12).

The identification of risk factors for recurrence would identify patients at risk and to implement an individualized strategy after surgery. Many authors have taken an interest in this subject and some factors, more or less reproducible, have been highlighted. The most recognized risk factor is smoking, which would multiply the risk of recurrence by 2.5 (4,13). Perianal CD (14), fistulizing phenotype and previous intestinal resection (15) were also recognized as risk factors for recurrence. The European Crohn's and Colitis organization (ECCO) has recently recognized the presence of myenteric plexitis as a risk factor (16). Positive histologic margins resection margins is a simple marker, whose impact on the risk of postoperative recurrence is debated. A few previous studies from small cohorts have presented controversial results (17). ECCO recently recognized, in the latest European consensus, that further studies were needed to assess the impact of histology on the risk of post-operative recurrence (16).

The objective of this study was therefore to evaluate the impact of positive histologic margins on the risk of recurrence after ileocecal resection in CD.

MATERIALS AND METHODS

Population

All patients operated for CD were included prospectively and consecutively in a database since 1992. In this database, patients who underwent ileocaecal resection at Amiens University Hospital between January 1, 1992 and December 31, 2016 and with at least one post-operative colonoscopy were identified. Patients with permanent ileostomy, or operated segment resection of the small intestine were excluded.

Data collection

Clinical data were collected retrospectively from Amiens University Hospital medical records. This collection was carried out in a standardized way by a single investigator. Demographic variables such as sex, date of diagnosis and smoking status at the time of surgery were collected; clinical variables included phenotype, disease location according to the Montreal classification (18), a history of bowel surgery as well as treatment exposition before and at the time of surgery . Surgical variables were also collected: date of surgery, indication, degree of emergency, laparoscopic or laparotomy approach, type of anastomosis, length of resection, date of stoma closure in case of temporary ileostomy and type of anastomosis. The histologic variables were prospectively collected including histologic involvement of resection margins (ileal and colic sections) and the presence of granuloma. Post-operative follow-up included: date of first post-operative colonoscopy and presence of endoscopic recurrence (Rutgeerts score), clinical and surgical recurrence as CD-related hospitalization, and any therapeutic changes (corticosteroids, immunosuppressants and biologics) during the follow-up.

Definitions

Positive resection margins was defined by the presence of acute inflammatory lesions on the margins including erosion, ulceration, and infiltration of the chorion by neutrophil, cryptic abscesses or cryptitis lesions. These criteria were prospectively examined on the margins of ileal and colonic resection. Clinical recurrence was defined by a Harvey-Bradshaw score > 4 (19) associated with therapeutic modification (initiation of corticosteroids, immunosuppressants or anti-TNF, as well as dose optimization), hospitalization or surgical resection. Endoscopic recurrence was defined by a Rutgeerts score ≥ 2 . Surgical recurrence was defined by the presence during follow-up of new bowel resection. Hospitalization was defined as any hospitalization that occurred after surgery in relation to CD. The recurrence time was defined as the time interval between the date of surgery (or date of restoration of continuity in case of protective ileostomy) and the recurrence.

Statistics

The quantitative variables were calculated as median (interquartile range), and the qualitative variables were calculated as percentages. The comparison of quantitative variables with the normal distribution was performed by the Student t-test or by the Mann-Whitney test for variables with a non-normal distribution. For qualitative variables, a chi-2 test or the exact Fisher test was used. A Cox model was used to identify factors associated with time to recurrence, each variable's effect was expressed as hazard ratio (HR) (95% confidence interval (CI)). All variables identified with univariate $p < 0.20$ were included in a multivariate model with backward selection method. The analysis was performed with SAS® software version 9.4 (SAS Institute, Cary, NC). The study was approved by the ethical review board / CNIL committee (Comite Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Sante - N°T.195, 16/07.2018) according to local guidelines with informed consent was obtained from each patient included in the study. The study

protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

RESULTS

Population

One hundred and twenty-five patients were prospectively identified. The characteristics of our population are detailed in **Table 1**. Half (49.6%, n=62) were female and the median age at surgery was 33 years (IQR (interquartile range), 24 - 42). Seven percent (n=9) of patients were operated on for an inflammatory behavior resistant to medical treatment, 46% (n=57) for stricturing complication (B2) and in 47% (n=59) for penetrating complication. Thirty-one percent (n=40) of patients were smokers at the time of surgery. A temporary ileostomy was performed in 36 patients (29%) and the median resection length was 36 cm (IQR, 27 - 50). Median follow-up time was 8 years (IQR, 4.3 - 15.2). Most of patient (n=66, 52,8%), did not receive any postoperative CD medication, 22 (17,6%) received 5-ASA, 14 (11.2%) received immunosuppressants and 15 (12%) anti-TNF.

Post-operative recurrence

Sixty percent (n=75) of patients experienced clinical recurrence with a median delay of 18.6 months (IQR, 5-42). Twenty-seven percent of patients (n=34) were hospitalized for CD with a median delay of 63.1 months (IQR, 31-132). Fifteen percent (n=19) of patients required further surgical resection after a median duration of 71 months (IQR, 40-103).

Impact of positive margins on recurrence

Fifty-six patients (44.8%) had positive histologic margins. There was no difference between patients with and without positive margins for the main risk factors of post-operative recurrence including gender, perianal CD, previous intestinal resection, and active smoking at surgery (**Supplementary Table 1**).

Five years after surgery, respectively 29 (51%) and 23 (34%) patients with positive and negative margins had clinical recurrence ($p=0.034$). At the end of follow-up, respectively 34 (60%) and 33 (47%) patients with positive and healthy margins had clinical recurrence ($p=0.07$) (**Figure 1**). The median time to recurrence was 3.4 years (IQR, 1.0-10) in patients with positive margins versus 9 years (IQR, 6-16) in patients with healthy margins ($p=0.0001$). Colonoscopy during follow-up was available for 122 of the 125 patients included. Endoscopic recurrence, as defined by a Rutgeerts score ≥ 2 , was observed in respectively 33/55 (60%) and 36/67 (53%) of patients with and without positive margins ($p=0.58$).

Exposure to corticosteroids, immunosuppressants and anti-TNF

Post-operatively, patients with positive margins were more often exposed to corticosteroids (50% versus 40%, $p=0.19$), immunosuppressants (64% vs 46%, $p=0.034$) and anti-TNF (47% vs 39%, $p=0.11$) respectively (**Supplementary Figure 1**).

Surgical recurrence and hospitalization

CD-related hospitalizations were observed in respectively 37.5% ($n=21$) and 18.8% ($n=13$) with positive and negative margins ($p=0.02$) (**Figure 2**). Fourteen patients (25%) with positive intestinal margins had new intestinal resection at the end of the follow-up compared to 5 patients (7%) with negative margins ($p=0.04$). Multivariate analysis confirms that positive resection margins was independently associated with time to surgical recurrence (HR, 4.7 (95%CI, 1.44-15.31) $p=0.01$) (**Table 2**). None of

the histological factor studied independently as erosion, ulceration, and infiltration of the chorion by neutrophil, cryptic abscesses or cryptitis lesions were significantly associated with recurrence.

Discussion

In this retrospective cohort study, we highlighted the interest of histological margins evaluation after ileocecal resection for CD. Positive intestinal margins were associated with an increased risk of clinical and surgical recurrence as well as CD-related hospitalization.

Most of patients with CD undergo surgery. Unfortunately, surgery is not curative. The rate of post-operative recurrence is variable according to the definition used, whether clinical, endoscopic, radiological or surgical. Overall, in population-based studies, clinical recurrence rate ranged from 28-45% and 36-61% at 5 and 10 years, respectively (4). The postoperative recurrence prevention strategy is based in 2018 on the presence or absence of different risk factors for recurrence. Smoking is the only factor consistently reported in clinical trials and increased by twice the risk of clinical recurrence. Penetrating disease, perianal CD and extensive bowel resection (> 50 cm) are also established as independent risk factors (4, 13-15). ECCO also recognized in its latest European consensus, the presence of granuloma and myenteric plexitis as risk factors independent of postoperative recurrence (16). ECCO recommends preventive treatment after resection in patients with at least one risk factor for recurrence and recognizes thiopurines or anti-TNFs as the treatment of choice (16). Other potential risk factors are still discussed and ECCO recently recommends new studies to clarify the impact of resection margins status.

Regarding the impact of resection margins, data are conflicting. To date, about ten studies have reported the impact of positive margins on the risk of recurrence (17, 20-33). These studies are, however, difficult to compare due to significant methodological differences, particularly in the definition of recurrence and positive margin. In our study, we have evaluated clinical recurrence defined as the combination of a Harvey-Bradshaw score > 4 and at least one therapeutic

modification, hospitalization or new resection and surgical recurrence. We chose to use definitions of recurrence because they are objective and excluded patients with isolated symptoms, not related to recurrent disease (34). The definition of positive margin was also very heterogenous in the current literature. To date, there is no consensus definition of histologic activity in CD and unlike UC, there is no validated histologic activity score. In our study, we used four items evaluating the presence of acute inflammatory lesions including erosion, ulceration, infiltration of the chorion by neutrophil-cells, cryptic abscesses or cryptitis lesions. The advantage of this definition is that it is simply feasible in clinical practice, even if its reproducibility will have to be evaluated, as well as the weight of the different histological lesions present in this definition independently. Short duration of follow-up for most of these studies may explain the absence of association between margins status and recurrence. The median follow-up of 8 years in our study seems appropriate to evaluate the impact of positive margins on long term outcome of CD. Different studies reported an impact of resection margins on postoperative recurrence risk. Lindhagen et al. (29) observed a recurrence rate of 73% in patients with major microscopic invasion of resection margins (ulcers, cryptic abscesses or granulomas), and 39% in patients free from margin invasion. Kinchen et al. (30) observed a surgical recurrence at 5 years of 15% in patients with positive margins as compared to 2.5% in patients with negative margins. Karesen et al. (27) observed a higher recurrence rate with positive margins compared to patients with negative resection margins (66% vs 14%,). Nygaard et al. found a recurrence rate at 1 year of 9% in patients with macroscopically and microscopically negative margins and 53% in patients with positive margins) and finally Krause et al. (32) observed after a median follow-up of 18 years, a recurrence rate of 31% in patients with negative margins compared to 83% for positive margins. More recently the REMIND group reported that transmural lesions at the margin (defined by mucosal ulceration or cryptitis,

submucosal fibrosis and lymphoplasmacytic infiltrate of the subserosa) were independently associated with early endoscopic recurrence and clinical recurrence (35). Finally, a recent meta-analysis, confirmed that involved histological margins at the time of index resection in CD is associated with recurrence (36).

Only impairment of the ileal margins and colic, assessed together, were associated with recurrence. **When we evaluated these lesions individually, there was a trend towards recurrence but significance was not reached which might result from the low statistical power.** Active inflammation at distal colonic resection margin after ileocecal resection were also previously identified as at high risk for postoperative recurrence both at the anastomotic site and the colon (37).

If histologic lesion at the resection margins seems to have a negative impact, the length of healthy resection margin remains to be defined. This issue is very important in a strategy of intestinal saving. Also, the physiopathological mechanisms by which positive margins influences the risk of recurrence will have to be determined. Several hypotheses can be advanced. First, positive margins could only be a surrogate marker of disease severity. Also, the persistence of lesions and pro-inflammatory cells on the margins and thus on the site of the anastomosis could promote recurrence, the anastomosis being the site of predilection for endoscopic recurrence.

We know well the negative points of our study. Its retrospective nature makes data collection more difficult. The uni-centric nature is also a limitation. The absence of systematic second reading by pathologist could also influence our results. The reproducibility of this definition would have to be determined. Our study also has some strengths. Patients identification as well as histologic margins evaluation were performed prospectively. Recurrence was defined by several strict and objective criterias. As compared to previous studies we used a simple definition of positive margins that seems easy to use in clinical practice. The follow-up period of our study allowed a long-term evaluation of the impact of the resection margins.

Conclusion

In conclusion, positive margins after ileocaecal resection in CD was associated with clinical and surgical recurrence. Positive resection margins should be included as a risk factor in current algorithms of postoperative prevention recurrence management.

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Figures

Figure 1. Risk of clinical recurrence at 5 years and at the end of the follow-up in patients with and without positive resection margins.

Figure 2. Risk of surgical recurrence and Crohn's Disease related hospitalization in patients with and without positive resection margins.

Tables

	n=125
Female gender (n, %)	62 (49.6%)
Age at diagnosis (years median, IQR)	25 [20-32]
Age at surgery (years median, IQR)	33 [24-42]
Duration of the disease (years median, IQR)	5 [1-11]
Localization (L1 : L2 : L3)	68 : 3 : 54
Phenotype (B1 : B2 : B3)	4 : 51 : 70
L4 (n, %)	18 (14.4%)
Ano-perineal lesions (n, %)	30 (24.0%)
Extra-intestinal manifestations (n, %)	14 (11.2%)
Previous intestinal surgery (n, %)	27 (21.6%)
Smoking at surgery (n, %)	40 (32.0%)
Prior treatment	
- Corticosteroids (n, %)	104 (83.2%)
- Aminosalicylates (n, %)	71 (56.8%)
- Immunosuppressants (n, %)	52 (41.6%)
- Anti-TNF α (n, %)	35 (28.0%)
- Vedolizumab (n, %)	0
- Ustekinumab (n, %)	1 (0.8%)
- Others (n, %)	8 (76.4%)
Treatment at surgery	
- Corticosteroids (n, %)	41 (32.8%)
- Aminosalicylates (n, %)	9 (7.2%)
- Immunosuppressants (n, %)	12 (9.6%)
- Anti-TNF α (n, %)	15 (12.0%)
- Vedolizumab (n, %)	0
- Ustekinumab (n, %)	0
- Others (n, %)	6 (4.8%)
Emergency surgery (n, %)	22 (17.6%)
Surgical indication	
- Inflammatory behavior resisting to medical therapy (B1) (n, %)	9 (7.2%)
- Stricture complication (B2) (n, %)	57 (45.6%)
- Penetrating complication (B3) (n, %)	59 (47.2%)
Laparoscopy (n, %)	39 (31.2%)
Derivation ileostomy (n, %)	36 (28.8%)
Normal ileal margins (n, %)	85 (68.0%)
Normal colonic margins (n, %)	94 (75.2%)
Length of resection (cm ; median, IQR)	36 [27-50]
Anastomosis	
- Stapled anastomosis (n, %)	65 (52.0%)

- Sutured anastomosis (n, %)	57 (45.6%)
Anastomotic technique	
- End-to-side (n, %)	12 (9.6%)
- Side-to-side (n, %)	68 (54.4%)
- End-to-end (n, %)	42 (33.6%)
Post-operative complications (n, %)	35 (28%)
Post-operative medications (n, %)	
- None	66 (52,8%)
- 5-ASA	22 (17,6%)
- Immunosuppressants	14 (11.2%)
- Anti-TNF	15 (12%)

Table 1. Population characteristics. IQR, interquartile range.

variables	Univariate analysis		Multivariate analysis	
	HR (IC95%)	P value	HR (IC95%)	P value
Age	1.02 [0.97 ; 1.07]	0.41		
Montreal loc				
1 vs. 3	0.54 [0.04; 6.77]	0.89		
2 vs. 3	0.37 [0.05; 3.07]	0.33		
Upper intestinal tract location	0.66 [0.19; 2.24]	0.50		
Extra-intestinal manifestation	0.94 [0.19; 4.64]	0.93		
Preoperative steroids	0.90 [0.30; 2.70]	0.85		
Preoperative IS	2.65 [0.90; 7.76]	0.07		
Surgery for fistulizing disease	1.26 [0.61; 2.60]	0.53		
Preoperative anti-TNF	4.35 [0.96;19.79]	0.05		
Length of intestinal resection	0.99 [0.97; 1.01]	0.54		
Type of anastomosis	0.41 [0.17 ; 0.95]	0.03		
Post-operative complications	0.53 [0.20 ; 1.41]	0.20		
Granuloma	1.06 [0.41 ; 2.76]	0.90		
Positive margins (ileal or colonic)	3.97 [1.33 ; 11.85]	0.01	4.69 [1.44 ; 15.31]	0.0104
Positive ileal margin	2.19 [0.81 ; 5.93]	0.12		
Positive colonic margin	2.03 [0.72 ; 5.75]	0.18		

Table 2. Impact of margins on the time to recurrence (uni and multivariate analyses) HR : Hazard ratio ; CI95 % : 95% confidence interval.

Figures

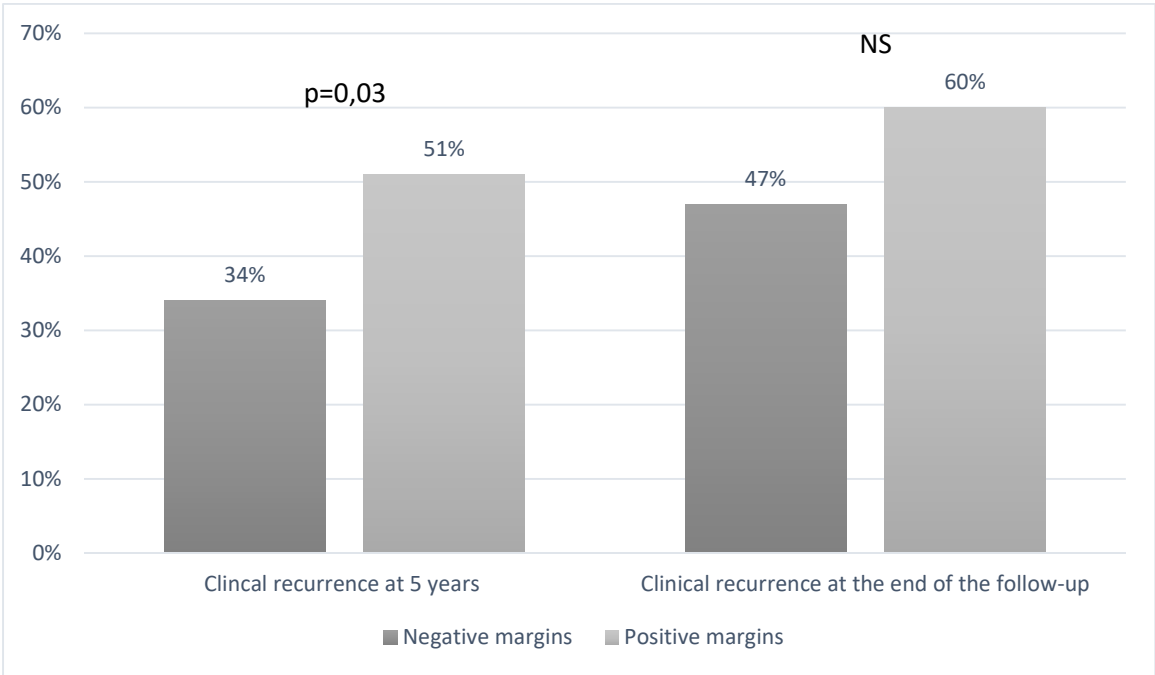


Figure 1. Risk of clinical recurrence at 5 years and at the end of the follow-up in patients with and without positive resection margins.

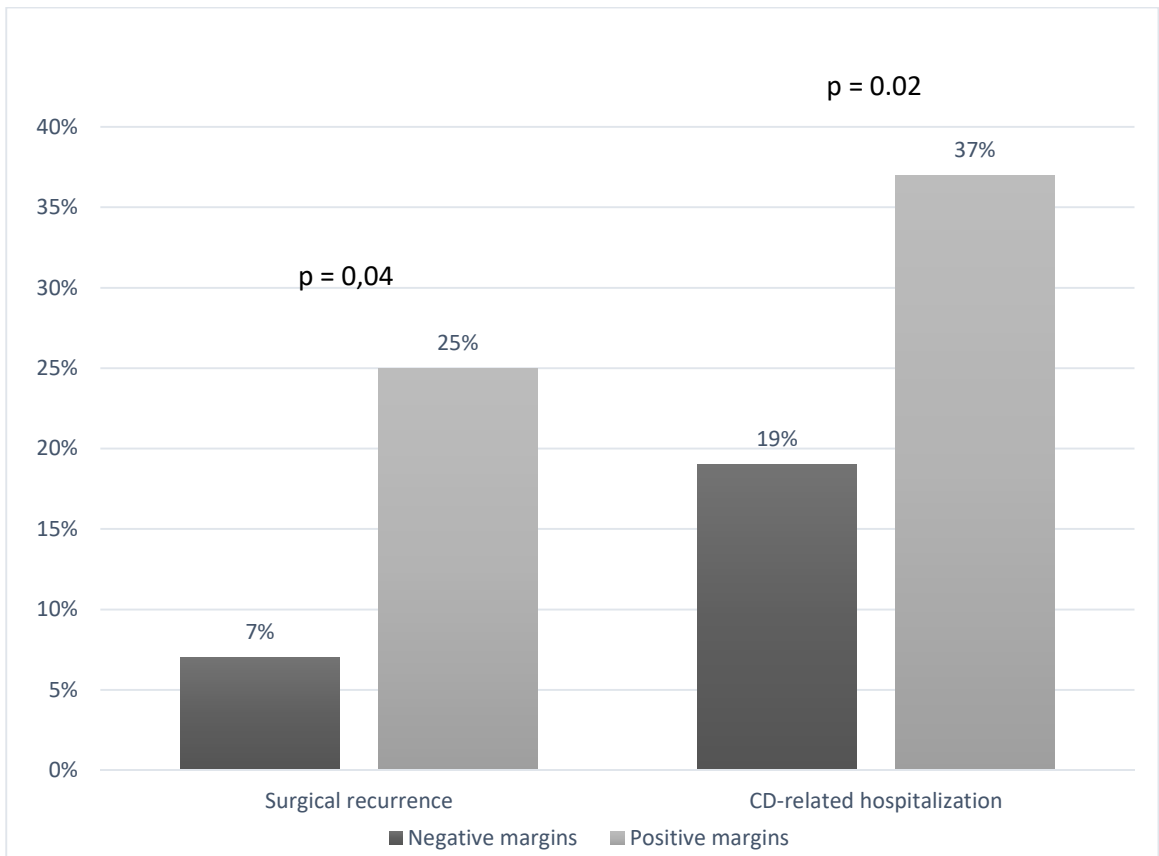


Figure 2. Risk of surgical recurrence and Crohn's Disease related hospitalization in patients with and without positive resection margins.