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Retrospective Study

Perforating and nonperforating indications in repeated surgeries for Crohn's disease

Wei-Song Shen, Xiao-Hui Huang, Rui-Qing Liu, Chen-Yang Li, Yi Li, Wei-Ming Zhu

Specialty type: Gastroenterology and hepatology**Provenance and peer review:** Unsolicited article; Externally peer reviewed.**Peer-review model:** Single blind**Peer-review report's scientific quality classification**Grade A (Excellent): 0
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Despite advances in medical therapy for Crohn's disease (CD), most patients with CD require repeated resection surgeries.

AIM

To analyze the perforating and nonperforating indications of repeated CD operations and identify the anastomosis characteristics for postoperative CD.

METHODS

We retrospectively reviewed 386 patients who underwent at least one resection for CD between 2003 and 2013. Clinical characteristics of each surgery were collected. Univariate and multivariate analyses were performed to determine risk factors for recurrence.

RESULTSThe indication for reoperation in CD tends to be the same as that for primary operation, *i.e.*, perforating disease tends to represent as perforating disease and nonperforating as nonperforating. Concordance was found between the first surgery and second surgery in terms of the indication for the operation ($P =$

0.006), and the indication for the third surgery was also correlated with that for the second surgery ($P = 0.033$). Even if the correlation of surgical indications between repeated operations, the rate of perforating indication for the second and third surgeries was significantly higher than that of the first surgery. In addition, the presence of perforating CD was a predictor of recurrence for both the first and second surgeries. Moreover, anastomotic lesions were the most common sites of recurrence after the operation. Based on the importance of anastomosis, anastomosis might be a new type of disease location for the classification of postoperative CD.

CONCLUSION

CD not only has stable characteristics but also progresses chronically. Perforation is a progressive surgical indication for Crohn's disease. For CD after surgery, anastomosis may be a new classification of disease location.

Key Words: Crohn's Disease; Anastomosis; Perforation; Nonperforating

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Core Tip: It was well-known that Crohn's disease (CD) is a chronic disease characterized by progressive bowel destruction. Our findings suggest that CD becomes more severe and more extensive with the increase in number of surgeries. CD not only has stable characteristics, but also progresses chronically. Perforation is a progressive surgical indication for CD. For CD after operation, anastomosis may be a new classification of disease location.

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INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) of unknown etiology; it is extremely difficult to predict the clinical course of CD patients. In recent years, the incidence of CD has increased dramatically in China[1]. Despite advances in medical therapy for CD (such as antitumor necrosis factor antibodies and immunosuppressive drugs), antitumor necrosis factor antibodies can effectively promote the healing of intestinal mucosa and reduce the operation risk and hospitalization rate. However, in clinical practice, up to 30% of patients have a loss of response to biological therapy. Most CD patients still require partial bowel resection at least once during the CD course[2,3].

Surgical intervention is necessary for patients with acute perforation, internal fistulae, peritoneal abscess, intestinal obstruction, toxic dilatation, hemorrhage, and/or failed response to medical therapy [4]. Surgery is effective in removing the lesions and relieving symptoms; however, surgical resection is not curative for CD, and postoperative recurrence is common. Recurrence may occur in 25%-38% of CD patients, necessitating a second surgery within 5 years postoperatively. Moreover, a third surgery owing to recurrent CD is required in an estimated 33% of these patients[5]. Postoperative prophylaxis can reduce CD recurrence rates[6], but only patients with risk factors for earlier postoperative recurrence should be considered for postoperative prophylaxis due to the risks of immunosuppressive therapy. Therefore, to delay postoperative recurrence, it is important to analyze the clinical characteristics and predict postoperative recurrence for surgical patients. Several studies have assessed the risk factors for postoperative CD recurrence. Reported risk factors for postoperative recurrence include a smoking habit, family history, young age at diagnosis, ileocolonic disease, perianal disease, preoperative duration and perforating lesions[7-10].

The aim of the current study was to compare the clinical characteristics between the first, second and third surgeries, analyze correlations of the perforating and nonperforating indications, and identify the anastomosis characteristics for postoperative CD.

MATERIALS AND METHODS

Patients

Data were retrospectively reviewed from CD patients treated between 2003 and 2013 in Jinling Hospital, Medical School of Nanjing University. All included patients were preoperatively diagnosed with CD based on conventional clinical features, abdominal computed tomography, and endoscopy, and the CD diagnosis was postoperatively confirmed by histological analysis of the surgical specimen. Patients who had undergone at least one surgical resection for CD were considered for study enrollment. Endoscopies were performed at 3 mo, 6 mo and every year after surgery. All patients were contacted by telephone and asked to participate in the study. All patients gave informed written consent. This study was approved by the Jinling Hospital Ethics Committee.

Definitions

Patient age and disease location were based on the Montreal classification[11]. Indication for surgery was defined as the main reason for surgical resection based on clinical features, preoperative diagnostic examinations, and intraoperative findings. The indications were classified into two categories based on the report by Simillis *et al*[12] perforating indications included acute free perforation, internal or external fistula, and abscess; nonperforating indications included intestinal obstruction, medical intractability, and hemorrhage. Recurrence was defined as the need for reoperative surgery.

Data collection

Clinical characteristics, including age at diagnosis, sex, age at the time of surgery, appendectomy history, preoperative duration, smoking history, perianal disease, indication for surgery, and disease location, were retrospectively collected for each patient by two independent individuals (W.S. and X.H.). We also collected operative records, including resection range and occurrence of postoperative intra-abdominal septic complications (IASCs). Serum albumin, C-reactive protein, and BMI were also collected after patient admission. The deadline for follow-up was February 2017. All patients were followed-up at regular intervals.

Statistical analysis

Statistical analysis was performed using SPSS version 19.0 (Chicago, IL, United States). Correlations of clinical characteristics between the repeated surgeries were tested for statistical significance using Pearson's χ^2 test. The paired-samples *t*-test was used to assess differences in recurrence-free survival after the first and second surgeries. For analysis of recurrence-free survival data related to perforating indication, cumulative survival curves were created using the Kaplan–Meier method; the difference between the curves was analyzed by the log-rank test. Univariate and multivariate survival analyses were carried out using the Cox proportional hazards model. Spearman's correlation coefficient test was used to assess associations of perforating indications for multiple operations. A value of $P < 0.05$ was considered statistically significant, and all P values were two-sided.

RESULTS

Clinical characteristics of patients

There were 386 hospitalized patients who had undergone at least one surgical resection in our department; 155 of these patients had undergone two surgical resections, and 41 of these 155 patients had undergone at least three surgical resections. A final total of 386 CD patients were included in this study. The clinical features are shown in Table 1. There were no significant differences between surgeries in sex, appendectomy history, smoking history, perianal disease or IASCs ($P > 0.05$).

Surgical indication between multiple operations

The perforating and nonperforating indications of the initial surgery were correlated with the surgical indication of the second surgery ($P = 0.006$, $r = 0.220$), and the surgical indication of the second surgery was also correlated with that of the third surgery ($P = 0.033$, $r = 0.334$) (Figure 1). Perforating disease tends to represent as perforating disease and nonperforating as nonperforating. Even with the correlation of surgical indications between repeated operations, the rate of CD perforation behavior as an indication for the second and third surgeries was significantly higher than that for the first surgery (Figure 2). Therefore, although CD can retain disease behavior after surgery, CD is a chronic disease characterized by progressive bowel destruction and will eventually develop a perforation. CD not only has stable characteristics but also progresses chronically.

Postoperative recurrence

After the first surgery, perforating indication (HR 1.456, 95%CI 1.051-2.016) and preoperative disease duration (HR 1.003, 95%CI 1.000-1.006) were significantly associated with recurrence-free survival in the

Table 1 Characteristics of repeated operations patients with Crohn's disease

	First surgery (<i>n</i> = 386), %	Second surgery (<i>n</i> = 155), %	Third surgery (<i>n</i> = 41), %	<i>P</i> value
Sex				0.405
Man	290 (76.69)	124 (80.00)	33 (80.49)	
Female	96 (23.31)	31 (20.00)	8 (19.51)	
Age (year)				0.037
A1 (≤ 16)	5 (1.30)	2 (1.29)	0 (00.00)	
A2 (17-40)	264 (68.39)	92 (59.35)	20 (48.78)	
A3 (> 40)	117 (30.31)	61 (39.35)	21 (51.22)	
Appendectomy				0.152
Yes	76 (19.69)	37 (23.87)	13 (31.70)	
No	310 (80.31)	118 (76.13)	28 (68.29)	
Smoking history				0.576
Never smoker	320 (82.90)	128 (82.58)	37 (90.24)	
Past smoker	49 (12.69)	23 (14.84)	3 (7.32)	
Active smoker	17 (4.40)	4 (2.58)	1 (2.44)	
Preoperative treatment				
Immunomodulator	97 (25.13)	48 (30.97)	12 (29.27)	0.362
Enteral Nutrition	178 (46.11)	80 (51.61)	16 (39.02)	0.288
5-aminosalicylates	32 (8.29)	23 (14.84)	4 (9.76)	0.074
Corticosteroids	49 (12.69)	30 (19.35)	7 (17.07)	0.130
Infliximab	8 (2.07)	5 (3.23)	1 (2.44)	0.743
Perianal disease				0.265
Yes	73 (16.77)	39 (25.16)	9 (21.95)	
No	313 (83.22)	116 (74.84)	32 (78.05)	
Indication for surgery				0.004
Free perforation	65 (16.83)	9 (5.81)	2 (4.87)	
Fistula or abscess	107 (27.72)	78 (50.32)	25 (60.97)	
Obstruction	162 (41.96)	57 (36.77)	10 (24.39)	
Medical intractability	41 (10.62)	5 (3.23)	1 (2.44)	
Hemorrhage	11 (2.85)	6 (3.87)	3 (7.32)	
Location				0.028
L1 (ileal)	145 (37.56)	56 (36.13)	10 (24.39)	
L2 (colonic)	47 (12.18)	7 (4.52)	5 (12.20)	
L3 (ileocolonic)	194 (50.26)	92 (59.35)	26 (63.41)	
IASCs				0.569
Yes	27 (6.99)	15 (9.68)	3 (7.32)	
No	359 (93.01)	140 (90.32)	38 (92.68)	

IASCs: Intra-abdominal septic complications.

univariate analysis. In multivariate analysis, only perforating indication significantly affected the outcome of recurrence and appeared to be an independent prognostic factor (HR 1.425, 95%CI 1.015-2.000) (Table 2).

Table 2 Univariate and multivariate analysis of risk factors associated with postoperative recurrence after first surgery

Covariates	Univariate			Multivariate		
	HR	95%CI	P value	HR	95%CI	P value
Age at diagnosis	1.000	0.987-1.014	0.966			
Preoperative duration	1.003	1.000-1.006	0.021	1.002	0.999-1.005	0.112
Age	1.005	0.992-1.018	0.496	1.004	0.991-1.018	0.533
Sex	0.934	0.628-1.387	0.734			
Appendectomy	1.288	0.874-1.898	0.200			
Smoking history	1.026	0.676-1.558	0.903	1.048	0.670-1.639	0.838
Preoperative treatment	0.915	0.630-1.330	0.642			
Perianal disease	0.925	0.606-1.413	0.719	0.951	0.619-1.461	0.819
Location	1.027	0.864-1.222	0.761	1.040	0.871-1.241	0.665
Perforating indication	1.456	1.051-2.016	0.024	1.425	1.015-2.000	0.041
Resection range	0.949	0.799-1.128	0.553			
IASCs	0.666	0.381-1.164	0.154			

IASCs: Intra-abdominal septic complications.

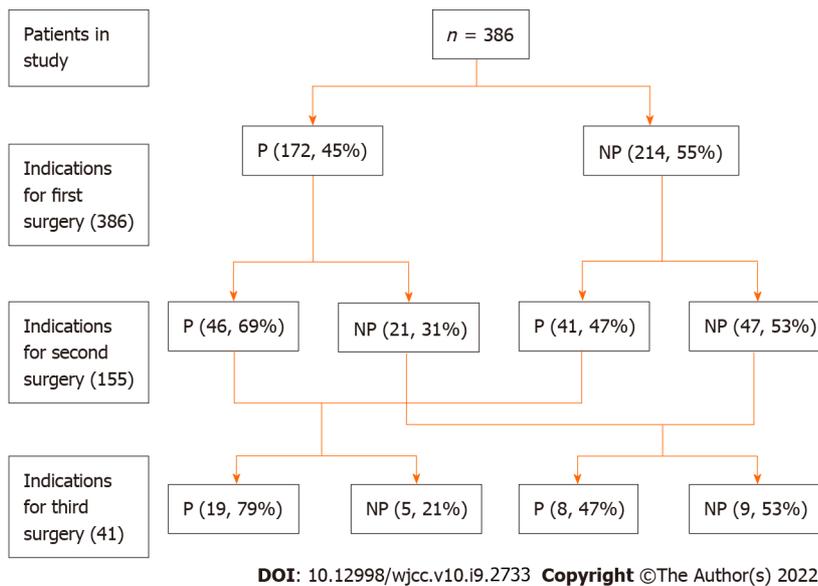


Figure 1 Correlations of perforating and nonperforating indications for Crohn's disease. P: Perforating indication; NP: Nonperforating indication.

Table 3 shows the results of the univariate and multivariate Cox proportional hazard model analyses after the second surgery. In the univariate analysis, only perforating indication (HR 2.036, 95%CI 1.043-3.968) was significantly associated with recurrence-free survival. In the multivariate analysis, none of the factors affected the outcome of recurrence.

Postoperative anastomosis characteristics

Anastomotic lesions were the most common sites of recurrence after the operation. In the second surgery, 79% of lesions occurred at anastomotic sites. The surgical indication of the second surgery was correlated with the behavior of anastomosis ($P = 0.000$, $r = 0.917$) (Figure 3). In the third surgery, 90% of lesions occurred at anastomotic sites. Concordance was found between anastomotic lesion behavior and indication for the third surgery ($P = 0.000$, $r = 0.940$) (Figure 4).

Table 3 Univariate and multivariate analysis of risk factors associated with postoperative recurrence after second surgery

Covariates	Univariate			Multivariate		
	HR	95%CI	P value	HR	95%CI	P value
Preoperative duration	0.998	0.990-1.007	0.666	1.001	0.991-1.011	0.872
Interval from first to second	1.001	0.992-1.010	0.831			
Age at diagnosis	1.012	0.984-1.041	0.406			
Sex	0.804	0.368-1.755	0.583			
Appendectomy	0.822	0.419-1.610	0.567			
Smoking history	0.918	0.323-2.606	0.872	1.228	0.371-4.065	0.737
Preoperative treatment	1.349	0.667-2.752	0.405			
Perianal disease	1.554	0.673-3.592	0.302	1.448	0.593-3.532	0.416
Age	1.008	0.980-1.036	0.590	1.009	0.977-1.042	0.579
Location	1.130	0.798-1.600	0.491	1.182	0.802-1.742	0.397
Perforating indication	2.036	1.043-3.968	0.037	1.919	0.959-3.846	0.065
Resection range	0.955	0.682-1.337	0.788			
IASCs	0.862	0.378-1.966	0.725			

IASCs: Intra-abdominal septic complications.

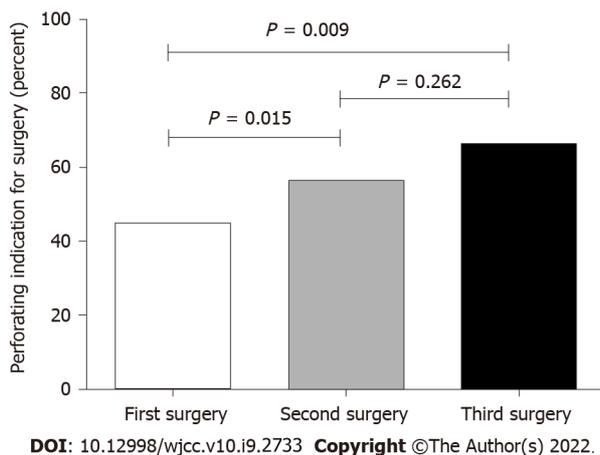


Figure 2 Percentage of perforating indications for Crohn's disease.

DISCUSSION

Due to the relatively low morbidity and clinical experience in CD in China, there is limited research on CD in our country, especially regarding surgical treatment. In the current study, we analyzed the clinical characteristics of repeated operations in CD, assessed the risk factors for surgical recurrence, and identified the clinical characteristics of perforating indications as common risk factors for postoperative recurrence among CD patients treated with different surgical frequencies. Moreover, our study analyzed correlations and anastomosis characteristics in repeated surgeries for Crohn's disease.

The evaluation of clinical characteristics included each operation of CD patients. There were no significant differences in sex, appendectomy history, smoking history, perianal disease or IASCs between the primary, second and third surgeries. Our data suggested that the surgical indication of the initial surgery was correlated with the surgical indication of the second surgery. Similarly, the surgical indication of the second surgery was also correlated with that of the third surgery. Perforating CD presents as perforating disease, and nonperforating CD presents as nonperforating disease[12]. Our study confirms this concept. However, the rate of perforating indications for the second and third surgeries was higher than that for the primary surgery. CD is a chronic disease characterized by progressive bowel destruction[13]. The respective rates of inflammation, stricture, and penetrating

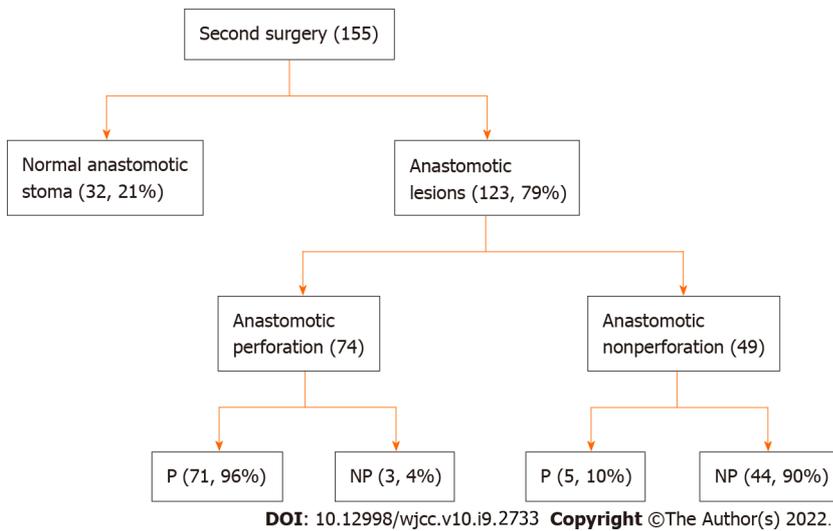


Figure 3 Anastomosis characteristics for the second surgery. P: Perforating indication; NP: Nonperforating indication.

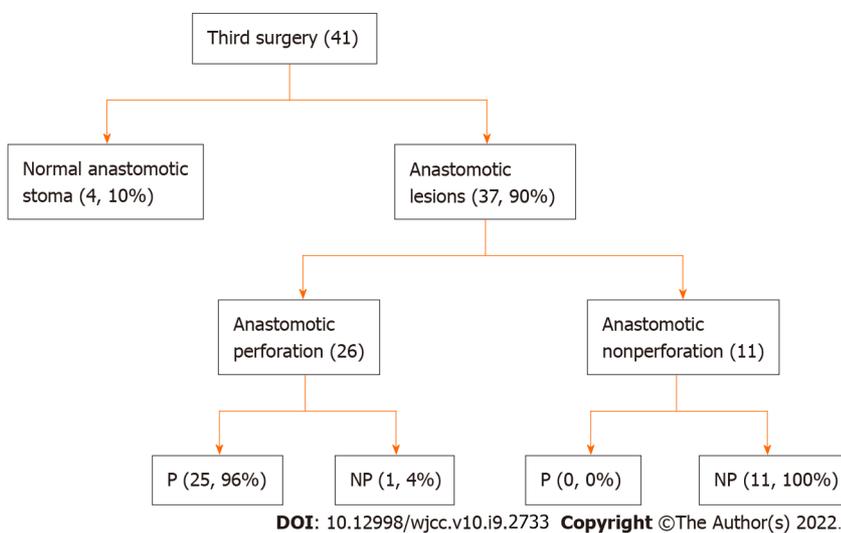


Figure 4 Anastomosis characteristics for the third surgery. P: Perforating indication; NP: Nonperforating indication.

disease are reportedly 12%, 18%, and 70% after 20 years[14], respectively, and most patients with CD will eventually develop a perforation. With the increase in surgical frequency and longer preoperative disease duration, the disease becomes more severe and more extensive. Our data showed that CD not only has stable characteristics but also progresses chronically, and perforation is a progressive surgical indication for Crohn's disease.

Postoperative recurrence is a major problem for CD patients[15,16]. Identifying the risk factors associated with postoperative recurrence will markedly benefit patients with CD and will permit doctors to maintain close postoperative surveillance in high-risk cases and optimize CD therapy[17,18]. Although there are conflicting results in the reports according to whether the perforating indication for surgery affects postoperative recurrence[19,20], some studies have indicated that perforating CD is a risk factor for earlier recurrence[21]. Our results showed that the perforating indication was a predictor of surgical recurrence, which confirmed the concept that the perforating indication for surgery was associated with decreased recurrence-free survival. Moreover, we found that a longer preoperative disease duration was significantly associated with a shorter period of postoperative recurrence after the first surgery. As the duration of CD symptoms before surgery may be uncertain, relatively few studies have shown a significant association between preoperative disease duration and earlier recurrence of postoperative CD. Our results agree with that of Lautenbach *et al*[22], who reported an association between higher recurrence rates and a longer preoperative duration. Antitumor necrosis factor antibodies have been proven to prevent postoperative recurrence[23]. However, infliximab therapy did not significantly affect the outcome of postoperative recurrence in the univariate and multivariate analyses in our study. Moreover, anastomotic lesions were the most common sites of recurrence after

the operation. anastomosis might be a new type of disease location for the classification of CD after surgery.

Several limitations of our study need to be considered. As most medical records were collected retrospectively, a potential bias may exist. Additionally, patients may not accurately remember their smoking habits, which may affect the significance of smoking as a risk factor. However, as an IBD center that focuses on surgical treatment in China, most data were accurately collected in our academic database or acquired by interviewing CD patients.

CONCLUSION

In conclusion, patients can retain their disease behavior after surgery, and the rate of perforating CD increases as the surgical frequency increases. CD not only has stable characteristics but also progresses chronically. Perforation is a progressive surgical indication for Crohn's disease. Anastomosis might be a new classification of disease location for postoperative CD. These factors may help to stratify patients for preventive treatment.

ARTICLE HIGHLIGHTS

Research background

It was well-known that Crohn's disease (CD) is a chronic disease characterized by progressive bowel destruction. Despite advances in medical therapy for CD, most patients with CD require repeated resection surgeries.

Research motivation

To delay postoperative recurrence, it is important to analyze the clinical characteristics and predict postoperative recurrence for surgical patients. Patients with risk factors for earlier postoperative recurrence should be considered for postoperative prophylaxis.

Research objectives

The aim of the current study was to analyze the perforating and nonperforating indications of repeated CD operations and identify the anastomosis characteristics for postoperative CD.

Research methods

Clinical characteristics of each surgery were collected. Univariate and multivariate analyses were performed to determine risk factors for recurrence.

Research results

Even if the correlation of surgical indications between repeated operations, the rate of perforating indication for the second and third surgeries was significantly higher than that of the first surgery. Anastomosis might be a new type of disease location for the classification of postoperative CD.

Research conclusions

CD not only has stable characteristics but also progresses chronically. Perforation is a progressive surgical indication for Crohn's disease. For CD after surgery, anastomosis may be a new classification of disease location.

Research perspectives

More study analyze the anastomosis characteristics for postoperative CD and develop new typing standards for postoperative CD.

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FOOTNOTES

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