

Combined Therapy With Early Initiation of Infliximab After Surgery for Perianal Fistulising Crohn's Disease : A Retrospective Cohort Study

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Abstract

Background: Recent studies have recognized that combined surgery and anti-TNF therapy could improve clinical outcomes in patients with perianal fistulising Crohn's disease (PFCD). However, the optimal timing for infliximab infusion after surgical intervention is uncertain. We aimed to determine the long-term efficacy of early initiation of infliximab after surgery among patients who received combination therapy for PFCD.

Methods: We performed a retrospective cohort study of PFCD patients who received combined infliximab and surgical treatment between 2010 and 2018 at a tertiary referral hospital. Patients were grouped according to the time interval between surgery and infliximab infusion, with < 6 weeks into early combination group and > 6 weeks into conventional combination group. The primary outcome was to compare fistula closure and surgical re-intervention between early and conventional combination groups. The secondary outcomes were predictors associated with these outcomes of early combination approach.

Results: One hundred and seventeen patients were included (73 in early combination, 44 in conventional combination). The median interval between surgery and initial infliximab infusion was 9.0 (IQR 5.5-17.0) days in early combination group and 188.0 (IQR 102.25-455.75) days in conventional combination group. After followed-up for a median of 36 months, 61.6% of patients in early combination group and 65.9% patients in conventional combination group derived fistula closure ($p=0.643$). The cumulative re-intervention rate was 23%, 32%, 35% in early combination group and 16%, 24%, 24% in conventional combination group, at 1, 2, and 3 years respectively ($P=0.235$). Presence of abscess (HR = 5.283; 95% CI, 1.61-17.335; $p = 0.006$) and maintenance infliximab therapy > 3 times (HR = 3.691; 95% CI, 1.233-11.051; $p = 0.02$) were associated with re-intervention in early combination group. Presence of abscess also negatively influences fistula closure (HR = 3.429, 95% CI, 1.216-9.668; $p = 0.02$).

Conclusion: Combined therapy with early initiation of infliximab after surgery could achieve promising results for PFCD patients. Durable drainage should be established for patients with concomitant abscess or requiring infliximab maintenance before infliximab initiation.

Background

The estimated incidence of perianal fistulising disease varies from 30% to 50% among patients with Crohn's disease (CD), which generally indicate aggressive disease patterns and poor prognosis [1-3]. The goal of therapy is to achieve adequate fistula closure and to reduce repeat procedures. Anti-TNF agents (infliximab or adalimumab) are effective in the induction and maintenance of fistula closure and are currently recommended as the first-line medical therapy for perianal fistulising Crohn's disease (PFCD) [4,5]. Further data suggest that combining surgery with infliximab could improve fistula closure and prevent fistula recurrence, compared with mono treatment alone [6-13]. However, proper timing between surgical intervention and commencement of medical therapy is still debated [3,5,14,15,16,17].

The traditional algorithm includes initial drainage with loose seton for 2-3 months, followed by infliximab infusion or definitive repair of the fistula based on the status of anorectal and intestinal inflammation [18,19]. However, this treatment modality may bring unnecessary delay in receiving proper medical treatment and increase risk of poor wound healing. As a tertiary referral center for PFCD, we first brought the concept of early combination approach into clinical practice in 2010. Infliximab therapy usually started within one week after surgical intervention, resulting in a high (89.3%) fistula closure rate and rapid clinical healing time (average 31 days)[20]. The high healing rate may contribute to the timely initiation of infliximab to control the inflammatory process and promote wound healing. Although no study has formally described this concept by far, most of the recent cohort studies have embraced early combination approach as the standard management of PFCD patients, with time intervals varying from 24 hours to 4 weeks between initial surgery and commencement of medical therapy [9,21-23]. Further data demonstrate that time interval between surgery and infliximab initiation longer than 6 weeks may negatively impact fistula closure, which underlines the importance of early combined treatment for patients with PFCD [24]. With the number of clinicians chooses early combination therapy increased [25], a direct comparison of long-term outcomes between early and conventional combined treatment is urgently required.

The purpose of current study was to compare fistula closure and surgical re-intervention between early and conventional combination treatment groups in patients with PFCD. We also try to identify predictive factors associated with these outcomes of early combination treatment approach in terms of surgical re-intervention and fistula closure.

Methods

Patients cohorts and study design

We retrospectively reviewed the medical records of all consecutive patients with perianal Crohn's disease treated at Affiliated Hospital of Nanjing University of Chinese Medicine, between July 2010 and January 2018. Patients who received combination therapy with surgery and infliximab for perianal fistulising disease were included. We excluded patients who didn't complete infliximab induction infusion (5 mg/kg at weeks 0, 2, and 6) and followed up less than 12 months. The diagnosis of PFCD was based on clinical, biological, radiologic, endoscopic, and pathologic evidence.

Two experienced colorectal surgeons (BY and YG) were involved in the surgical treatment of all included patients. Perianal surgical procedures included surgical drainage with/without seton insertion, fistulotomy, rectal advancement flap (RAF), and Ligation of the intersphincteric fistula tract (LIFT). Patients with abscess underwent surgical drainage first, followed by infliximab infusion. The seton removal was at the discretion of the treating physician following certain principles of our department [20]. Definitive surgical procedures (fistulotomy, RAF, or LIFT procedures) were attempted if no evidence of active proctitis and sepsis exit.

Based on a previous study in which a time interval of 6 weeks between surgery and infliximab initiation was correlated with fistula closure, we defined time interval shorter than 6 weeks as early combination therapy and longer than 6 weeks as conventional combination therapy [24].

Study definition and outcome measures

Fistulas were classified as "simple" or "complex" according to the American Gastroenterology Association (AGA) [26]. Proctitis was defined as ulceration and/or inflammation in the anorectum [5]. Clinical fistula closure was defined as complete closure of the fistula's external opening without discharge or discomfort. The surgical procedure at inclusion was defined as the initial surgery. Additional inpatient surgical procedure for recurrent fistula/abscess after initial surgery was defined as surgical re-intervention (procedures for seton replacement and wound revision were not included). The treating physicians evaluated the patients at every hospital admission for infliximab infusion or surgical intervention. A telephone interview was conducted to inquire about the symptoms and maintenance medications at the end of follow-up.

The primary outcome was to compare fistula closure and surgical re-intervention between early and conventional combination treatment groups. The secondary outcomes were predictors associated with surgical re-intervention and fistula closure of early combination treatment modality.

Statistical analysis

Quantitative variables are described as mean \pm SD or median and interquartile range (IQR, P25-P75). Categorical variables are presented as counts and percentages of the cohort. For statistical inference, normally distributed quantitative variables with equal variances were compared using two independent sample *t*-test; otherwise, the Mann–Whitney U test was used. Categorical variables were compared using the chi-square test or Fisher's exact test. The re-intervention free survival curves between early combination and conventional combination groups were compared by using a log-rank test with Kaplan–Meier analysis. Univariate and multivariate logistic regression analyses were performed to identify predictors associated with surgical re-intervention and long-term fistula closure in early combination cohort. The results were expressed as hazard ratios (HRs) with 95% confidence intervals (CI) and corresponding *p*-value. All statistical analyses were performed using the SPSS 22.0 software (SPSS, Chicago, Illinois, USA) were used for statistical analyses, with *p* < 0.05 was considered statistically significant.

Results

Patients characteristics and treatment modalities

The full-chart review was performed on 141 patients with perianal Crohn's disease treated in our center. Among them, 2 patients were excluded for non-fistulising disease, 5 patients for not receiving perianal surgery, 6 patients for incomplete infliximab induction regime, and 11 patients for lack of baseline and/or

follow-up data. A total of 117 patients were eventually included, with 73 patients in early combination group and 44 patients in conventional combination group. Their baseline characteristics are presented in Table 1.

There were no differences in patient demographics, previous surgical and medical management, fistula complexity, proctitis, and luminal phenotype between two groups. The median time interval between initial surgical procedures and first infliximab infusion was 9.0 (IQR, 5.5-17.0) days in early combination group and 188.0 (IQR, 102.25-455.75) days in conventional combination group. The proportion of anorectal stricture tends to be higher in early combination group than in the conventional combination group (37% vs. 20.5%, $p = 0.067$). In early combination group, seton placement were more often used (95.9% vs 75.0%, $p = 0.001$), while fistulotomy were less often utilized (2.7% vs 18.2%, $p = 0.011$) (Table 2) compared to conventional combination group.

After a median follow-up of 36 (IQR, 23.5–58.5) months after infliximab initiation, a total of 36 (30.8%) patients had undergone at least one additional perianal procedure after initial surgery. No significant difference in surgical re-intervention rate was found between two groups (34.2% vs. 25%, $p = 0.294$). The cumulative proportion of patients who remained free of re-intervention after initial surgery are demonstrated with Kaplan–Meier survival curves, and there was no significant difference between two groups by using the log-rank test ($p = 0.235$) (Figure.1). The cumulative probability of receiving surgical re-intervention was 23%, 32%, 34% in early combination group and 16%, 25%, 25% in conventional combination group, at 12, 24, and 36 months respectively.

Seventy-four (63.2%) patients have achieved fistula closure at the end of follow-up. Among them, 57 (48.7%) patients have achieved fistula closure without any re-intervention after initial surgeries (re-intervention free fistula closure). No differences in total fistula closure (61.6% in early combination group vs 65.9% in conventional combination group, $p = 0.643$) and re-intervention free fistula closure (45.21% in early combination group vs 54.55% in conventional combination group, $p = 0.328$) were found between different treatment groups (Table 2). At last follow-up, only 11% of patients were still maintaining with infliximab. The proportion of patients with ongoing infliximab treatment was similar between the two groups (13.7% in early combination group and 6.8% in conventional combination group, $p = 0.524$). Meanwhile, 36.8% of patients had stopped medical therapy after thorough evaluation and discussion between patients and physicians. We did not observe differences of patients who stopped medication (35.6% in early combination group and 38.6% in conventional combination group, $p = 0.743$). Forty-six percent of patients converted medical treatment to immunomodulators, including azathioprine (35.9%) and thalidomide (9%). No differences were detected in patients maintained with immunomodulators between two groups (Table 2).

Risk factors associated with surgical re-intervention and fistula closure of early combination treatment modality

We then explored the risk factors associated with surgical re-intervention in early combination group. On univariate analysis, had abscess at baseline (HR = 4.727; 95% CI, 1.523-14.672; $p = 0.007$) and

maintenance infliximab therapy more than 3 infusions (HR = 3.243; 95% CI, 1.169-8.996; $p = 0.024$) were related to the surgical re-intervention. On multivariate analysis, presence of abscess resulted in a 5-fold increased risk of re-intervention (HR = 5.283; 95% CI, 1.61-17.335; $p = 0.006$), and maintenance infliximab therapy more than 3 infusions increased over 3-fold risk of re-intervention (HR = 3.691; 95% CI, 1.233-11.051; $p = 0.02$) during the course of follow-up (Table 3). When concerning clinical fistula closure in early combination group, presence of abscess at baseline was negatively associated with fistula closure in univariate and multivariate analysis (HR = 3.429, 95% CI, 1.216-9.668; $p = 0.02$) (Table 4).

Discussion

Patients with PFCD represent a more aggressive and disabling disease course [2]. To reduce the need for multiple operations and associated comorbidities, a combination of surgery with anti-TNF agents targeted at optimization of perianal and luminal diseases simultaneously has been suggested as the preferred treatment modality [3,5,16,17]. An important factor that should be taken into consideration when adopting combination therapy is time interval between surgical and medical treatments. In current study, we directly compared early combination approach with conventional combination approach. At a median follow-up of 3 years, the fistula closure rate in both groups are beyond 60% (61.6% in early combination vs. 65.9% in conventional combination). Our finding is similar to a retrospective study also using early combination therapy, with 2-4 weeks between fistula surgery and infliximab induction therapy. Fifty-nine percent of patients with PFCD completely healed after a combination of operative treatment and infliximab [23]. Some recent studies highlight the benefit of early introduction of the biological agent after surgical drainage of sepsis [9,20-24]. The essential reason to support the concept of early combination therapy is the rapid therapeutic response of infliximab for both luminal and fistulous disease, thus timely infliximab delivery could promote fistula healing [18,27]. In an observational study of 129 patients, clinical response and remission for the fistulous disease occurred at a median of 9 days (ranging from 5 to 47 days) and 10 days (ranging from 6 to 54 days) respectively [28]. In ACCENT I trial, 58% of patients responded to a single infusion of infliximab within 2 weeks [29]. There is no difference in fistula closure between two combination approaches. It needs to be emphasized that significantly more patients in conventional combination group had fistulotomy than in early combination group (18.2% vs. 2.7%) at first attempt. Definitive surgery (such as fistulotomy, RAF, or LIFT) is justified by its effectiveness of fistula closure and decreasing repeat surgery for PFCD, compared with seton drainage along [18,21,23]. However, it could only be attempted in highly selected simple fistula without proctitis and abscess. For complex PFCD, placement of a non-cutting seton is still the treatment of choice. Almost all patients (95% of patients) in early combination group received seton placement as the initial surgery, still achieved a 62% fistula closure rate. The promising result may attribute to the multimodality approach we applied in daily practice, which included preoperative MRI-guided drainage of all sepsis and early initiation of anti-TNF, followed by early removal of setons. This may indicate that timing instead of type of interventions plays an important role in managing PFCD patients.

Heterogeneity in outcome definition hampers effective data analysis and comparison between different studies about PFCD treatments. In solutions try to address this issue, we used the need for fistula-related

re-intervention as the primary endpoint. Since repeat surgery may act as a surrogate marker for fistula relapse and avoiding this event is the essential goal for PFCD management [30-32]. In the current study, 30% of patients required at least one repeat surgery through the follow-up period. There was a trend toward a higher re-intervention rate in early combination group (34%) as compared with conventional combination group (25%). This may be due to the higher proportion of anorectal stricture and abscess in early combination group, which increased the complexity of management. However, no significant difference in total and cumulative re-intervention was found between the two groups. Our finding is similar as recently reported by a multicenter study from Europe, 32% of PFCD patients who received multimodal treatment required repeating perianal fistula-related surgery [32].

Identifying the predictors affecting long-term outcomes of early combination therapy remains the goal of directing future personalized therapy. However, the relevant study focus on this field is scarce [21,24,33]. Previous studies have identified multimodality treatment, seton removal, therapy with biological agents, and complete fistula response was associated with reduced surgical intervention [32,34]. In our study, the presence of abscess increased risk of surgical re-intervention and adversely impacted long-term fistula closure in early combination group. Concerns have been raised that use of infliximab might increase perianal abscess formation or fistula recurrence because of the rapid closure of the external fistula opening and persistent inflammation of the residual tract [35,36]. Literature remains controversial regarding the impact of infliximab on perianal infectious complications. Two population-based studies have observed the rising trend of abscess drainage since the introduction of infliximab [37,38]. On the contrary, data from the ACCENT II study fail to demonstrate the association between abscesses development and infliximab therapy [39]. Our findings indicate that for patients associated with abscesses at the time of surgery, starting infliximab too early may increase the risk of surgical re-intervention and compromise long-term fistula closure. In a small case series of early combination therapy, 12 of 22 complex perianal fistula had abscess that required drainage. Long-term clinical fistula healing was only achieved in 18% of patients [9]. One could speculate that concomitant abscess cavity may require a longer time of drainage to allow the inflammatory process to settle down before infliximab therapy is scheduled.

Maintenance infliximab therapy more than 3 times is another risk factor for surgical re-intervention in early combination group. Unlike previous studies, which showed that maintenance therapy with infliximab could reduce the risk of surgery and improve fistula closure in patients with PFCD [4,24]. This difference, however, may due to patients who need infliximab maintenance therapy more than 3 times in our study usually have more refractory fistulas, which required intermittent surgical intervention for local optimization. It also could be due to the potential increased risk of abscess formation with infliximab maintenance therapy, which also involves repeat surgical drainage. In our study, only 13% of patients in early combination group had ongoing infliximab therapy at the last follow-up, while almost half of the patients had switched to immunomodulators. The low infliximab maintenance rate was mainly due to the expense of infliximab was not covered by insurance in China during study period, and the cost is approximately \$2000 per infusion. Several cohort studies have demonstrated promising fistula healing in patients who only received induction or short-term maintenance infliximab therapy, followed by

immunomodulators maintenance therapy [9,18,23]. We hypothesize that early use of biologics for a limited duration to achieve a quick response, followed by cheaper immunosuppressant agents, could be considered as a cost-effective alternative for patients with PFCD.

Our study has several limitations: (1) A higher proportion of our cases received early combination approach leading to a significantly smaller conventional combination group and made it difficult to obtain a statistical difference between some results. (2) Due to the retrospective feature, objective fistula severity measurements such as MRI score or PDAI score were not routinely collected during our study. Although rectal MRI was performed in all included patients before treatment, a great percent of patients didn't receive MRI re-examination during follow-up. (3) All cases were collected from a single tertiary academic center, leading to the inclusion of a high number of patients with complex fistulas, and whether these data apply to patients with simple PFCD is uncertain. (4) The time interval of combination therapy was wide between different patients, especially in the conventional combination group; however, this may reflect the complexity of decision-making in PFCD management.

The strengths of this study include (1) The relatively large sample size in a single institution with two experienced surgeons performing all of the surgeries. (2) We measured perianal surgical re-intervention and long-term clinical fistula closure as endpoint definitions, which are clinically relevant parameters in reflecting real-world practice. (3) We only included patients who have finished infliximab induction therapy and have been followed up over one year, which is robust enough to provide reliable long-term outcomes.

In conclusion, early initiation of infliximab therapy after surgery results in promising long-term fistula closure in a significant proportion of PFCD patients with an acceptable surgical re-intervention rate. For patients with concomitant perianal abscesses or requiring infliximab maintenance therapy, a longer interval is warranted to establish durable drainage before beginning infliximab therapy. In patients with PFCD who receive early combination therapy, maintenance with immunomodulators such as azathioprine could be a reasonable alternative. The optimal timing to initiate treatment is still needed to be determined in future studies.

Abbreviations

CD: Crohn's disease; PFCD: Perianal fistulising Crohn's disease; RAF: Rectal advancement flap; LIFT: Ligation of the intersphincteric fistula tract; AGA: American Gastroenterology Association; IQR: Interquartile range; HRs: Hazard ratios; CI: confidence intervals; BMI: Body mass index; 5-ASA: 5-aminosalicylic acid.

Declarations

Ethics approval and consent to participate

The study was reviewed and approved by the Ethics Committee of the Affiliated Hospital of Nanjing University of Chinese Medicine (2017NL-049-02). Written informed consent was obtained from all enrolled patients.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

PZ conducted the study, acquired the data, drafted the manuscript. BLY designed the study, revised the manuscript. YFG, HJC, MMX and YRL contributed to the treatment and follow-up of patients. J.F.S: analysed and interpreted the data. All authors read and approved the final manuscript.

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Tables

Table 1 Baseline characteristics of early combination and conventional combination groups at infliximab initiation

Characteristics	early combination (n=73)	conventional combination (n=44)	p-value
Gender (male), n (%)	56 (76.7)	28 (63.6)	0.128
Age at inclusion, years (IQR)	25.0 (20.0-29.0)	24.0(21.0-31.75)	0.547
BMI, kg/m ² (mean ± SD)	18.98±2.77	19.12±2.91	0.810
Mean disease duration, months (IQR)			
Luminal disease	9.0 (1.0-39.0)	4.5 (1.0-24.0)	0.294
Perianal disease	12.0 (3.0-35.0)	19.0 (5.25-30.5)	0.354
Smoking status, n (%)			0.511
Non-smokers	69 (94.5)	39 (88.6)	
Ex-smokers	3 (4.1)	4 (9.1)	
Active smokers	1 (1.4)	1 (2.3)	
Initial presentation of CD, n (%)			0.029
Perianal	40 (54.8)	33 (75.0)	
Luminal	33 (45.2)	11 (25.0)	
Types of fistula, n (%)			0.614
Anorectal	68 (93.2)	39 (88.6)	
Invade to adjacent organ ¹	5 (6.8)	5 (11.4)	
Complex fistulas (AGA), n (%)	66 (90.4)	40 (90.9)	1.000
Proctitis, n (%)	18 (24.7)	12 (27.3)	0.828
Anorectal stenosis, n (%)	27 (37.0)	9 (20.5)	0.067
Presence of abscess, n (%)	42(57.5)	20(45.5)	0.205
Previous perianal surgery, n (%)	39 (53.4)	22 (50.0)	0.849
Disease behavior, n (%)			1.000
B1-inflammation	47 (64.4)	28 (63.6)	
B2-stricturing	25 (34.2)	16 (36.4)	
B3-penetrating	1 (1.4)	0 (0)	
Disease location, n (%)			0.447

L1-ileal	16 (21.9)	10 (22.7)	
L2-colonic	10 (13.7)	3 (6.8)	
L3-ileocolonic	40 (54.8)	29 (65.9)	
L4-upper gastrointestinal	7 (9.6)	2 (4.6)	
Previous medical treatment, n (%)			0.753
No	31 (42.5)	22 (50.0)	
infliximab	2 (2.7)	2 (4.5)	
Immunomodulators	10 (13.7)	6 (13.6)	
5-ASA	30 (41.1)	14 (31.8)	

¹Vagina or urethra.

IQR, interquartile range; BMI, body mass index; CD, Crohn's disease; AGA, American Gastroenterology Association; 5-ASA, 5-aminosalicylic acid.

Table 2 Comparison of outcomes between early combination and conventional combination groups

Characteristics	early combination (n=73)	conventional combination (n=44)	p-value
Duration of follow-up, months (IQR)	32.0 (21.0-60.5)	37.5 (33.5-57.25)	0.021
Initial surgery, n (%)			0.001
Seton drainage	70 (95.9)	33 (75.0)	0.001
Fistulotomy	2 (2.7)	8 (18.2)	0.011
RAF	0 (0)	2 (4.5)	0.296
LIFT	1 (1.4)	1 (2.3)	1
Medical treatment at last follow-up, n (%)			0.761
Infliximab	10 (13.7)	3 (6.8)	0.524
Immunomodulators	33 (45.2)	21 (47.7)	0.979
5-ASA	4 (5.5)	3 (6.8)	0.934
None	26 (35.6)	17 (38.6)	0.743
Re-intervention, n (%)	25 (34.2)	11 (25.0)	0.294
Fistula closure, n (%)	45 (61.6)	29 (65.9)	0.643
Re-intervention free closure rate, n (%)	33 (45.21)	24 (54.55)	0.328

IQR, interquartile range; RAF, rectal advancement flap; LIFT, ligation of the intersphincteric fistula tract; 5-ASA, 5-aminosalicylic acid.

Table 3 Univariate and multivariate analyses on predictors of surgical re-intervention in early combination group (n = 73)

HR, hazard ratio; CI, confidence interval.

Table 4 Univariate and multivariate analyses on predictors of long-term fistula closure in early combination group (n = 73)

HR, hazard ratio; CI, confidence interval.

Figures

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI)	p-Value	HR (95%CI)	p-Value
Gender (male)	0.941 (0.302-2.938)	0.917		
Age at inclusion	0.983 (0.92-1.05)	0.614		
Complex fistula	3.429 (0.389-30.197)	0.267		
Proctitis	0.698 (0.260-1.872)	0.475		
Anorectal stenosis	0.938 (0.343-2.559)	0.9		
Presence of abscess	4.727 (1.523-14.672)	0.007	5.283(1.61-17.335)	0.006
Previous perianal surgery	0.917 (0.348-2.414)	0.86		
Disease behavior				
B1-inflammation				
B2/B3-stricturing/penetrating	0.594 (0.208-1.692)	0.329		
Disease location				
L1-ileal				
L2-colonic	2.2 (0.431-11.219)	0.343		
L3-ileocolonic	0.834 (0.236-2.955)	0.779		
L4-upper gastrointestinal	2.933 (0.469-18.333)	0.25		
Maintenance with infliximab				
<=3 times				
>3 times	3.243 (1.169-8.996)	0.024	3.691(1.233-11.051)	0.020

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI)	p-Value	HR (95%CI)	p-Value
Gender (male)	0.456 (0.152-1.373)	0.163		
Age at inclusion	1.042 (0.977-1.111)	0.213		
Complex fistula	1.625 (0.293-9.007)	0.578		
Proctitis	1.2 (0.452-3.186)	0.714		
Anorectal stenosis	2.462 (0.922-6.572)	0.072		
Presence of abscess	3.429 (1.216-9.668)	0.02	3.429(1.216-9.668)	0.02
Previous perianal surgery	0.8 (0.311-2.06)	0.644		
Disease behavior				
B1-inflammation				
B2/B3-stricturing/penetrating	2.133 (0.798-5.704)	0.131		
Disease location				
L1-ileal				
L2-colonic	1.111 (0.22-5.616)	0.899		
L3-ileocolonic	0.897 (0.27-2.988)	0.86		
L4-upper gastrointestinal	2.222 (0.365-13.538)	0.386		
Maintenance with infliximab				
<=3 times				
>3 times	1.319 (0.512-3.396)	0.566		
Need re-intervention	2.383 (0.882-6.440)	0.087		

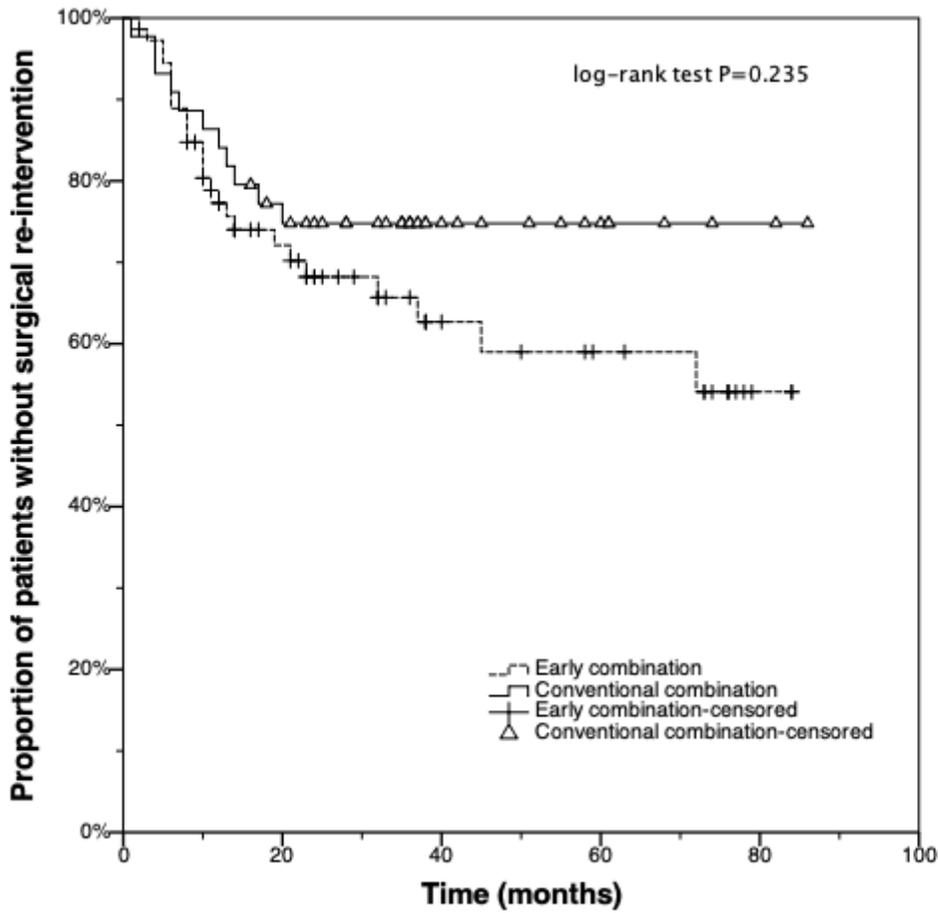


Figure 1

Kaplan–Meier curves comparing the cumulative probability of remaining on re-intervention free status after initial surgery between early combination and conventional combination groups