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IDENTIFICATION OF THE OPTIMAL MEDICAL AND SURGICAL MANAGEMENT FOR PATIENTS WITH PERIANAL FISTULISING CROHN'S DISEASE

Short title: Management of perianal Crohn's disease

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ABSTRACT (Word = 250)

Aims: The aims of our study were to assess the best medical and surgical approaches for Perianal Crohn's Disease (PCD) in order to identify an optimal combined medical and surgical treatment.

Methods: Medical records of all patients with PCD treated with TNF α antagonists in two referral centers between 1998 and 2018 were reviewed. Predictors of long-term outcomes were identified using a Cox proportional hazard model.

Results: A total of 200 patients were included. Fifty-three patients (26.5%) were treated with adalimumab and 147 (73.5%) with infliximab. Combination of TNF α antagonist with an immunosuppressant and presence of proctitis were independently associated with fistula closure. Seton was placed in 127 patients (63.5%) before starting biological therapy. Eighty patients (40%) underwent additional perineal surgery. Prior PCD surgery, seton positioning, additional perineal surgery, and additional surgery within 52 weeks of anti-TNF α treatment were associated with an increased rate of fistula closure. Finally, medical combination therapy (anti-TNF α plus immunosuppressant) along with seton placement and additional surgery within one year was the best management for PCD patients ($p=0,02$).

Conclusion: Combined medical and surgical management is required for the treatment of PCD patients. Medical combination therapy associated with seton placement and additional surgery within one year is the best management for PCD patients.

Key words: Crohn's disease, perianal fistula, medical and surgical management, combination therapy

Introduction

Crohn's disease (CD) is an immune-mediated inflammatory disorder which can affect the entire digestive tract from the mouth to the anus^{1,2}. In addition, up to 50% of patients have extraintestinal manifestations that mainly involve skin, joints and eyes². Perineal disease remains one of the main challenges in the management of CD³, including fistulising and non-fistulising perianal lesions^{2,4}. Perianal fistulising Crohn's disease (PCD) is frequent and can occur in up to one third of CD patients⁵.

PCD remains one of the most dreaded complications for CD patients due to an associated disabling disease course⁶. Moreover, PCD drastically alters the patients' quality of life and increases patients' disability due to pain, secondary psychological dysfunction, physical and sexual impairment, and the onset of faecal incontinence in up to 24% of cases⁷⁻⁹. The overall management of PCD aims to relieve pain, to close the fistula tract, to avoid abscess recurrence, and to preserve faecal continence^{10,11}.

However, the best management for PCD is still unclear because of the low level of evidence in the current literature and unfortunately, proctectomy with a definitive stoma is still required for refractory PCD in 8 to 40% of cases¹¹. Historically, surgical treatment was the only option available for patients with PCD, but the introduction of TNF α antagonists and particularly infliximab (IFX) revolutionised their management by being included in the therapeutic options and allowing long-term sustained remission for most PCD patients^{12,13 14}. Efficacy of IFX in fistula healing was demonstrated in two prospective clinical trials^{7 15}, showing that patients treated with IFX had a significantly higher rate of fistula closure compared with placebo (68% and 36% vs 26% and 19%, respectively). Similarly, in a post-hoc analysis of a phase III, multicentre, randomized trial (CHARM trial)¹⁶ complete fistula closure was observed in 33% of patients after 56 weeks of treatment with adalimumab (ADA) and in 13% of patients in the placebo group. Perianal surgery is essential to drain abscesses, reduce the risk of sepsis, avoid early abscess recurrence, and potentially increase the rate of success¹⁷. A recent systematic review and meta-analysis⁷ showed that combination of anti-TNF α and surgical intervention was superior to anti-TNF α alone for the treatment of PCD. A combination of medical and surgical treatment is thus necessary to achieve PCD remission, but the optimal management remains to be determined¹⁸. Although a combined medical and surgical strategy may be seen in the short term, data on the long term outcomes are scarce. The aims of our study were to assess the best medical management and the optimal surgical treatment for PCD in order to identify an optimal combined medical and surgical treatment for PCD in a large cohort of patients.

Materials and methods:

All hospital records of adult patients (age >18 years) with an established diagnosis of CD and treated for the first time with TNF α antagonists for CD between 1998 and 2018 in two tertiary referral centres (University Hospital of Rennes and University Hospital of Nancy, France), were reviewed. All adult patients with PCD documented by an experienced proctologist at the first anti-TNF α administration were included. The following data were collected: sex, date of birth, age at diagnosis, Montreal Classification at first anti TNF α infusion (B1, B2, B3 for disease phenotype; L1, L2, L3, L4 for disease localization), prior treatment, immunosuppressants, previous perianal and abdominal surgeries, type of anti TNF α used (ADA or IFX), treatment duration, concomitant use of immunosuppressants or corticosteroids, perianal surgery after IFX/ADA initiation (including seton placement). IFX was administered intravenously at a dose of 5 mg/kg at weeks 0, 2, and 6 (induction phase) and subsequently every 8 weeks for the maintenance therapy. All patients treated with ADA received 160 mg subcutaneously at week 0, 80 mg at week 2, followed by a maintenance regimen every 2 weeks. Anti-TNF treatment may be optimized during the maintenance regimen either by increasing the dose and/or shortening the interval of administration or both. Perianal CD lesions were classified as follows: ulcers were divided into superficial fissures (U1) and deep ulcers (U2), while abscesses and strictures were defined as 'present' or 'absent'. All proctologic reports mentioning the evolution of PCD lesions after first anti-TNF α infusion were reviewed until the last available visit. All perianal surgery after anti-TNF α initiation were recorded, including seton drainages, fibrin glue injection, fistulotomy, rectal advancement flap, use of a plug, LIFT surgery and radiofrequency (consisting of superficial thermal destruction of the fistula tract using a short radiofrequency catheter, not currently recommended).

The Nancy IBD cohort and the Rennes IBD cohort has been registered with the French National Data Protection Commission (Commission Nationale de l'Informatique et des Libertés; reference: N81404720 and N1412467, respectively), as requested for clinical studies in France. The Commission supervises the implementation of the January 6, 1978 act, regarding data processing, data files and individual liberties, as amended on August 6, 2004, to protect the personal data of individuals. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by our institution's human research committee. All examinations were performed according to the routine clinical practice at that time in our hospitals.

Statistical analysis

Quantitative variables were described as median and percentile (I.Q.R. for Inter Quartile Range: 25% and 75%). Categorical variables were presented as counts and percent of the cohort. Events were analyzed using survival analysis. Medical treatment and surgical treatment were first evaluated separately to avoid the influence of any variable on statistical analysis and to focus on each individual treatment. From these two separate analyses an optimal medical and surgical algorithm was proposed

for PCD. The fistula closure was defined as the absence of any discharge from the fistula and the closure of the external opening at two consecutive visits and was used to assess the efficacy of each treatment. The cumulative probabilities of fistula closure were estimated using the Kaplan Meier method. With regard to fistula closure, the time to healing was defined as the time interval between the first administration of anti-TNF α drug and the definitive fistula closure or last known follow-up. We also performed a univariate analysis using the log-rank test to identify predictive factors of each event. Cut-off values were calculated by receiver operating characteristic (ROC) analysis and were used to analyze the continuous variables in order to determine the most appropriate cut-off and to reduce the risk of bias related to arbitrarily defined cut-offs employing each outcome as a classification variable. Independent predictors of fistula closure were identified using a multivariate analysis. All significant variables with p values <0.05 in the log-rank test were retained in the model and integrated into a Cox proportional hazards regression model. The results were shown as hazard ratios (HRs) with 95% confidence intervals (Cis). Statistical analyses were performed using JMP® Pro 13.2.0 software.

Results

Study population

The baseline characteristics at first anti-TNF α administration are listed in Table 1. A total of 200 CD patients with PCD were included. Eighty-four patients (42%) were male. The median age at CD diagnosis was 23 years (IQR, 18–31.5). According to the Montreal classification, 38 patients (19%) experienced a penetrating complication (B3), and 89 patients (44.5%) had ileo-colic involvement (L3). Proctitis was associated with PCD in 41% of the patients and 84 patients (42%) had a concomitant abscess. Deep ulcerations (U2) were detected in 22% of cases according to the Cardiff classification. Stenosis was present in 21% of patients. Most patients, 171/200 (86%) had a complex perianal fistula according to the American Gastroenterological Association classification. Eighty patients (40%) had already been treated with immunosuppressive drugs before starting anti-TNF α therapy. 48 patients (24%) had a history of perineal surgery including abscess drainage and/or seton placement, while 33 patients (16.5%) had undergone abdominal surgery.

Medical management associated with fistula closure

At inclusion, 53 patients (26.5%) were treated with ADA and 147 (73.5%) with IFX. 119 patients (59.5%) received a concomitant immunosuppressive drug (purin analog in 105 cases [52,5%] and methotrexate in 14 cases [7%]). Dose optimization (77 [38%] patients in the overall cohort) was performed in a higher percentage of patients in the ADA group than in the IFX group (60.3% vs 30.6% respectively, p=0.0001). Fistula closure was observed in 102 patients (51%) after a median time of 58 weeks following anti-TNF α initiation. The cumulative probabilities of fistula closure were 26.8%, 54.2%, and 69.8% at 1, 3, and 5 years from starting therapy, respectively. In the multivariate analysis, combination therapy [HR=1.55 (1.04-2.38) p=0.03], and concomitant proctitis with or

without anal ulceration [HR=1.74 (1.149-2.718) p=0.0086] were associated with fistula closure. Conversely, patients with B1 behavior according to the Montreal classification were less likely to experience fistula closure [HR=0.6, (0.39-0.92) p=0.02] (Table 2).

Surgical management and surgical factors associated with fistula closure

At baseline 127 patients (63.5%) had a seton before starting TNF α antagonist. Seton removal without additional surgery was performed in 62/127 patients (48.8%), while 14 patients (11%) required loose seton during their follow-up. Eighty patients (40%) underwent additional perineal surgery: new drainage in 38 cases (47.5%), fistulotomy in 19 (23.7%), treatment with fibrin glue in 13 (16.2%), endorectal advancement flap in 6 (7%), ligation of inter-sphincteric fistula tract (LIFT) procedure in 2 (2%), PLUG positioning in 1 (1%), and radio frequency in 1 (1%). One patient was treated with both PLUG positioning and radiofrequency. Fifty-four patients (67.5%) underwent surgery within one year of anti-TNF α initiation and 26 patients (32.5%) after one year. The type of surgery was not associated with fistula closure (p=0.16). By contrast, the delay between anti-TNF α initiation and the occurrence of additional surgery was related to fistula closure, considering a cut-off value of 52 weeks for the analysis (p=0.006). In the univariate analysis all surgical factors were associated with fistula closure: prior PCD surgery, seton at inclusion, additional perineal surgery, and additional surgery within 52 weeks (Table 3). In the multivariate analysis the need for additional surgery within 52 weeks was the most important factor (Table 3).

Optimal medical and surgical management of Perianal fistulising Crohn's disease

The best medical and surgical strategies were analyzed in order to identify the optimal combined therapy. The comparison of different surgical strategies revealed that treatment with ADA or IFX associated with seton insertion and early additional surgery within 52 weeks was the best management for fistula closure (p=0.02, Figure 1). The cumulative probabilities of fistula closure following this approach were 43.8%, 82.2%, and 93.7% at 1, 3, and 5 years, respectively. Interestingly, the positive effects of surgery occurred when PCD patients were also treated with combined medical therapy (anti-TNF α drug plus immunosuppressive drug) (Figure 2). The cumulative probabilities of fistula closure following this management were 44.1%, 90.3%, and 98.8% at 1, 3, and 5 years, respectively.

Discussion

Control of clinical symptoms, achievement of mucosal healing, and resolution of the inflammatory state evaluated at imaging are validated CD targets¹⁹. Several trials have shown that healing rates of PCD were increased when anti-TNF α therapy was combined with seton placement and/or fistula tract curettage^{17,20}. Moreover, a recent randomized controlled trial (PISA)²¹ comparing three different therapeutic approaches for PCD patients (seton drainage, long-term anti-TNF, and surgical closure

after anti-TNF induction) was stopped early because patients treated only with seton placement had an increased rate of fistula-related re-intervention (defined as surgical re-interventions and/or (re)start of anti-TNF therapy) within one year.

Our study assessed medical and surgical treatments for PCD patients in order to identify the best combined approach. Cumulative probabilities of fistula closure after anti-TNF α therapy were 26.8% and 69.8% at 1 and 5 years respectively. These results are in line with literature evidence. In a retrospective study by Bouguen et al.²² including 156 PCD patients, rates of fistula closure of 40% and 65% were detected at 1 and 5 years respectively in patients treated with IFX. In our work no statistically significant difference was found in the rate of fistula closure between ADA and IFX, suggesting that these two drugs had similar efficacy. However, patients treated with ADA needed more dose optimization compared with the IFX group (60.3% vs 30.6% respectively, $p=0.0001$), implying a reduced efficacy at the usually recommended dose for ADA. The discrepancy in dose optimization rate may be due to pharmacokinetic differences between the two drugs that reach target tissues in different concentrations. Nonetheless, this could be overcome with therapeutic drug level monitoring, allowing achievement of the optimal concentration of the biological drug and helping decide appropriately on dose optimization²³⁻²⁵. A systematic review²⁶ including six studies found that the use of local anti-TNF α agents was related to partial/complete fistula closure in a rate varying from 40% to 100%. As already highlighted in the SONIC trial²⁷, combination therapy achieves a higher rate of clinical and endoscopic remission in patients with moderate to severe CD compared with biological or immunosuppressive therapy alone. The improved efficacy of combination therapy compared with biological therapy alone may be due to reduced antibody formation against TNF α inhibitors²⁸. However, so far there are no prospective trials about combination therapy in PCD and this is therefore not recommended currently in guidelines¹⁴, although this strategy would seem to be the best medical approach to control perianal fistulas.

Finally, patients with active proctitis or anal ulceration at baseline were more likely to have fistula closure during follow-up. The mucosal healing of the rectum was unfortunately not retrieved from the charts so this lack of data made it impossible to assess whether luminal remission induced by TNF antagonist is associated with fistula closure. This might be explained by the different pathophysiological origins of perianal fistulising disease: cryptoglandular and that originating from anal/rectal ulceration. The closure of the internal opening by anti-TNF could be the reason for the higher rate of response observed in those with ulceration.

As far as surgical treatment is concerned, additional perineal surgery was performed in 40% of patients but the type of intervention (new drainage, fistulotomy, application of fibrin glue, endorectal advancement flap, LIFT procedure, PLUG positioning, and radio frequency) did not significantly influence fistula closure. Some words of caution are needed regarding fistulotomy that was performed for simple fistula. Fistulas can be considered simple even in the case of CD, in case of single fistulas, unbranched, with low tract and without supralevator extension.²⁸ The factors mainly related to fistula

closure were optimization of medical treatment with combination therapy (TNF α inhibitor plus immunosuppressive drug) and additional perianal surgery within the first year. Also placement of a seton before starting biological therapy and before undergoing additional proctologic surgery was predictive of fistula closure. Interestingly, timing of the additional surgery was significantly associated with fistula closure as patients treated with surgery within 52 weeks had an increased success rate. The rationale for the impact of the timing of surgery on fistula healing is not clear, but re-intervention in tissues still inflamed, infected, and not fibrotic could allow the fistula tract to be cleaned, facilitating drainage and fistula closure. The complex pathophysiology of perianal fistula remains a mixture of a primary chronic immune disorder and an infection induced reaction that may explain the value of the second surgery which might drain the infection and allow treatment of the immune disease by TNF antagonist.

A randomised, double-blind, placebo-controlled, phase 3 trial³⁰ assessed safety and efficacy of stem cells for the treatment of complex perianal fistulas in patients with CD. The primary endpoint of clinical and radiological remission at week 24 was achieved in 50% of the patients in the stem cells group and in 34% of the patients of the placebo group (p value = 0,024). Importantly, all enrolled patients underwent clinical examination under anaesthesia, fistula curettage, and seton placement two weeks before the study started in order to homogenize the two experimentation arms. It should therefore be emphasized that in the two groups analyzed, surgery had a crucial role in therapeutic management and that the control group consisted of patients who underwent surgery rather than a being a true placebo group.

The large sample size is a strength of this article. However, there are some limitations: the retrospective study design, which may result in selection bias and secondly the lack of magnetic resonance (MR) data. MR is useful in pre- and post- operative assessment of PCD patients to better define fistula healing, but it was not routinely performed during the study period since it was not recognized as a standard procedure for pre- and post-surgical evaluation at that time.

In conclusion, treatment of CD patients with anal and perineal fistulas is much debated. Therapeutic strategies and techniques are not yet codified and need to be standardized. A combined medical and surgical therapeutic approach allows the best management for PCD patients. The administration of immunosuppressant drugs should be added to medical therapy of anti-TNF α inhibitors, as combination therapy seems to be related to higher rates of fistula closure. Seton placement and additional surgery in the first year of treatment appear to promote therapeutic success and optimization of healing of perianal disease. Further prospective trials are needed to identify the optimal surgical intervention for these patients.

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Tables and Figures

Table 1: Baseline characteristics

Table 2: Medical and disease phenotype factors associated with fistula closure (univariate and multivariate analysis)

Table 3: Surgical factors associated with fistula closure

Figure 1: Cumulative probabilities of fistula closure according to surgical management

Figure 2: Cumulative probabilities of fistula closure according to surgical management and the presence (B) or not (A) of a combination therapy

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Table 1: Baseline characteristics

Variable	Patients (N=200)
Gender (M:F) – n (%)	84:116
Median age (years) – median (IQR)	23 (18-31.5)
PCD at diagnosis – n (%)	79 (39.5%)
Montreal classification at first infliximab infusion – n (%)	
Disease location	
L1 – ileal	36 (18)
L2 – colonic	69 (34.5)
L3 – ileo-colonic	89 (44.5)
L4 – upper digestive tract	13 (6.5)
Disease behavior	
B1 – non-penetrating non-stricturing	147 (73.5)
B2 – stricturing	12 (6)
B3 – penetrating	38 (19)
Perianal disease according to the Cardiff classification – n (%)	
Ulcerations	
U0	127 (63.5)
U1	29 (14.5)
U2	44 (22)
Fistula	200 (100)
Stenosis	21 (10.5)
Associated proctitis	82 (41)
Associated abscess	84 (42)
Prior treatment – n (%)	
Surgery	48 (25)
Major abdominal surgery	33 (16.5)
Proctectomy	15 (7.5)
Immunosuppressant	
Purin analog (Azathioprine/6-mercaptopurine)	74 (37)
Methotrexate	6 (3)
Treatment at anti-TNF initiation – n (%)	
Type of anti-TNF	
ADA	53 (26.5)
IFX	147 (73.5)
Concomitant medications – n (%)	

Steroids	24 (1.2)
Purin analog (Azathioprine/6-mercaptopurine)	105 (52,5)
Methotrexate	14 (7)
Antibiotics	74 (37)
Placement of seton – n (%)	127 (63.5)
Median duration of seton drainage before IFX (weeks) – median (IQR)	3 (0.46-11.9)

M: male; F: female; n: number; IQR: Inter Quartile Range; PCD: perianal fistulizing Crohn's disease; TNF: tumor necrosis factor, IFX: infliximab; ADA: adalimumab

Table 2: Medical and disease phenotype factors associated with fistula closure (univariate and multivariate analysis)

	Univariate analysis (Log-rang)	Multivariate analysis HR (CI95), p-value
Characteristics at inclusion		
Age at diagnosis	0.08	
Sex	0.13	
History of ileocolic surgery	0.69	
Abscess at diagnosis	0.27	
Time between drainage and ant- TNF α initiation	0.85	
Phenotype		
B3 – penetrating	0.09	HR=0.60 (0.39-0.92), 0.02
B2 – stricturing	0.09	
B1 – non-penetrating non-stricturing	0.03	
L4 – upper digestive tract	0.38	
L3 – ileo-colonic	0.06	
L2 - colonic	0.34	
L1 – ileal	0.34	
PCD at diagnosis	0.32	
Perineal disease		
Associated proctitis and/or anal ulceration	0.02	HR=1.75 (1.15-2.72), 0.008
Ulceration (0,1,2)	0.56	
Medical treatment		
Associated immunosuppressant	0.04	HR=1.56 (1.04-2.38), 0.03
Antibiotics	0.15	
Steroids	0.22	
Anti-TNF α optimisation	0.55	

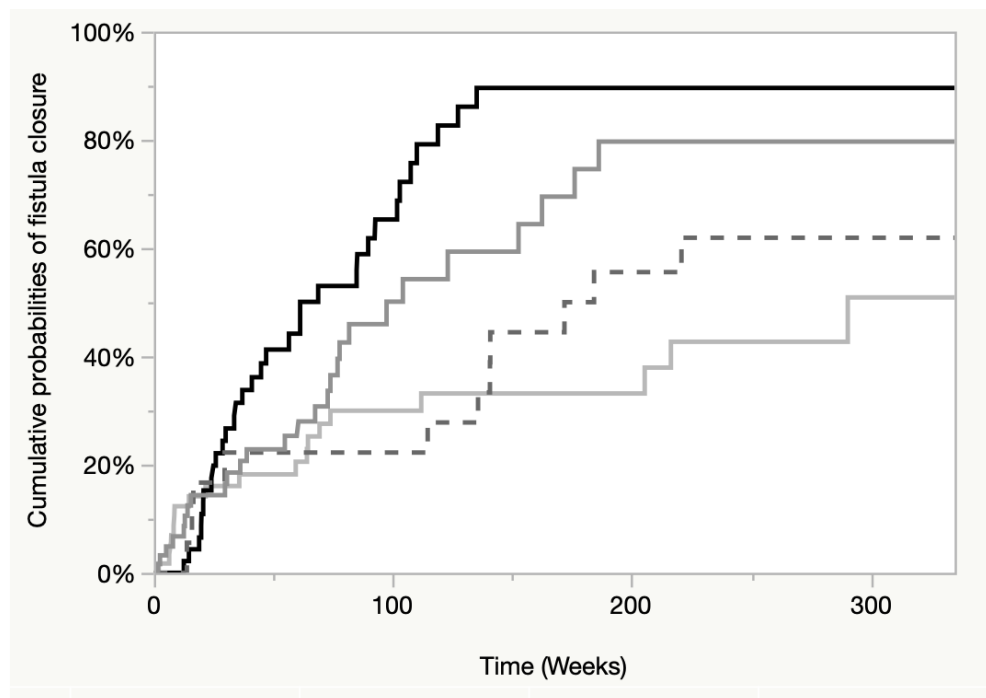
TNF: tumor necrosis factor; HR: hazard ratio; CI: confidence interval.

Table 3: Surgical factors associated with fistula closure

	Univariate analysis (log-rang)	Multivariate analysis HR (CI95), P value
Prior PCD surgery	0.007	1.53 (0.70-3.27), 0.27
Seton at inclusion	0.005	1.15 (0.61-2.32), 0.66
Complementary perineal surgery	0.004	1.03 (0.58-1.86), 0.91
Complementary surgery within 52 weeks	<0.0001	2.18 (1.22-3.99), 0.007

PCD: perianal fistulizing Crohn's disease; HR: hazard ratio; CI: confidence interval.

Fig. 1

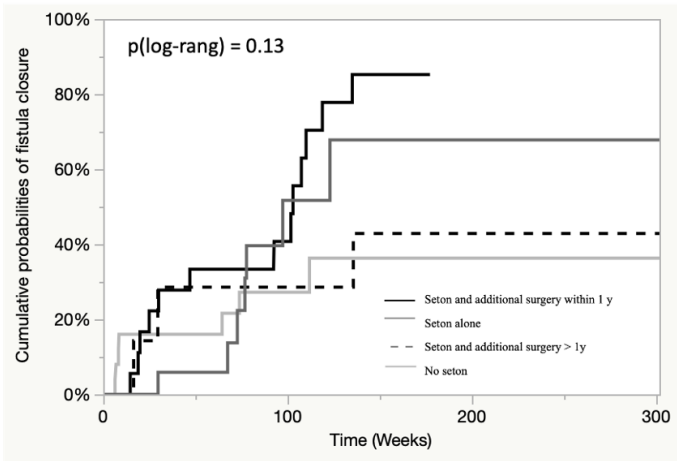


—	Seton and additional surgery within 1 y	47	11	11	2
—	Seton alone	62	13	5	4
- -	Seton and additional surgery > 1y	18	15	9	5
—	No seton	58	24	15	6

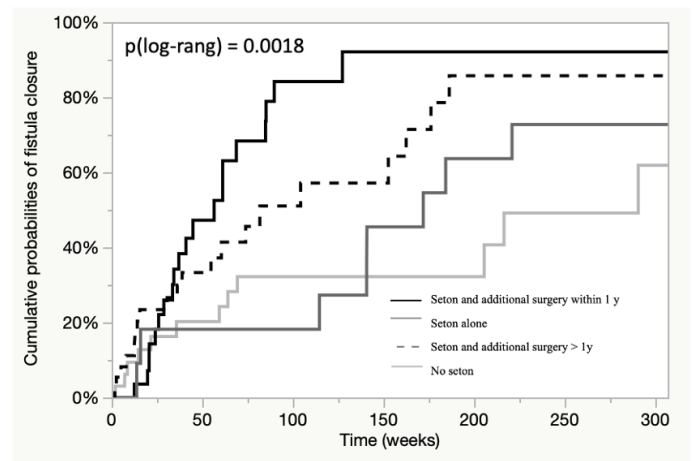
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Fig. 2

A: absence of combination therapy



B: combination therapy



—	19	9	0	0
—	25	5	3	2
- -	7	6	5	3
—	25	9	7	4

—	28	3	2	1
—	37	9	3	3
- -	11	10	5	3
—	33	16	9	4