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**NATURAL HISTORY OF PERIANAL CROHN'S DISEASE: LONG-TERM
FOLLOW-UP OF A POPULATION-BASED COHORT**

Short title : Natural history of perianal Crohn's disease

Charlène BROCHARD¹, Marie-Laure RABILLOUD², Stéphanie HAMONIC³, Emma BAJEUX³, Maël PAGENAULT², Alain DABADIE⁴, Agathe GERFAUD⁵, Jean-François VIEL³, Isabelle TRON⁶, Michel ROBASZKIEWICZ⁷, Jean-François BRETAGNE², Laurent SIPROUDHIS¹, Guillaume BOUGUEN¹ (Groupe ABERMAD)

¹ CHU Rennes, Univ Rennes, INSERM, CIC1414, Institut NUMECAN (Nutrition Metabolism and Cancer), F-35000 Rennes, France

² CHU Rennes, Univ Rennes, F-35000 Rennes, France

³ Department of Public Health, University Hospital of Pontchaillou, Rennes, France

⁴ CHU Rennes, INRAe, INSERM, Univ Rennes, Institut NUMECAN (Nutrition Metabolism and Cancer), F-35000 Rennes, France

⁵ Paediatric Unit, University Hospital, Rennes, France

⁶ Observatoire Regional De Santé Bretagne, Rennes, France.

⁷ CHU Brest, Univ Brest, F-29000 Brest, France

Correspondence to:

Guillaume Bouguen

Service des Maladies de l'Appareil Digestif

2 rue Henri le Guillou

35033 Rennes cedex, FRANCE

Telephone (0033)-2-99-28-43-17/Fax (0033)-2-99-28-41-89

Email: guillaume.bouguen@chu-rennes.fr

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Contributors: MLR, MP, AD, IT, MR, AG, LS performed the research; EB, JFV, JFB, LS and GB designed the research study; SH and GB performed statistical analyses; CB, EB et JB analysed the data; CB and GB wrote the paper; All authors approved the final version the final version of the manuscript.

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ABSTRACT (n=250)**Background and aims**

The natural history of perianal Crohn's disease (PCD) remains poorly described and is mainly based on retrospective studies from referral centres. The aim of this study was to assess the incidence, outcomes and predictors of the onset of PCD.

Methods

All incident cases of patients diagnosed with possible CD were prospectively registered from 1994 to 1997 in Brittany, a limited area in France. At diagnosis, the clinical features of perianal disease were recorded. All patient charts were reviewed from the diagnosis to the last clinic visit in 2015.

Results

Among the 272 out of 331 incident CD patients followed up, 51 (18.7%) patients had PCD at diagnosis. After a mean follow-up of 12.8 years, 93 (34%) patients developed PCD. The cumulative probabilities of perianal CD occurrence were 22%, 29%, and 32% after 1 year, 5 years, and 10 years, respectively. The cumulative probabilities of anal ulceration were 14%, and 19% after 1 year and 10 years, respectively. Extraintestinal manifestations were associated with the occurrence of anal ulceration. The cumulative probabilities of fistulizing PCD were 11%, 16%, and 19% after 1 year, 5 years, and 10 years, respectively. Extraintestinal manifestations, rectal involvement and anal ulceration were predictors of fistulizing PCD. The cumulative probability of developing anal stricture was 4% after 10 years.

Conclusions

PCD is frequently observed during CD, in approximately one-third of patients. These data underline the need for targeted therapeutic research on primary perianal lesions (proctitis, anal ulceration) to avoid the onset of fistulizing perianal disease.

Keywords: Perianal Crohn's disease, population based, outcomes, natural history

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disease whose natural history is characterized by periods of remission and relapse with a heterogeneous disease course¹. Perianal CD encompasses a wide range of entities², including non-fistulizing (fissures, ulcers and strictures) and fistulizing lesions (fistulas, abscesses and rectovaginal fistulas). It is now well established that perianal CD is a predictive factor for a disabling disease course³⁻⁶. More recently, several studies have shown that perianal CD drastically impairs these patients' social and sexual life and impairs quality of life⁷⁻⁹.

The treatment of both fistulizing and non-fistulizing anal disease remains a challenge in clinical practice. Despite a multidisciplinary approach including anti-TNF treatment and surgeries, perianal CD is still difficult to cure, with common recurrences that may still lead to the need for proctectomy with definitive stoma for 8 to 40% of cases¹⁰⁻¹².

Although perianal involvement was documented as a possible manifestation of CD in 1965¹³, few studies have been conducted, and these studies are mostly descriptive or retrospective and focused on perianal fistula that precluded a comprehensive view of perianal CD¹⁴⁻¹⁶. Up to 17% of patients might present with isolated perianal lesions before the diagnosis of CD^{5, 14}. The reported cumulative incidence after the diagnosis of CD ranged from 13% to 30%^{4,14,15}. Data related to non-fistulizing anal disease are often lacking¹⁷. Superficial fissures and cavitating ulcers may constitute 21 to 35% and 5 to 10% of perianal lesions, respectively¹⁸⁻²². Anorectal strictures were noted in 9% to 22% of patients in referral centre studies^{19,20}. These data remain controversial due to the study designs and lack of long-term follow-up. Improved knowledge of the natural history of perianal CD is thus emergently required to improve the management of CD and to prevent the onset of perianal CD, particularly perianal fistula.

The aims of this study were therefore to assess the natural disease course of perianal CD and to identify factors associated with the development of perianal CD in a population-based cohort.

METHODS

THE ABERMAD REGISTRY

The ABERMAD registry included all incident CD cases between 1994 and 1997 in a large administrative area of western France (Brittany), with almost 3 259 700 inhabitants representing 4.6% of the national French population. The Brittany is divided into four departments: Côtes d'Armor, Finistère, Morbihan and Ille et Vilaine. Only patients who resided in the defined study area at the time of diagnosis of their disease were included.

The establishment of the ABERMAD registry was carried out according to that of the EPIMAD register as described elsewhere²³⁻²⁵. Briefly, adult and paediatric gastroenterologists (n=139) of Brittany practising in the private or public sector prospectively referred all patients consulting for symptoms compatible with inflammatory bowel disease for the first time between 1994 and 1997. An interviewer practitioner completed a standard questionnaire for each patient at the gastroenterologist's consulting room.

The main collected data were age, sex, year of diagnosis, time between the onset of symptoms and diagnosis, and clinical, endoscopic, radiological and histological findings at the time of referral by the gastroenterologist. Endoscopic and radiological findings were prospectively collected at diagnosis. Data from colonoscopy, upper gastrointestinal endoscopy, small bowel transit and barium enema were gathered prospectively at diagnosis. A panel of four expert gastroenterologists reviewed each case independently. They assigned a diagnosis of definite, probable or possible CD, ulcerative colitis, unclassifiable chronic colitis or acute colitis according to the validated Lennard-Jones criteria²⁶.

STUDY POPULATION

For the purpose of the study, only patients with a definite diagnosis of CD were included. From 1994 to 1997, 272 out of 331 patients with a probable or definite diagnosis of CD in the ABERMAD registry and had a follow-up constituted the study population. Data were extracted from the files of gastroenterologists and from hospital medical records. An interviewer collected the extracted data with standardized questionnaires specifically designed for the study from date of CD diagnosis until the last follow-up or date of the last medical record. All charts of the patients were reviewed between 2014 and 2015 to assess the long-term outcomes of the cohort.

DESCRIPTION OF COLLECTED DATA

The following data were collected: family history of inflammatory bowel disease, CD location, disease behaviour according to the Montreal classification²⁷, and extraintestinal manifestations. An upper gastrointestinal location (L4) could be associated with an ileal (L1), colonic (L2) or ileocolonic (L3) location. Rectal involvement was differentiated. Perianal lesions were described at CD diagnosis as follows: presence or absence of anal fistula, anal ulceration, and anal stricture. Other non-specific Crohn's perianal lesions were not considered, such as haemorrhoids and skin tags. The outcome of the diagnosed perianal disease and the occurrence of new perineal lesions during the follow-up were retrieved from the patient charts according to the main items of the Hughes classification (presence or absence of ulceration, fistula, stricture)²⁸. Anal surgeries were recorded separately. All treatments during the study period were recorded, including the use of 5-aminosalicylates (5-ASA), corticosteroids (oral and topical steroids), purines (azathioprine, 6-mercaptopurine), methotrexate (MTX), and antitumour necrosis factor (TNF) therapies (infliximab [IFX] and adalimumab [ADA]). All hospitalizations related to CD were retrieved from the follow-up records. The study was approved by the ethics committee (n° 13.64). All authors had access to the study data and reviewed and approved the final manuscript.

STATISTICAL ANALYSIS

A descriptive analysis of the population study was conducted, specifying the baseline demographic, clinical, and endoscopic characteristics. The quantitative data are expressed as medians with IQRs (interquartile ranges), and the qualitative data are expressed as numbers and percentages. Kaplan-Meier survival curves were plotted for variables of interest with censored data. Variables of interest were the onset of any perianal lesion, perianal ulceration, perianal fistula, or perianal stricture at diagnosis or during the follow-up. Factors potentially associated with these outcomes were tested in univariate analysis using the log rank test. Additionally, variables that had a p-value <0.15 in the univariate analysis were included in a multivariate Cox proportional hazard model. Only variables that had a p-value <0.05 in multivariate analysis were retained in the final model. The results are reported as hazard ratios (HRs) and 95% confidence intervals (CIs). The proportional hazards assumption was checked for each factor, and the interaction between time and non-constant covariates was introduced in the model if required. Interactions were tested between all significant factors in the Cox model. Statistical significance was defined as p<0.05. All analyses were performed using the statistical software program SAS 9.3 (SAS Institute Inc. Cary, NC).

RESULTS

STUDY POPULATION

A total of 93/272 (34.2%) patients developed PCD during the follow-up period. Among them, 51/93 (54.8%) CD patients presented a perianal lesion at diagnosis: an anal fissure was reported for 41 (15.1%) patients, a perianal fistula was reported for 12 (4.4%) patients, and no patient had strictures. The baseline characteristics of the CD patients who developed perianal disease are summarized in **Table 1**. Among the 59 patients without follow-up data, 2 patients had perianal disease at diagnosis. A complete colonoscopy at diagnosis was performed for 249 patients (92%), and a rectal location was reported in 105 (41%) patients.

PERIANAL DISEASE OUTCOMES

After a mean follow-up of 12.8 years (6.2), a total of 93 (34.2%) patients experienced PCD. The **Table 1** compared the CD characteristics between patients with and without PCD. As expected, patients with PCD were younger with more complicated luminal CD. At the end of follow-up, 15 patients still had perianal lesions: a stricture for 6 patients and fistula for 5 patients. Overall, 44/93 patients (47.3%) had anal surgery mainly for perianal fistula with a mean of 2 (0.35) anal surgeries per patient. A stoma was required for 10 out of the 93 patients (10.7%). In addition, patients with PCD were more likely treated with immunosuppressants (57/93 [61%] vs 45/179 [25%] patients, $p=0.0001$) and/or anti-TNF (44/93 [47%] vs 16/179 [9%], $p=0.0001$). The cumulative probabilities of developing perianal CD (perianal ulceration or fistula or stricture) were 27% (23%-33%) after 1 year, 31% (26%-37%) after 5 years, 33% (28%-39%) after 10 years, and 34% (29%-40%) after 15 years (**Figure 1**). Among patients without perianal CD, the cumulative probabilities of developing perianal CD (perianal ulceration or fistula or stricture) were 4% (2%-7%) after 1 year, 11% (8%-15%) after 5 years, 17% (13%-23%) after 10 years, and 22% (17%-29%) after 15 years.

According to the multivariate analysis including age at diagnosis (age<40), colonic location (Montreal L2 and colonic location), extraintestinal manifestations, and rectal involvement (**Table 1**), the factors associated with an increased risk of perianal CD were extraintestinal manifestations at diagnosis (HR=2.20 [1.3-3.7]; $p=0.004$) and rectal involvement (HR=1.58 [1.03-2.46]; $p=0.04$) (**Table 2**). The cumulative probabilities of developing perianal CD according to these 2 factors are illustrated in **Figure 1**. A sub-analysis of rectal involvement

showed that the type of endoscopic lesion (aphthous lesions, superficial ulceration, deep ulcer) was associated with the risk of developing perianal lesions (**Supplementary Figure 1**).

ANAL ULCERATION OUTCOMES

A total of 61 (23%) patients experienced anal ulceration. The cumulative probabilities of developing anal ulceration were 14% (10%- 18%) after 1 year, 17% (14%- 22%) after 5 years, 19% (15%- 25%) after 10 years, and 21% (16%-26%) after 15 years (**Figure 2**). According to the multivariate analysis including age at diagnosis (age<17), colonic location (Montreal L2) and extraintestinal manifestations, the factors associated with an increased risk of anal ulceration were extraintestinal manifestations (HR=2.17 [1.19-3.96]; p=0.01) (**Table 2, Figure 2**).

FISTULIZING PERIANAL OUTCOMES

A total of 53 (20%) patients experienced fistulizing perianal CD. The cumulative probabilities of developing fistulizing perianal CD were 11% (8%-15%) after 1 year, 16% (12%- 20%) after 5 years, 19% (14%-24%) after 10 years, and 20% (16-26%) after 15 years (**Figure 3**). Only isolated anal ulcerations prior to the onset of perianal fistula were taken into account to identify the predictors of fistulizing PCD. According to the multivariate analysis including colonic location, ileal location, rectal involvement, extraintestinal manifestations, and anal ulceration, the factors associated with an increased risk of fistulizing perianal CD were extraintestinal manifestations (HR=2.19 [1.04-4.61]; p=0.04), rectal involvement (HR=2.22 [1.18-4.22]; p=0.01) and anal ulceration (HR=2.39 [1.25-4.56]; p=0.008) (**Table 2**). The mean time between the onset of anal ulceration and perianal fistula was 9 months (+/-7). The cumulative probabilities of developing fistulizing perianal CD according to these 3 factors are illustrated in **Figure 3**.

ANAL STRICTURE OUTCOMES

The cumulative probabilities of developing anal stricture were 2% (1%-4%) after 1 year, 3% (2%- 7%) after 5 years, 4% (2%- 7%) after 10 years, and 5% (3%-9%) after 15 years. Anal stricture was never observed without a prior history of perianal lesion.

DISCUSSION

In the present population-based study, 32% of patients developed perianal CD within 10 years of their diagnosis of CD. The cumulative incidences of anal ulceration and fistulizing perianal CD were 19% after 10 years. Extraintestinal manifestations, rectal involvement and anal ulceration were associated with the onset of fistulizing perianal CD. These data should encourage practitioners to efficiently treat patients presenting with rectal involvement and/or anal ulceration to avoid the onset of fistulizing perianal disease.

The cumulative incidence rates of perianal CD after 5 and 10 years of follow-up were 29% and 32%, respectively, in our study. A similar trend was observed in other population-based cohorts (5). The incidence rates of perianal fistulizing CD after 5 and 10 years of follow-up were 16% and 19%, respectively, which were roughly similar to the rates in other studies^{4, 14, 15, 29}. The incidence rates of anal ulceration CD after 5 and 10 years of follow-up were 16% and 19%, respectively, in our study. To the best of our knowledge, this is the first study to report the incidence rates of anal ulceration CD. Perianal CD is often reduced to fistulizing perianal CD^{30,31}, while anal ulceration CD is frequent and associated with more severe disease in both luminal and perianal locations³¹. Importantly, anal ulceration at baseline was associated with the onset of fistulizing perianal CD in our study. Of note, the incidence rate of non-fistulizing PCD was particularly high at diagnosis and stable over time, contrary to that of fistulizing PCD, which doubled during follow-up. This emphasizes the importance of physicians considering this location for decision making and the need to improve the evidence of effective treatment for this location³².

Rectal involvement was associated with the onset of fistulizing perianal CD. Patients with rectal involvement at baseline were twice as likely to develop perianal lesions, particularly fistulizing perianal CD. A rectal location is a known risk factor for radical surgery (diverting stoma, proctectomy) or the need for repeat surgery when associated with perianal fistulizing CD^{32,33}. The authors suggested that remission of an active rectal location concomitant to perianal fistula was important due to the association with the risk of radical surgery^{32,33}. Importantly, the present study suggested efficiently treating patients with rectal involvement regardless of the severity of rectal disease, as this approach might prevent the occurrence of fistulizing perianal CD.

Finally, extraintestinal manifestations were associated with the onset of both anal ulceration and fistulizing perianal CD. The relationship between these two features has never been reported. A possible theory might be that perianal CD could be part of the extraintestinal manifestations. An argument found in the literature is the more frequent prevalence of these 2 diseases in Asians³⁴.

The main strengths of this work are the sample size, the duration of follow-up and the systematic assessment of fistulizing and non-fistulizing perianal CD in a population-based cohort. Standardized questionnaires and recommended classifications^{27,28} were used. Each case was reviewed independently by expert gastroenterologists. Finally, all gastroenterologists of Brittany practising in the private or public sector participated, which reduced bias in the selection of patients. However, some limitations must be noted. There was no endoscopic review and no central reading of the endoscopy results. The diagnosis rates of anal or rectal stricture was probably underestimated. The anatomical classification of fistulas was not collected and it was not possible to differentiate rectovaginal fistulas from other types of fistulas. Perianal lesions such as skin tags, hemorrhoids were not recorded. Finally, deep and superficial ulcerations, as well as simple and complex fistulas, were not differentiated.

In conclusion, almost one-third of patients with CD developed perianal lesions. Extraintestinal manifestations, rectal involvement and anal ulceration were associated with the onset of fistulizing perianal CD. Remission of these active primary lesions is needed to avoid the onset of complicated and disabling fistulizing perianal disease.

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Table and figure legends

Table 1: Baseline characteristics of patients according to the occurrence or not of perianal Crohn's Disease

Table 2 Risk factors associated with the risk of developing perianal Crohn's disease, anal ulceration and perianal fistulizing disease

Figure 1: Kaplan-Meier curves for overall time to perianal lesion (1A), time to perianal lesion stratified according to extraintestinal manifestation (1B), time to perianal lesion stratified according to rectal involvement (1C) and time to perianal lesion stratified according to extraintestinal manifestation and rectal involvement (1D)

Figure 2: Kaplan-Meier curves for time to anal ulceration (2A), and Cox model curve for time to anal ulceration stratified according to extraintestinal manifestation (2B),

Figure 3: Kaplan-Meier curve for overall time to perianal fistulizing disease (3A), time to perianal fistulizing disease stratified according to prior anal ulceration (3B), time to perianal fistulizing disease stratified according to extraintestinal manifestation (3C) and time to perianal fistulizing disease stratified according to rectal involvement (3D)

Supplementary Figure 1: Kaplan-Meier curves for time to perianal lesion stratified according to the presence of aphthous lesion (rectal involvement, assessed by endoscopy) (A), stratified according to the presence of superficial ulceration (rectal involvement, assessed by endoscopy) (B), and stratified according to the presence of deep ulcers (rectal involvement, assessed by endoscopy) (C)

Table 1: Baseline characteristics of patients according to the occurrence or not of perianal Crohn's Disease

	Perianal Crohn's disease n (%) or median [IQR 25-75]	No Perianal Crohn's Disease n (%) or median [IQR 25-75]	Log rank
N	93 (34.2)	179 (65.8)	
Age at diagnosis (year)	25.0 (18.9-37.5)	30.7 (22.8-48.9)	0.01
Male sex	37 (39.8)	89 (49.7)	0.11
Time from symptom onset to diagnosis (year)	4 (1.0-11.5)	2 (1.0-8.0)	0.93
Age at diagnosis (Montreal classification)(year)			0.03
A1 – < 17	18 (19.3)	18 (10.1)	
A2 – <40	55 (59.1)	99 (55.3)	
A3 – ≥ 40	20 (21.0)	62 (34.6)	
Behaviour at diagnosis			0.02
B1 – inflammatory disease	47 (50.5)	121 (67.6)	
B2 – stricturing disease	40 (43.0)	49 (27.4)	
B3 – fistulizing disease	6 (6.5)	9 (0.5)	
Phenotype at diagnosis			0.13
L1 – ileal disease	11 (11.8)	30 (16.9)	
L2 – colonic disease	41 (44.1)	57 (32.0)	
L3 – ileo-colonic disease	41 (44.1)	90 (50.1)	
L4 – upper GI tract involvement	22	39	
Rectal location at diagnosis	45 (50.5)	60 (34.4)	0.0164
Extraintestinal manifestations at diagnosis	19 (21.6)	16 (9.9)	0.0137

Table 2 Risk factors associated with the risk of developing perianal Crohn's disease, anal ulceration and perianal fistulizing disease

Baseline factor	Risk factor for perianal Crohn's disease				Risk factor for anal ulceration				Risk factor for perianal fistulizing Crohn's disease			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)
Male sex	0.22	1.30 (0.86-1.98)	-	-	0.45	1.22 (0.73-2.03)	-	-	0.28	1.37 (0.77 – 2.42)	-	-
Time from symptom onset to diagnosis	0.85	1.00 (0.98-1.01)	-	-	0.87	1.00 (0.98-1.02)	-	-	0.94	1.0 (0.98 – 1.02)	-	-
Age at diagnosis	0.05		0.29		0.04		0.06		0.46		-	
A1 - <17		ref				ref				ref		
A2 - <40		0.94 (0.54-1.54)				0.51 (2.7-0.95)				0.88 (0.32– 2.37)		
A3 - ≥ 40		0.59 (0.33-1)				0.42 (0.20– 0.88)				1.32 (0.56 – 3.16)		
<i>Disease Location</i>												
L1 – ileal disease	0.08	0.56 (0.29-1.08)	0.23		0.11	0.53 (0.23-1.21)	0.11		0.05	0.41 (0.16 – 1.07)	0.29	
L2 – colonic disease		ref				ref				ref		
L3 – ileocolonic disease		0.65 (0.41-1.01)				0.61 (0.36-1.04)				0.55 (0.30 – 1.98)		
L4 – upperGI tract involvement	0.89	1.03 (0.64-1.69)	-		0.48	1.22 (0.69-2.17)	-		0.40	0.73 (0.36-1.51)	-	
<i>Behaviour at diagnosis</i>	0.93		-		0.68		-		0.65		-	
B1 – inflammatory disease		ref				ref				ref		
B2 – stricturing disease		1.08 (0.68-1.71)				1.10 (0.64-1.92)				0.73 (0.37 – 1.43)		
B3 – fistulizing disease		0.92 (0.29-2.93)				0.46 (0.06-3.36)				0.98 (0.24 – 4.07)		
<i>Clinical features at diagnosis</i>												
Anal ulceration	-	-	-		-	-	-		0.004	2.29 (1.29 – 4.06)	0.008	2.39 (1.25-4.56)
Extraintestinal manifestations	0.004	2.12 (1.27-3.54)	0.004	2.20 (1.30-3.70)	0.01	2.17 (1.19-3.96)	0.01	2.17 (1.19-3.96)	0.03	2.14 (1.08 – 4.21)	0.04	2.19 (1.04-4.61)
<i>Endoscopic features at diagnosis</i>												
Ileal location	0.36	0.79 (0.48-1.31)	-		0.31	0.73 (0.39-1.34)	-		0.07	0.52 (0.26 – 1.06)	0.49	
Colonic location (without rectal disease)	0.11	1.50 (0.90-2.51)	0.92		0.23	1.45 (0.78-2.69)	-		0.15	1.70 (0.82 – 3.53)	0.42	
Rectal location	0.02	1.62 (1.06-2.50)	0.04	1.58 (1.03-2.46)	0.20	1.40 (0.84-2.34)	-		0.01	2.1 (1.16 – 3.80)	0.01	2.22 (1.18-4.22)

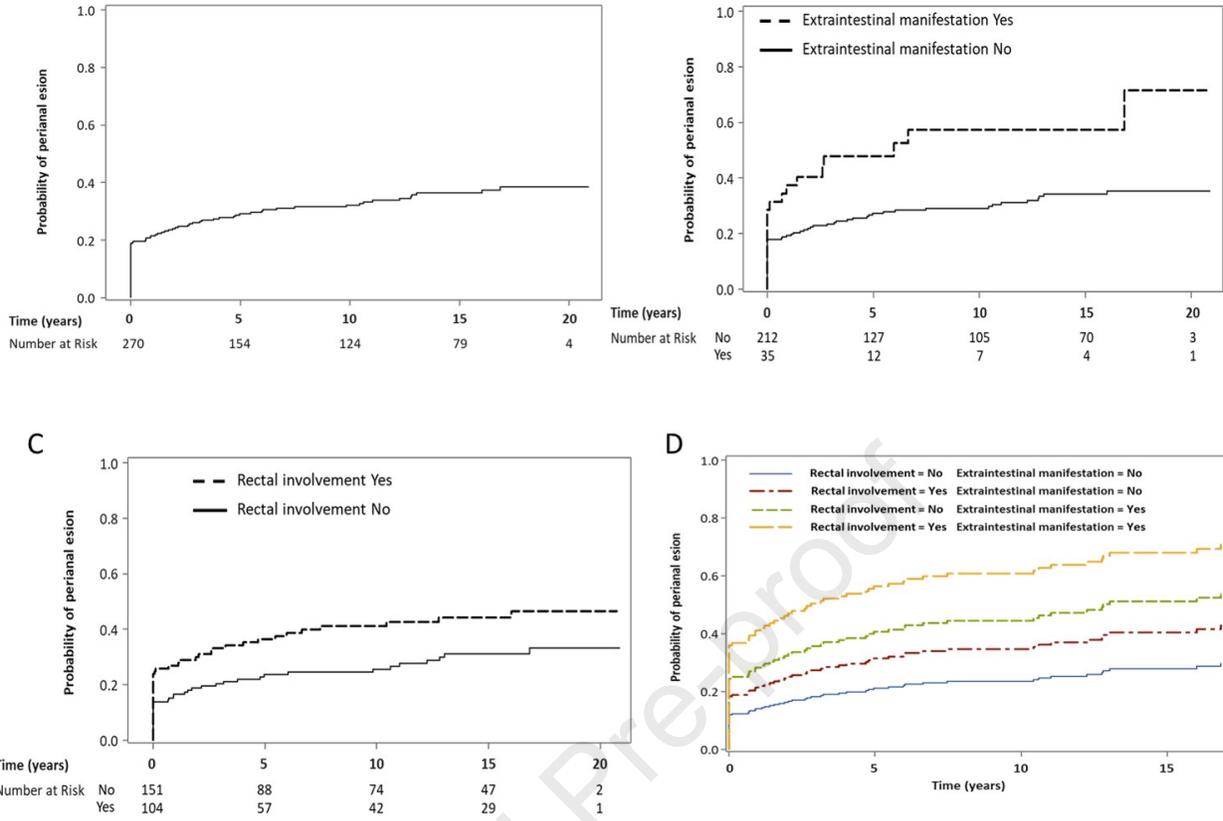


Fig. 1

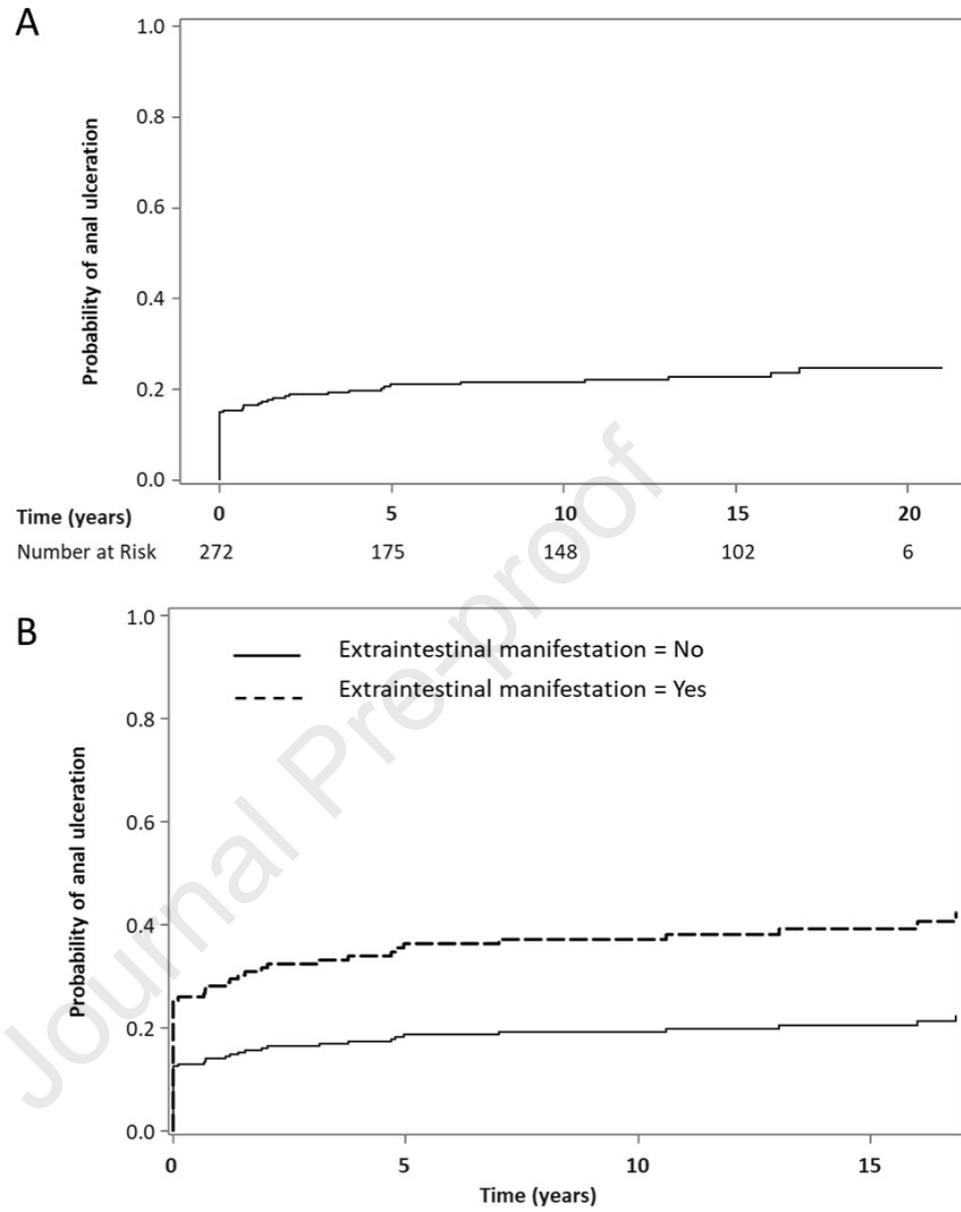


Fig. 2

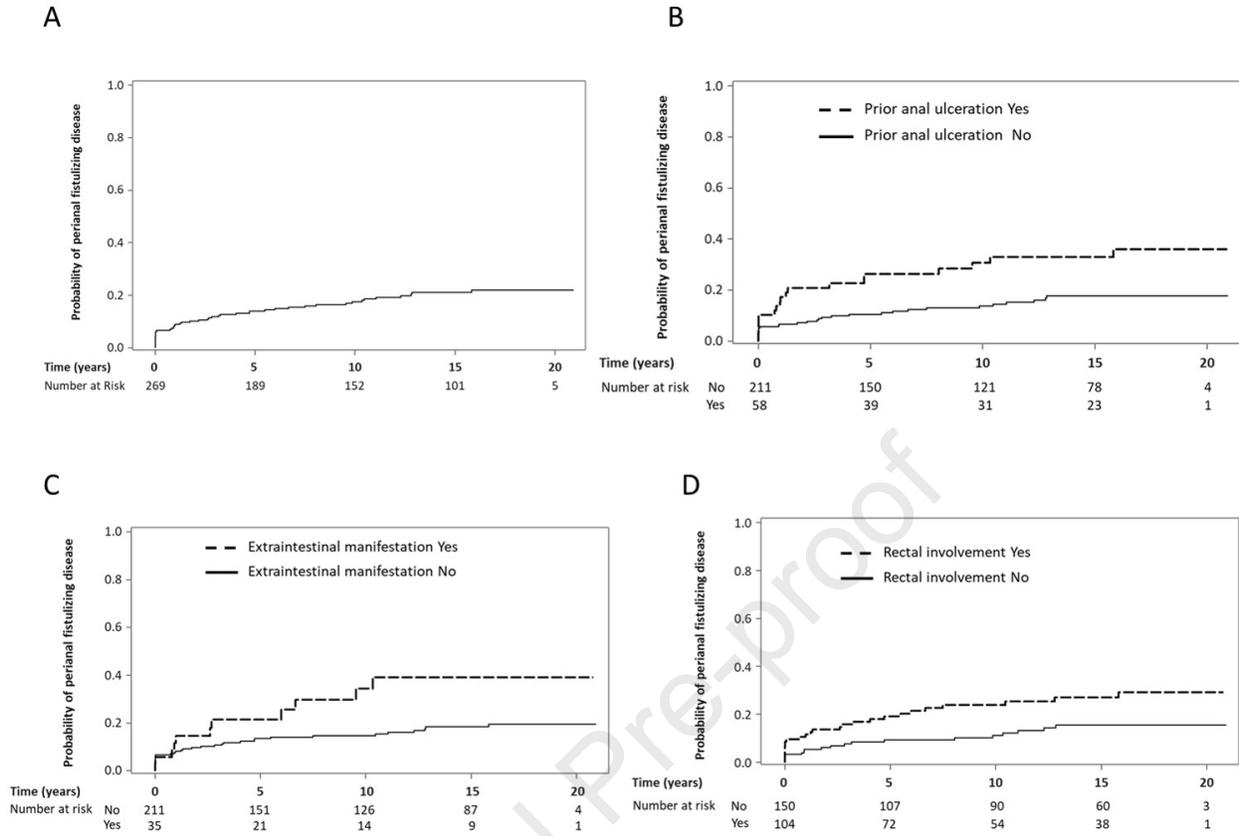
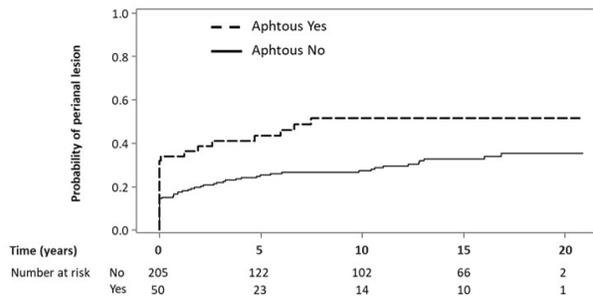
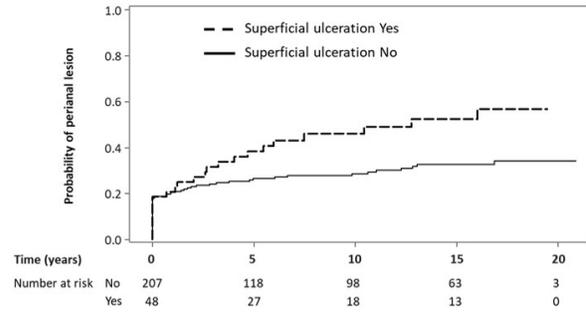


Fig. 3

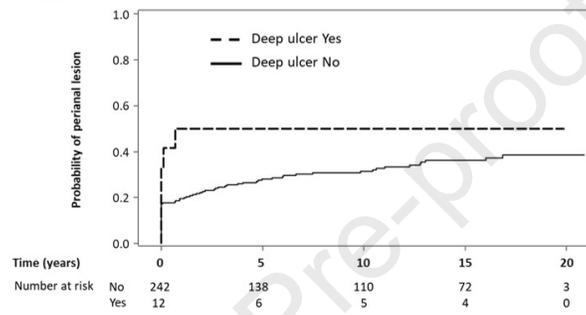
A



B



C



Suppl. Fig. 1

What you need to know

BACKGROUND

The natural history of perianal Crohn's disease (PCD) is poorly described and based on retrospective studies.

FINDINGS

The cumulative probabilities of PCD occurrence were 22%, 29%, and 32% after 1 year, 5 years, and 10 years, respectively. Extraintestinal manifestations, rectal involvement and anal ulceration were predictors of fistulizing PCD.

IMPLICATIONS FOR PATIENT CARE.

PCD is frequently observed during CD. This emphasizes the importance of physicians considering this location for decision making and the need to improve the evidence of effective treatment for this location.