

Healing of rectal advancement flap for anal fistula in patients with and without Crohn's disease: a retrospective cohort analysis

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Abstract

Background

Surgical closure of anal fistulas with rectal advancement flap is an established standard method, but in some cases, it has a high degree of healing failure. There are few studies in literature with a small number of cases examining differences between patients with and without Crohn's disease (CD). The aim of this study was to identify risk factors for anal fistula healing failure after advancement flap between patients with cryptoglandular fistulas and patients with CD.

Methods

From January 2010 to October 2020, 155 rectal advancement flaps (CD patients = 55, non-CD patients = 100) were performed. Patients were entered into a prospective database and retrospectively analyzed for healing rates.

Results

Median follow up was 189 days (95 % CI: 109–269). Overall complication rate was 5.8 %. Total healing rate for all rectal advanced flaps was 56 %. CD patients were younger (33 vs. 43 years, $p < 0.001$), more often female (76 vs. 30 %, $p < 0.001$), had more immunosuppressant medication (65 vs. 5 %, $p < 0.001$), more vaginal fistulas (29 vs. 8 %, $p = 0.001$) and more protective stomas (49 vs. 2 %, $p < 0.001$) than patients without CD. However, there was no difference in the healing rate of patients with or without CD (47 % vs. 60 %, $p = 0.088$).

Conclusions

Patients with anal fistulas without and with Crohn's disease have the same healing rate. Although patients with CD differ in their patient-specific characteristics, no independent factors for the occurrence of anal fistula healing failure could be determined.

Trial registration:

Not applicable due to the retrospective study design.

Background

Anal fistulas are a common problem and a typical indication for anal surgery. The incidence in Europe ranges from 1 to 2 per 10,000/year¹. Most anal fistulas are cryptoglandular fistulas and usually originate

from the proctodeal glands ². Patients with Crohn's disease (CD) patients suffer the second most from anal fistulas ³. Injuries, cancer or immunosuppressive diseases are less common causes.

Treatment of anal fistulas is difficult with sometimes high healing failure, sphincter damage, incontinence, and impaired quality of life. A variety of treatment options exist, including fistulotomy for superficial fistula course or seton drainage ^{4,5}. Fistula closure can also be performed by surgical reconstructive and sphincter preserving methods like mucosal or submucosal rectal advancement flap or LIFT (ligation of intersphincteric fistula tract) procedure ⁶⁻⁹. The results after LIFT or advanced flap were examined separately in a large review for cryptoglandular and CD fistulas with a comparable result ⁹. However, there was no comparison between cryptoglandular and CD fistulas in this study. In addition, application of biomaterial like fibrin, collagen or even autologous stem cells have also been developed for fistula closure ^{10,11}. Despite the large number of different treatment options, no procedure has achieved a breakthrough in the treatment of anal fistulas and the healing rates are still unsatisfactory. In the literature, the healing rate of the above procedures has a wide range. The rectal advancement flap seems to have the best healing rates between 30 and 100 % ¹²⁻¹⁴. In this technique, the internal fistula opening is closed with a flap including the lamina muscularis and the mucosa of the rectum wall. The external opening of the fistula is excised or debrided. Previous studies described poor results after advancement flap in the presence of active Crohn's disease are described ^{15,16}. Proctitis or stenosis should therefore be ruled out prior to the advancement flap procedure. If inflammation is present, systemic or topical therapy should be instituted, especially in CD patients.

So far, studies regarding healing rates of anal fistulas in CD patients are rare ^{17,18}. Prospective studies date from the 1990s and examine only a small number of CD patients. In addition, there are few studies, some of which have small case numbers, comparing the results of an advancement flap for CD-associated anal fistulas and cryptoglandular anal fistulas ^{16,19,20}. The remaining few retrospective studies on CD anal fistulas deal with various surgical treatments, including seton drainage and fistulotomy, without a focus on advancement flaps ²¹.

The primary aim of this study was to compare the healing rate after rectal advancement flap for anal fistulas in patients with cryptoglandular fistulas and patients with Crohn's disease. The second aim was to identify risk factors for healing failure in CD patients.

Methods

Patients

The study protocol was approved by the Medical Ethical Committee of Charité – Universitätsmedizin Berlin (EA4/149/20). From January 2010 to October 2020, 155 rectal advancement flaps were performed for patients with anal fistula in Charité – Universitätsmedizin Berlin, Campus Benjamin Franklin. Data analysis included both CD patients and patients with cryptoglandular fistulas. In CD patients, the

indication for an advancement flap was a healed perianal abscess and a CD-free rectal mucosa. All rectal advanced flaps were performed by surgeons experienced in proctology and Crohn's disease in our department.

Aim, design, settings

Data were collected from the hospital's electronic patient record system (EHS) in a prospective database and retrospectively evaluated. The primary aim was fistula healing. It was defined as complete healing of the fistulous tract (clinically and in anal endoscopic ultrasound) without the need for reoperation or replacement of the seton drain. In contrast, healing failure was defined as evidence of a recurrent fistula that required at least seton drainage or reoperation. For evaluation, patients' age, diagnosis, gender, immunosuppressant medication, ASA (American Society of Anesthesiologists) score, body mass index (BMI), rectovaginal fistula course, protective stoma and complication rate (Clavien-Dindo classification) were documented. Nicotine and alcohol abuse were not recorded due to the lack of documentation.

Statistics

Since most variables did not show a normal distribution, non-parametric tests were used for statistical comparison. Continuous variables are displayed as median (minimum - maximum) and categorical variables are displayed as count (percentage). The Mann-Whitney U test was used to compare two independent groups. Group comparisons for categorical variables were performed with the chi-square test. The level of significance was 0.05 (2-sided) for each statistical testing. P values concerning secondary endpoints were considered exploratory and are presented without Bonferroni correction. P values less than 0.2 were enrolled in a multivariable logistic regression model to identify independent risk factors. Kaplan-Meier estimates were calculated for the healing rate with the last available contact date. The log rank test was used for the comparison between patients without and with CD. We assumed that loss to follow-up was missing not at random (MNAR) and did not address this with specific statistical measures. The statistical analysis was performed with SPSS Statistics Software 25.0 (IBM, Armonk, NY, USA).

Results

Patients

Between January 2010 and June 2020, 155 mucosal advancement flap operations for patients with anal fistula were performed (table 1). The study included 55 CD patients and 100 non-CD patients. Most patients had complex fistulas: 83 % had a trans-sphincteric fistula and 15 % a vaginal fistula course. 41 patients (26 %) received immunosuppressant medication. Median healing over all flaps was 56 %. Nine patients (5.8 %) developed acute complications (hematoma, bleeding) with the need for redo surgery.

Table 1: General patient data over all advanced flaps.

	n = 155
Pathogenesis	
Crohn's disease	55 (35)
Cryptoglandular	100 (65)
Fistula course	
Vaginal	24 (15)
Trans-sphincteric	128 (83)
Supra-sphincteric	2 (1)
Inter-sphincteric	1 (1)
Ostomy	39 (25)
Age, years	40 (12 - 73)
Sex, female	71 (46)
ASA, 1 - 2	144 (93)
BMI, m ² /kg	25 (17 - 44)
Immunosuppressant medication	41 (26)
Anti-TNF	28 (18)
Anti-Interleukin	1 (0.5)
Anti-Integrin	5 (3)
Other	7 (4.5)
Fistula healing	86 (56)
Complications	9 (5.8)
Mortality	0
Follow up, days (95 % CI)	189 (109 - 269)

Median (min - max) for continuous variables, count (percentage) for categorical variables, except for Follow up: median (95 % CI). ASA Score = American Society of Anesthesiologists Score, BMI = Body mass index.

Risk of anal fistula healing failure after advancement flap for all patients

In table 2 the univariate analysis showed female gender, immunosuppressant medication and vaginal fistula course as significant influencing factors for healing failure. Crohn's disease, BMI, ASA 1 and 2 or the presence of protective stoma showed no influence on anal fistula healing failure. P values less than 0.2 from the univariable analysis were enrolled in a multivariable logistic regression model to identify independent risk factors for healing failure. Logistic regression analysis could not find any independent influencing factor on the healing after rectal advancement flap.

Table 2: Factors affecting anal fistula healing failure in all patients.

	Healing n = 86 (56 %)	Healing failure n = 69 (44 %)	Missing	P value	Logistic regression	
					Odds ratio (95% CI)	P value
years	43 (12 - 73)	36 (14 - 64)	0	0.063	0.987 (0.961 - 1.013)	0.319
female	32 (37)	39 (56)	0	0.013	1.803 (0.806 - 4.034)	0.152
, m ² /kg	25 (17 - 42)	25 (17 - 44)	4	0.460	-	-
, 1 - 2	78 (91)	66 (97)	0	0.191	0.440 (0.095 - 2.033)	0.293
unosuppression,	17 (20)	24 (35)	0	0.027	2.262 (0.812 - 6.295)	0.118
ogenesis			0	0.088	0.589 (0.213 - 1.628)	0.308
Crohn's disease	26 (30)	29 (42)				
Other	60 (70)	40 (58)				
nal fistulas	9 (38)	15 (62)	0	0.044	0.507 (0.171 - 1.499)	0.219
ective stoma	19 (22)	20 (29)	0	0.213	-	-

ASA Score = American Society of Anesthesiologists Score, BMI = Body mass index.

Advancement flap in CD patients

Table 3 shows differences in characteristics of patients with and without CD. CD patients were significantly younger, more female, received more immunosuppressant medication and had a lower BMI than non-CD patients. In addition, CD patients were more likely to have protective ostomy. There were significantly more patients with vaginal fistulas among CD patients. However, the healing rate of anal fistula did not differ between CD and non-CD patients (p = 0.088).

Table 3: Characteristics for patients without and with Crohn's disease (CD).

	CD patients n = 55	Non-CD patients n = 100	Missing	P value
Age, years	33 (14 - 66)	43 (12 - 73)	0	< 0.001
Sex, female	41 (75)	30 (30)	0	< 0.001
BMI, m ² /kg	24.4 (17.3 - 34.9)	25.6 (16.5 - 43.6)	4	0.033
ASA, 1 - 2	54 (98)	90 (90)	0	0.051
Immunosuppression, yes	36 (65)	5 (5)	0	< 0.001
Vaginal fistula	16 (29)	8 (8)	0	0.001
Ostomy	27 (49)	12 (12)	0	< 0.001
Fistula healing	26 (47)	60 (60)	0	0.088

CD = Crohn's disease, ASA Score = American Society of Anesthesiologists Score, BMI =

Body mass index.

A subgroup analysis was performed for CD patients to identify possible influencing factors for anal fistula healing failure (table 4). Neither age nor sex, gender, BMI or ASA showed a significant influence on fistula healing after advancement flap. A vaginal fistula course or the presence of a protective stoma were also irrelevant to the healing process. Only in immunosuppressant medication was there a significant difference between healing and healing failure in the univariable analysis. P values less than 0.2 from the univariable analysis were enrolled in a multivariable logistic regression model to identify independent risk factors for healing failure. Logistic regression analysis could not find any independent influencing factor on the healing after rectal advancement flap.

Table 4: Factors for healing failure of advanced flaps in CD patients.

	Healing n = 26	Healing failure n = 29	P value	Logistic regression	
				Odds ratio (95% CI)	P value
Age, years	33 (20 - 66)	31 (14 - 54)	0.428	-	
Sex, female	17 (65)	24 (82)	0.122	1.491 (0.324 - 6.857)	0.608
BMI, m ² /kg	24.5 (17.3 - 33.7)	24.4 (19.1 - 34.9)	0.873	-	
ASA, 1 - 2	25 (96)	29 (100)	0.473	-	
Immunosuppressant medication	14 (54)	22 (76)	0.025		0.555
Non	12 (46)	7 (24)		-	-
Anti-TNF	13 (93)	15 (68)		2.669 (0.704 - 10.118)	0.149
Anti-Interleukin	1 (7)	0		n/a	0.999
Anti-Integrin	0	7 (32)		n/a	1.000
Vaginal fistula	5 (19)	11 (38)	0.109	0.349 (0.081 - 1.505)	0.158
Stomy	12 (46)	15 (52)	0.444	-	

ASA Score = American Society of Anesthesiologists Score, BMI = Body mass index. n/a - due to missing values, no odds ratio could be determined.

Healing failure

The median follow-up for CD patients was 210 days (95 % CI: 53 – 368). Non-CD patients had a median follow-up of 89 days (111 – 267). Two patients (1 %) were lost to follow-up. Healing failure occurred in 69 (44 %) of 155 advancement flaps. Kaplan-Meier estimates for fistula healing failure did not differ between patients with cryptoglandular fistulas and patients with CD (figure 1).

The CD and non-CD patients with anal fistula healing failure were further classified in two categories according to the time of relapse occurred. An early relapse was predefined if it is reported within 14 days, and a late relapse later than 14 days. Of 29 CD patients with anal fistula healing failure, 8 patients (28 %) had a median early relapse of 10 days (6 – 12) and 21 patients (72 %) had a median late relapse of 84 days (29 – 1016). Of 40 non-CD patients with anal fistula healing failure, 14 (35 %) patients had a median early relapse of 8 days (4 – 14) and 26 patients (65 %) had a median late relapse of 85 days (16 – 1521). The difference for both early ($p = 0.552$) and late ($p = 0.082$) healing failure was not significant.

Discussion

Patients with Crohn's disease (CD) present a special and demanding group with a known increase in perioperative morbidity^{22,23}. This also includes the surgical treatment of CD-associated anal fistulas. Since there is little evidence on healing rates after advancement flap in CD^{18,24–26}, our aim was to analyze potential risk factors for healing failure in this particular group of patients.

We could show that CD patients represent a special group of patients with sometimes complicated anal fistulas that significantly differs from patients with cryptoglandular fistulas. Nevertheless, CD patients did not have an increased risk of healing failure in comparison to patients with cryptoglandular fistulas. Although CD patients were significantly younger and more female, had a smaller BMI, and were taking immunosuppressant drugs more frequently, no independent risk factors for healing failure of anal fistula after advancement flap were identified. This is a comparative study on this subject. In the past, most studies dealt with either only CD patients or only cryptoglandular fistulas^{7,24,27}.

Various risk factors for failure of fistula healing are known in the literature. In previous work, obesity has identified as a risk factor for healing failure of anal fistulas^{28,29}. This statement is not in line with our results. Although our results showed that non-CD patients had a significantly higher BMI than CD patients, there was no influence of BMI on anal fistula healing in either CD or non-CD patients. It therefore remains unclear whether BMI affects the healing after rectal advancement flap.

Another common risk factor for postoperative healing disorders is nicotine abuse, especially in CD patients^{30,31}. Previous data showed that there was no influence of nicotine, even excessive smoking, on anal fistula recurrence^{32,33}. We have not dealt with nicotine abuse in our work. As this is a retrospective data analysis, this value was not fully documented and could therefore not be adequately assessed.

Vaginal fistulas are known to be associated with healing disorders after anal fistula repair. Different studies demonstrated this effect for different surgical therapies such as internal and external flaps^{18,34}. In the past and to this day, a proctectomy is required in some cases³⁵. Vaginal fistulas occurred more frequently in CD patients in our study. However, this did not affect the healing rate. We therefore believe that the inclusion of patients with vaginal fistulas is feasible and does not introduce a significant bias.

A proximal bowel diversion is previously reported to be associated with lower recurrence rates after anal fistula surgery. However, studies do not agree on whether and when, depending on the severity of the underlying disease, a positive effect can be achieved^{36,37}. In our work, CD patients were more likely to have a protective stoma, but this did not affect the healing rate. It can therefore be assumed that other factors such as the course of the fistula or the severity of Crohn's disease may play a role in the fistula healing.

Apart from its retrospective character, a possible limitation of our study could be the heterogeneous group of patients, including CD and non-CD patients as well as patients with complex fistulas. On the one hand, however, we have made a division into CD and non-CD patients and analyzed these separately. On the other hand, complex fistulas are typical for CD patients and should therefore be specifically included in the analysis. Including all the patients above, it was possible to conduct a detailed analysis for rectal advancement flap with high number of patients achieving important results generally for anal fistula treatment and particularly for CD patients. To the best of our knowledge, this is the study with the highest number of patients in total and with CD patients in particular on this subject.

Conclusions

Patients with Crohn's disease often present with complicated anal fistulas. However, the healing rate after rectal advancement flap is the same as that of patients with cryptoglandular fistulas.

List Of Abbreviations

CD	-	Crohn's disease
CI	-	Confidence interval
LIFT	-	Ligation of intersphincteric fistula tract
ASA	-	American Society of Anesthesiologists score
BMI	-	Body mass index
MNAR	-	Missing not at random

Declarations

Ethics approval and consent to participate: The study protocol was approved by the Ethics Committee of the Charité – Universitätsmedizin Berlin (EA4/149/20). Since this is a retrospective study, a written declaration of consent from the patient based on the legal basis of Section 25 of the State Hospital Law (LKG Berlin) is not required. This was approved by the Ethics Committee of the Charité – Universitätsmedizin Berlin (EA4/149/20). This study was performed in accordance with the Declaration of Helsinki.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analyzed 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: The idea and initial findings were made by IP, CS and CH. Data acquisition, analysis and interpretation were done by CS and KSL with input from all authors. During writing this manuscript by CS and KSL, IP and CH were involved in constant discussions and improvements of manuscript. All authors read and approved the final manuscript.

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Figures

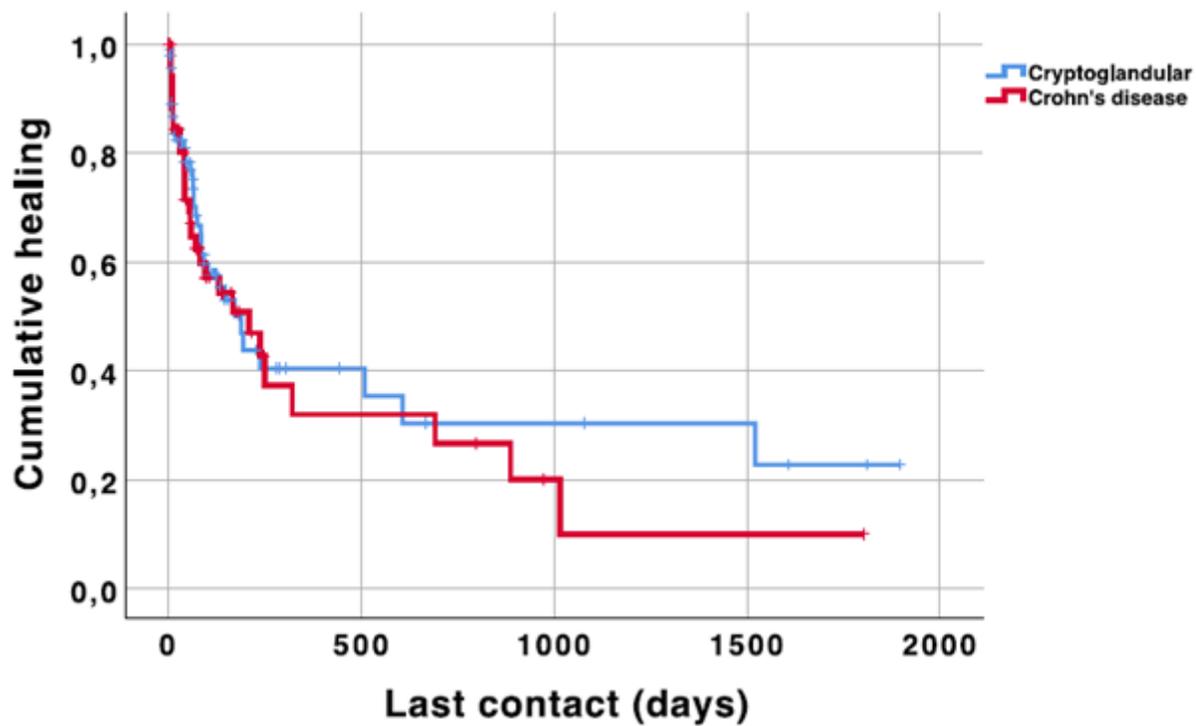


Figure 1

Kaplan-Meier estimates for fistula healing.