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ABSTRACT

Aim: Rectal flap advancement is still a part of therapeutic management of anal fistulas. Data on the outcome of rectal flap advancement in patients with Crohn's Disease (CD) is scarce. Our objective was to ascertain rates of failure of rectal flap advancement and to determine predictive factors for failure, with a special focus on CD.

Method: The patients details, the characteristics of the fistula and the main clinical and therapeutic events were prospectively assessed among patients who underwent rectal flap advancement. All patients had a partial-thickness rectal flap advancement. Failure of primary rectal flap advancement was defined as the occurrence at least one of the following items: abscess, discharge, visible external opening, further drainage procedure. The rates of failure of rectal flap and the predictive factors of failure were assessed.

Results: Eighty-seven patients (34 patients with Crohn's disease) were included. The median [IQR] follow-up was 13.3 [3.8-38.1] months. The cumulative failure rates were 15.9% [10.3-23.6], 23.0% [16.0-31.8], 31.6% [22.9-41.8] and 41.3% [30.5-53.0] at 3, 6, 12 and 24 months respectively. These data were comparable in Crohn's patients. Those with a supralevator fistula (HR= 2.53 [1.01-7.71], p= 0.0476) and patients who had fewer than 2 fistula drainages before rectal flap (HR= 3.19 [1.40-8.23], p= 0.005) were associated with higher rectal flap

failure rates. In Crohn's disease patients, the absence of biological therapy at referral was predictive of failure.

Conclusions: Rectal flap advancement is a satisfactory option for the therapeutic management of anal fistula, including Crohn's disease populations. Fistula drainage is needed before performing this surgical technique

What does this paper add to literature?

This paper adds a precise estimate (34%) of failure of rectal flap advancement for anal fistula. This proportion was comparable between patients with and without Crohn's Disease. Analyses highlighted that efficient fistula drainage is needed before performing this surgical technique.

INTRODUCTION

The therapeutic management of complex anal fistulas is challenging, particularly in the presence of Crohn's disease (CD). Surgical treatment options a fistula plug, fibrin glue injection or ligation of the intersphincteric fistula tract [1]. Rectal flap advancement is one of the sphincter-sparing techniques. The superiority of rectal flap advancement compared to an anal plug has been shown in two randomized controlled trials [2,3]. Advancement flaps were first described by Noble in 1902 and modified in 1912 [4] and 1948 [5]. The rates of failure vary from 0 to 47.2% [6]. This discrepancy could result from differences in technique, anatomy, evaluation of outcomes and duration of follow-up. Data on the effectiveness of rectal flap advancement in patients with CD are scarce[7−10]. However, anal fistulas in CD are commonly higher and can be more complex than the more common fistulas of

cryptoglandular origin. Assessment of rectal flap advancement in treatment of fistulising perianal CD could therefore provide useful information.

The aim of the present study was thus to determine the rates of failure of rectal flap advancement for anal fistula and to identify predictive factors, with a special focus on CD.

METHODS

Study Population

All prospective relevant data recorded between January 2006 and July 2017 in our proctology unit data base were reviewed. Consecutive patients who underwent rectal flap advancement during this period were included. The rectal flap advancement was proposed to patients who had a large internal orifice or who were in failure of sphincter saving strategy (collagen plug, fibrin glue injection or ligation of the intersphincteric fistula tract). The following data were recorded: gender, age, obesity, smoking habits, past medical and surgical history including sphincter-sparing surgery (fibrin glue, collagen plug, ligation of the intersphincteric fistula tract) and fistula drainage. Obesity was defined by a Body Mass Index (BMI) $\geq$ 30 kg/m^2. The characteristics of the fistula were assessed and recorded on the day of the rectal flap procedure. Complex fistulas were defined as deep trans-sphincteric fistulas, supralevator fistulas, fistulas with associated abscess formation or secondary tracks, anovaginal fistulas or horseshoe fistulas. The rest were defined as simple. Other characteristics which were recorded included if there was an infra or supralevator fistula, horsehoe fistula or an anovaginal fistula. Supralevator fistula were all fistula with a primary track extending into supralevator space . In patients with Crohn's disease (CD), the following data were recorded : age at diagnosis, luminal CD phenotype according to the Montreal classification at diagnosis [11], treatments (including immuno-suppressants, TNFα antagonists), surgery (including ileal and/or colonic resection, stoma), anatomical classification of perianal CD according to the

Cardiff-Hughes classification [12], CD activity using the Harvey-Bradshaw Index [13] (HBI) and perineal activity with the Perineal Disease Activity Index (PDAI)[14].

Surgical Technique

The patients were admitted on the day of the intervention and received preoperative prophylaxis (metronidazole 1000 mg) orally, according to the French recommendations. With the patient in Lloyd Davis position, the external opening was enlarged and the fistulous tract was excised as far as possible without reaching the external sphincter. The internal opening of the fistula was excised. Two to three stitches provided a plication of the muscle, facing and occluding the internal opening. Then, the submucosal area was dissected to create a flap with a button hole shape. The plicated muscle was covered with the mucosal flap thus produced. All stitches were performed with dissolvable sutures. The occlusion of the track was verified at the end of the procedure injecting a fluid. The patients were discharged on the day of the procedure. The rectal flap advancements were performed by two surgeons (LS : 85% and TW : 15%). There was no prior bowel preparation but analgesics and softeners stools were used on the postoperative period (3 weeks).

After a minimum follow-up of 12 weeks, the failure of rectal flap advancement was defined as the occurrence at least one of the following items: abscess, purulent discharge, visible external opening or further drainage procedure.

At each visit, a medical assessment with clinical examination was conducted. In CD patients, medical therapeutic interventions were recorded (introduction or optimization of immunosuppressant/biological therapy).

In patients for whom the rectal flap procedure failed, therapeutic interventions during the follow-up were recorded, including fistula drainage, fistulotomy, second rectal flap advancement or ligation of the intersphincteric fistula tract.

Follow-up was defined as the duration between the day of the first rectal flap procedure and the first assessment of rectal flap failure or the last visit for patients for whom the procedure was successful.

Statistical analysis

Quantitative variables are presented as medians and percentiles (interquartile range: 25% and 75%). Categorical variables are presented as numbers and percentage of the cohort. The main outcome was the sustained healing of the fistula tract. For continuous variable, cut-off values were determined by the median. The median number of drainage procedures was 1 and we chose the cut off of 2, being more clinically relevant. The cumulate probabilities of failure of rectal flap advancement were estimated from the first rectal flap procedure (at referral) to the occurrence of failure using the Kaplan–Meier method with 95% confidence intervals [CIs]. To identify factors associated with failure of rectal flap advancement, first a univariate analysis was performed using the log-rank test. Then, we used a Cox model to present the results as hazard ratios (HRs) with 95% confidence intervals [CIs]. To identify independent predictors of each outcome by multivariate analysis, all significant and independent variables with p-values <0.1 in the log-rank test were retained and integrated into a Cox proportional hazards regression model for failure of rectal flap advancement. The results are shown as hazard ratios (HRs) with 95% confidence intervals [CIs]. No multivariate analysis was performed in the CD population on account of the small size of this subgroup. Statistical analyses were performed using JMP Pro 10.0.0 software.

Ethical considerations

This study was approved by the "Commission Nationale Informatique et Liberté" (CNIL n°1412467).

RESULTS

Study population at baseline

602 patients with anal fistulas identified from the prospective database, 202 (33.6%) with Crohn's. 87 patients from this group underwent one rectal anal flap advancement, 34 (39.1%) with Crohn's. The characteristics of the population are summarized in **Table 1**. The fistula tracts were complex in 78 cases (89.8%) and supralevator in 63 cases (72.4%). Rectovaginal or anovulvar tract fistulas were reported in 19/52 women (36.5%). 36 patients, (41.4 %) had horseshoe fistulas. All patients had drainage using seton prior to the flap. At referral, the median duration between the last surgical drainage and the rectal flap procedure was 5.8 [3.9-10.4] months; 32 patients (37.7%) had had more than 2 fistula drainages and 24 (27.6%) had had previous sphincter-sparing surgery. Among these 24 patients, 9 had had occlusion of the tract with fibrin glue and 3 with fistula plug.

The characteristics of the CD patients (median age: 39.6 [27.5-46.9] years) are summarized in **Table 2**. At referral, median CD duration was 83.9 [36.6-162.4] months and median duration between the last surgical drainage and the rectal flap procedure was 6.0 [4.0-11.1] months. No patient had ulceration or rectal inflammation. Median HBI and median PDAI were 1.5 [1-3.3] and 5 [3-7] respectively. Only 3 patients (8.8%) had HBI >4: 29 patients had biological therapy (85.3%) and 11 had combination therapy (33.3%) at referral. Among the 5/34 (14.7%) with CD who were not on biological therapy, 2 were on thiopurines, 1 patient had active neoplasia and 2 patients refused biological therapy.

Follow-up evaluation

The median follow-up after referral was 13.3 [3.8-38.1] months. The overall failure rate is quantified and illustrated in **Figure 1**. The cumulate failure rates were 15.9% [10.3-23.6], 23.0% [16.0-31.8], 31.6% [22.9-41.8] and 41.3% [30.5-53.0] at 3, 6, 12 and 24 months

respectively. To date, failure of rectal flap advancement has been observed in 34.1% (N=29) of the overall population and in 33.3% (N=11) of the CD population. The characteristics of patients with and without failure of the rectal flap procedure are reported in **Table 1** (overall population) and **Table 2** (CD population).

Figure 2 illustrates the following variables that were associated with significantly higher failure rates in the overall population (univariate analyses). These were no past history of sphincter-sparing surgery, horseshoe fistula, supralevator fistula and fewer than 2 fistula drainages before rectal flap advancement. In a multivariate analysis including horseshoe fistula, supralevator fistula and fewer than 2 fistula drainages before rectal flap advancement, the factors significantly associated with failure of rectal flap advancement in the overall population were supralevator fistula (HR= 2.53 [1.01-7.71], p= 0.0476), and fewer than 2 fistula drainages before rectal flap advancement (HR= 3.19 [1.40-8.23], p= 0.005). In CD patients, the absence of biological therapy at referral was the only factor associated with failure of rectal flap procedure in univariate analysis (**Table 2**).

Among the 29 patients for whom the procedure failed, 9 patients underwent at least one further rectal flap advancement, and failure of the procedure was observed in 7 patients. Among the remaining 22 patients where the procedure failed, 15 (51.7%) had a further fistula drainage, 4 (13.8%) had a intersphincteric ligation of the tract and 3 (10.3%) had fistulotomy. According to the most recent information, the fistula healed in 70 (80.5%) patients and 17 (19.5%) had a persistent fistula.

DISCUSSION

The present study quantified the failure rate and assessed predictive factors for failure of rectal flap advancement in patients suffering from anal fistulas. Approximately one third had primary failure. This proportion was comparable between patients with and without CD. The anatomy of the fistula was the most important factor predicting success or failure.

The main strengths of this work are the sample size, the systematic clinical evaluation and that the surgery were performed by a small group of surgeons experts in the field of proctology . These data was recorded in a prospective database using recommended classifications and validated scales [13,14]. In CD patients, disease characteristics and both therapeutic and surgical strategies were recorded.

However, this study has several limitations. The study design was a retrospective analysis of a prospective database. Because this study was performed in a tertiary referral centre, the recruitment of patients might have resulted in selection bias. Magnetic resonance imaging (MRI) was not performed for all consecutive patients so that this data could not be assessed. The median follow-up was 13 months, which while longer than other studies, might be an under-estimate of a much higher failure rate in the longer term. Finally, faecal incontinence was not assessed.

The failure rate for rectal flap advancement reported in our cohort is comparable with some data in the literature [9,15–18]. In a recent meta-analysis [6], the pooled failure rate for rectal flap advancement was 21%, with better results in case of full-thickness flap (7.4%) than for partial-thickness flap (19%). In our study, the surgeons performed partial thickness flap and the failure rate was higher (34.1%) than that reported by the meta-analysis. The anal fistulas

were mainly complex fistulas (89.8%) and/or horseshoe fistulas (41.4%) in the present study. These factors have been described as predictive of failure [19]. In studies including complex fistulas [16,19], the failure rates were comparable to ours. Differences between published series could be explained by the fact that the analysis concerned a single surgical procedure in the present work while the other studies enrolled patients who underwent several subsequent rectal flap advancements.

Our study highlighted the fact that anatomical features of the anal fistula, which included horseshoe fistulas and supralevator fistulas, were associated with the failure of the procedure. This contrasts with a previous study [17], which concluded that the complexity of the fistula was not predictive of failure of rectal flap advancement. However, this study excluded CD patients and patients with rectovaginal fistulas, thus not taking into account patient characteristics that have been reported as predictive of failure. Another report was in line with the present study [19] but the size of the cohort was small. Given that unresolved sepsis is a common cause of flap failure and that complex fistulas need more frequent drainage interventions, effective fistula drainage with several interventions is therefore needed to avoid rectal flap failure. These considerations are in line with the identification of the factor "fewer than 2 fistula drainages" as being predictive of failure. In our opinion, efficient fistula drainage needs to be ascertained before performing this technique. In this field, MRI assessment could be the optimal evaluation prior to rectal flap advancement.

It has been reported that smoking [16] and obesity [20] are predictive factors associated with failure of rectal flap advancement. Neither of these two factors was identified as predictive of failure in the present study. The number of obese patients was small in our study (N=6; 6.9%), especially among CD patients (N=1; 2.9%), which could explain in part why obesity was not associated with rectal flap failure.

Importantly, the failure rate for rectal flap advancement was comparable in patients with and without CD. This contrasts with previous studies [7,9] that concluded that patients with CD had lower healing rates. However, the statistical methods were not detailed in these studies and the endpoint was overall healing and not primary healing. In fact, very few studies have included CD patients. Joo et al [10] identified small intestine localisation as a factor predictive of failure. But biological therapy and disease activity were not assessed. The present study suggests that biological therapy impacts rectal flap outcome. This data highlights the importance of the combined approach (medical and surgical) in perianal CD.

Certain questions remain unanswered. In order to improve the therapeutic management of perianal CD, randomized studies comparing rectal flap advancement and other sphincter-sparing techniques, including medical treatments are needed, as are evaluations of fecal incontinence. Studies evaluating therapeutic combinations in perianal CD would be useful. Innovative treatments such as stem cell injections deserve to be compared to techniques such as the advancement flap. A recent study [2] promotes the advancement flap over new minimally invasive strategies.

In conclusion, rectal flap advancement remains a good sphincter-sparing treatment, both in CD and in the general population. Anatomical features of the anal fistula could affect the failure rate of rectal flap advancement (supralevator and insufficiently drained fistulas, absence of biological therapy in CD) and this requires careful pre-operative evaluation.

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Table 1: Characteristics of study group (N=87) at referral and univariate analyse (log rank) to identify items associated with failure

	All population N=87 n (%) or median [IQR 25-75]	Healing fistula N=58 n (%) or median [IQR 25-75]	Failure N=29 n (%) or median [IQR 25-75]	p-value (log rank)
General characteristics				
Sex ratio (Female)	52 (59.8)	33 (56.9)	19 (65.5)	0.45
Age	43.7 [34.3-54.4]	44.8 [34.1-57.9]	41.1[39.5-49.4]	0.30
Obesity (yes)	6 (6.9)	5 (8.6)	1 (3.4)	0.47
Crohn disease (yes)	34 (39.1)	23 (39.7)	11 (37.9)	0.56
Smoking	32 (36.8)	21 (36.2)	11 (37.9)	0.47
Smoker	11 (12.6)	9 (15.5)	2 (6.9)	
Former smoker	44 (50.6)	28 (48.3)	16 (55.2)	
No smoker				
Characteristics of the fistula				
Simple/Complex	9/78 (10.2/89.8)	8/58 (13.8/86.2)	1/28 (3.4/96.6)	0.09
Infra/ Supralevator	24/63 (27.6/72.4)	19/39 (32.8/67.2)	5/24 (17.2/82.8)	0.08
Horseshoe (yes)	36 (41.4)	20 (34.4)	16 (55.2)	0.07
Recto/ano vaginal fistula (yes)	19 (35.5)	10 (30.3)	9 (47.4)	0.15
Anal surgery				
≥ 2 fistula drainages before rectal flap	32 (37.7)	26 (44.8)	7 (24.1)	0.04
Sphincter sparing surgery before rectal flap	24 (27.6)	19 (32.7)	5 (17.2)	0.09

Table 2: Characteristics of population with Crohn's disease (N=34), patients with fistula healing and patients with failure of rectal flap advancement and univariate analyse (log rank)

	Population with Crohn disease N=34 n (%) or median [IQR 25-75]	Failure N= 11 (33.3) n (%) or median [IQR 25-75]	Healing fistula N= 23 (66.7) n (%) or median [IQR 25-75]	p-value (log rank)
General status				
Sex ratio (Female)	23 (67.6)	9 (81.8)	14 (60.9)	0.34
Age	39.6 [27.5-46.9]	41.1 [33.8-48.9]	34.6 [23.8-46.9]	0.47
Obesity (yes)	1 (2.9)	0 (0)	1 (4.3)	0.56
Smoking				0.96
Smoker	12 (35.3)	4 (36.3)	8 (34.8)	
Former smoker	7 (20.6)	2 (18.2)	5 (21.7)	
No smoker	15 (44.1)	5 (45.5)	10 (43.5)	
Luminal disease (Montreal classification)				
A1/A2/A3	4/24/6 (11.8/70.6/17.6)	1/9/1 (9.1/81.2/9.1)	3/15/5 (13.0/65.3/21.7)	0.71
B1/B2/B3	26/1/7 (76.5/2.9/20.6)	8/1/2 (72.2/9.1/18.2)	18/0/5 (78.3/0/21.7)	0.44
L0/L1/L2/L3	2/6/13/12 (5.9/17.7/38.3/35.3)	2/1/6/2 (18.2/9.1/54.5/18.2)	5/7/10/1 (21.7/30.5/43.5/4.3)	0.11
Previous surgical intestinal resection	8 (23.5)	4 (36.4)	4 (17.4)	0.14
Crohn's disease duration	84.0 [36.6-162.4]	86.7 [42.6-279.8]	74.1 [25.5-135.2]	0.12
HB > 4	3 (8.8)	2 (18.2)	1 (4.4)	0.26
Peri anal disease (day of rectal flap)				
PDAI > 5	15 (44.1)	7 (63.6)	8 (34.8)	0.12
Stricture (yes)	5 (14.7)	2 (18.2)	3 (13.0)	0.73
Simple/Complex	2/32 (5.9/94.1)	0/11 (0/100.0)	2/21 (8.7/91.3)	0.27
Infra/ Supralevator	7/27 (20.6/79.4)	1/10 (9.1/90.9)	6/17 (26.1/73.9)	0.17
Horseshoe (yes)	15 (44.1)	6 (54.5)	9 (39.1)	0.54
Recto/ano vaginal fistula (yes)	8 (34.8)	4 (44.4)	4 (28.6)	0.45
Biological therapeutic & thiopurines				

Anti TNF alpha				
. before the rectal flap	29 (85.3)	7 (63.6)	22 (95.7)	0.0122
. introduced-optimized (day of rectal flap)	8 (24.2)	2 (20.0)	6 (26.1)	0.67
Thiopurines				
. before rectal flap	21 (36.7)	2 (20.0)	10 (43.5)	0.35
Combotherapy	11 (33.3)	1 (10.0)	10 (43.5)	0.16
Anal surgery				
≥ 2 fistula drainages before rectal flap	15 (44.1)	3 (27.3)	12 (52.2)	0.13
Sphincter sparing surgery before rectal flap	12 (35.3)	3 (27.3)	9 (39.1)	0.22

HB: Harvey Bradshaw score; PDAI: perineal disease activity index;

Figure 1: The cumulate probabilities of failure rate were 15.9% [10.3-23.6], 23.0% [16.0-31.8], 31.6% [22.9-41.8] and 41.3% [30.5-53.0] at 3, 6, 12 and 24 months respectively.
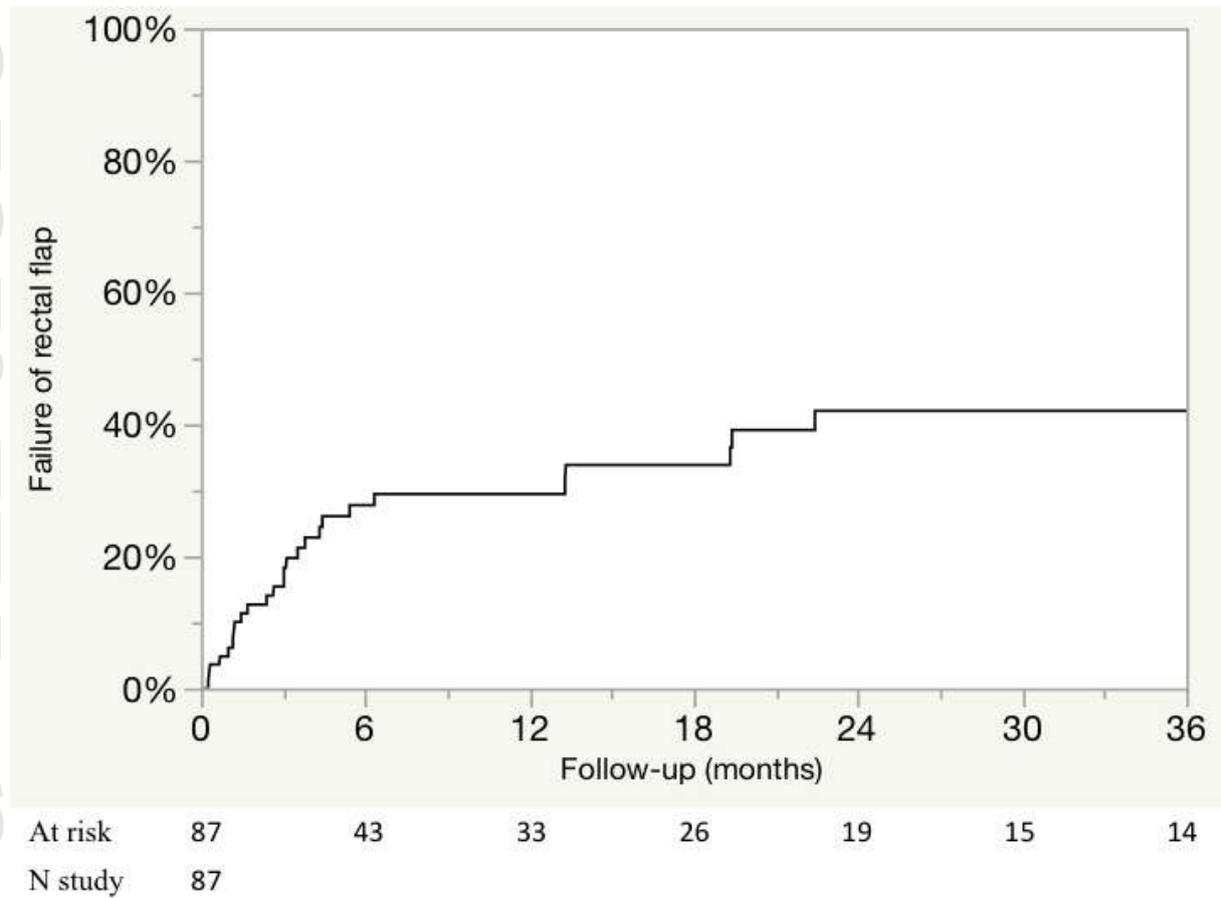
Figure 2: Factors associated with significantly higher failure rates (univariate analyses and Log rank tests). Patients with no past history of sphincter-sparing surgery (A), and those with horseshoe fistula (B), supralevator fistula (C) and fewer than 2 fistula drainages before rectal flap advancement (D) had significantly higher rectal flap advancement failure rate.