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ORIGINAL ARTICLE

Long-term outcomes of a bioactive matrix enriched with an autologous platelet concentrate for the treatment of complex anal fistulae

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Abstract

Background Treating complex anal fistulae (CAF) remains a clinical challenge. Regenerative fistula treatment (RFT) with a bioactive matrix enriched with autologous platelet concentrate (Obsidian RFT®) has shown potential in healing CAF while preserving continence, but its long-term efficacy is still debated. This study aims to report the outcomes of RFT in patients with CAF.

Methods A retrospective analysis of a prospective database of patients with CAF treated with RFT between February 2021 and November 2023 at a single center was conducted. Patients were included if they completed at least a 6-month follow-up. The primary outcome was fistula healing at last available follow-up. Secondary outcomes included unscheduled reoperation and anorectal function.

Results A total of 31 patients were treated with Obsidian RFT, 17 of whom completed the 6-month follow-up. Nine of the patients were women. The median age was 47 (24–63) years, and eight had inflammatory bowel disease. High transsphincteric fistulae were observed in 52.9% of patients. At a median follow-up of 21.8 (8–36) months, a 53% success rate was achieved. Approximately half of patients required at least one additional procedure owing to CAF persistence or recurrence. There were no reports of morbidity or mortality, and no worsening of continence was observed.

Conclusions This pilot study demonstrated that nearly half of the patients treated with RFT for CAF achieved long-term healing, with no adverse effects on continence and an excellent safety profile. Larger studies are needed to draw definitive conclusions.

Keywords Complex anal fistulae · Regenerative fistula treatment · Complications · Continence

Introduction

Complex anal fistulae (CAF), both idiopathic and occurring in the context of inflammatory bowel diseases (IBD), still represent an unresolved challenge regarding the most appropriate surgical treatment options [1, 2].

This choice should consider many variables: the anatomy of the fistula, the underlying cause, and the proportion of the sphincter muscle component involved in the pathology [1, 3]. However, surgical treatment of CAF is still associated with high recurrence rates and carries high risk of complications, especially in women and in anterior fistulae [2, 4–6].

The surgical approach to CAF is most often performed in steps, consisting of the placement of a loose seton and subsequent definitive surgical treatment. This approach allows the surgeon to set up an initial control/elimination of the acute sepsis and defers the removal of any chronic granulation tissue until later [4]. Among the most used surgical treatments, fistulotomy achieves the highest cure rates, but it brings about a higher risk of worsening incontinence or the onset of de novo incontinence (in up to 10% of cases) [7]. Advancement flaps represent a viable option for CAF, but success rates range from 40% to 80% [7–11]. Even with these procedures, continence disturbances remain a potential complication, with an estimated occurrence rate of around 20% [7].

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To prevent postoperative continence disturbances and complications, several minimally invasive techniques have been proposed, including ligation of the intersphincteric fistula tract (LIFT), fibrin glue injection, video-assisted anal fistula treatment (VAAFT), fistula laser closure (FiLaC), and the placement of acellular dermal matrix (ADM). These treatments aim to combine a good cure rate with preservation of sphincter function, with success rates ranging between 12.5% and 88% [5, 8, 9, 12–18]. However, few studies have reported the long-term outcomes of such procedures.

Biocompatible materials offer a new treatment option for CAF. Among them, regenerative fistula treatment (RFT) with the Obsidian RFT® matrix has been proposed, which consists of a bioactive, 100% autologous matrix that incorporates both platelets and concentrated growth factors. These components activate and protect thrombocytes from potential damage, thereby promoting soft, connective, and vascular tissue regeneration. Therefore, it is indicated for the treatment of extrasphincteric, intersphincteric, transsphincteric, and suprasphincteric fistulae. [19–23]. The Obsidian RFT® is activated locally upon application in the fistula track, facilitated by the natural proteolytic absorption of the matrix. This activation process typically spans over a period of 4–7 days, during which continuous stimulations promote the healing process. This treatment is compatible with various surgical approaches and can be combined with other local interventions. It is characterized by simplicity and ease of use, and in addition, respects the anatomy and physiology of the anal canal. [19–23]. However, there is a need for long-term outcome data and assessment of the safety of this procedure.

The objective of this study is to assess the long-term healing rates of CAF treated with RFT and to identify any associated complications and effects on continence.

Methods

This pilot study, conducted at a single center, involved a retrospective analysis of patients with CAF treated at Vall d'Hebron University Hospital, Barcelona, Spain, whose data were extracted from a prospectively maintained database. The study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [23].

Inclusion and exclusion criteria

All patients with CAF who underwent RFT surgery with an autologous bioactive matrix (Obsidian RFT®) between February 2021 and June 2024 were evaluated for inclusion.

Inclusion criteria included: diagnosis of CAF, age above 18 years at the time of surgery, having undergone at least one prior surgical procedure for perianal sepsis, and having completed a follow-up period of at least 6 months. Patients with simple anal fistulae and who did not complete at least 6-month follow-up were excluded.

In patients with active IBD, it is essential to first address the endoluminal disease with medical treatment while placing a loose seton on the fistula tract.

Second, when the inflammatory disease is well controlled, the seton is removed. If the fistula continues being symptomatic with active suppuration after 3 months, then RFT could be considered in these patients.

Definitions

Patients underwent endoanal ultrasound and/or magnetic resonance imaging (MRI), and CAF were described according to Park's classification. Fistulae were defined as "complex" if they were high or middle transsphincteric, suprasphincteric, extrasphincteric, or rectovaginal.

Disease persistence was defined as persistence of discharge or symptoms of perianal sepsis after surgery. Clinical recurrence was defined as the presence, upon clinical examination, of any perianal suppuration at gentle compression. Continence disturbance was defined as the occurrence of flatus or liquid or solid accidents after RFT treatment in patients who were continent before treatment, or as worsening of continence compared to baseline.

Endpoints and outcome measures

The primary endpoint was defined as clinical fistula healing, indicated by the absence of discharge at last available follow-up visit. The number of patients with clinically active CAF served as the outcome measure. Secondary endpoints encompassed adverse events associated with RFT, need for additional surgery, impact on continence, and identification of factors associated with recurrence.

Surgical technique and RFT treatment

Prior to definitive surgery, patients undergo an examination under anaesthesia (EUA) to assess the fistula's anatomy. A loose seton is inserted on the CAF tract and remains in place for 4–6 weeks before RFT treatment. No bowel preparation nor enemas are administered before RFT treatment. The procedure is conducted under epidural anesthesia. Patients are positioned in lithotomy position for posterior CAF and in prone position for anterior CAF. Aqueous chlorhexidine is used for perianal antisepsis.

The loose seton is removed, and a fistula brush is employed to clean and debride the fistula tract. The tract is flushed with saline solution (37 °C), and debridement is repeated as necessary. Following each debridement, the

tract is flushed again. Then, the internal orifice of the CAF is closed by a Z-suture and RFT is applied.

The procedure comprises the following steps: (1) the internal CAF orifice is closed with a Z-suture; (2) saline irrigation is conducted through the external CAF orifice to ensure no leakage from the internal CAF orifice is detected; (3) the suture is then loosened, and the Obsidian RFT endoscopic catheter is inserted through the external CAF orifice, reaching the internal orifice; RFT is applied continuously while slowly retracting the catheter using the "Jet No Air" setting; (4) the Z-suture is tied, and any remaining RFT is injected around the closure of the internal CAF orifice; and (5) the external CAF orifice is left open.

The procedure is shown in Fig. 1 and Supplementary Video 1.

Postoperative management and follow-up schedule

After undergoing RFT treatment, patients are provided with post-procedural instructions to ensure optimal recovery. These include avoiding strenuous activities for 1 week following surgery and using analgesics as needed for perianal discomfort for up to 3 days.

The first follow-up appointment is scheduled 15 days after surgery. A second follow-up appointment occurs another 15 days later. Subsequent follow-up appointments are scheduled every 3 months during the first year post-surgery,

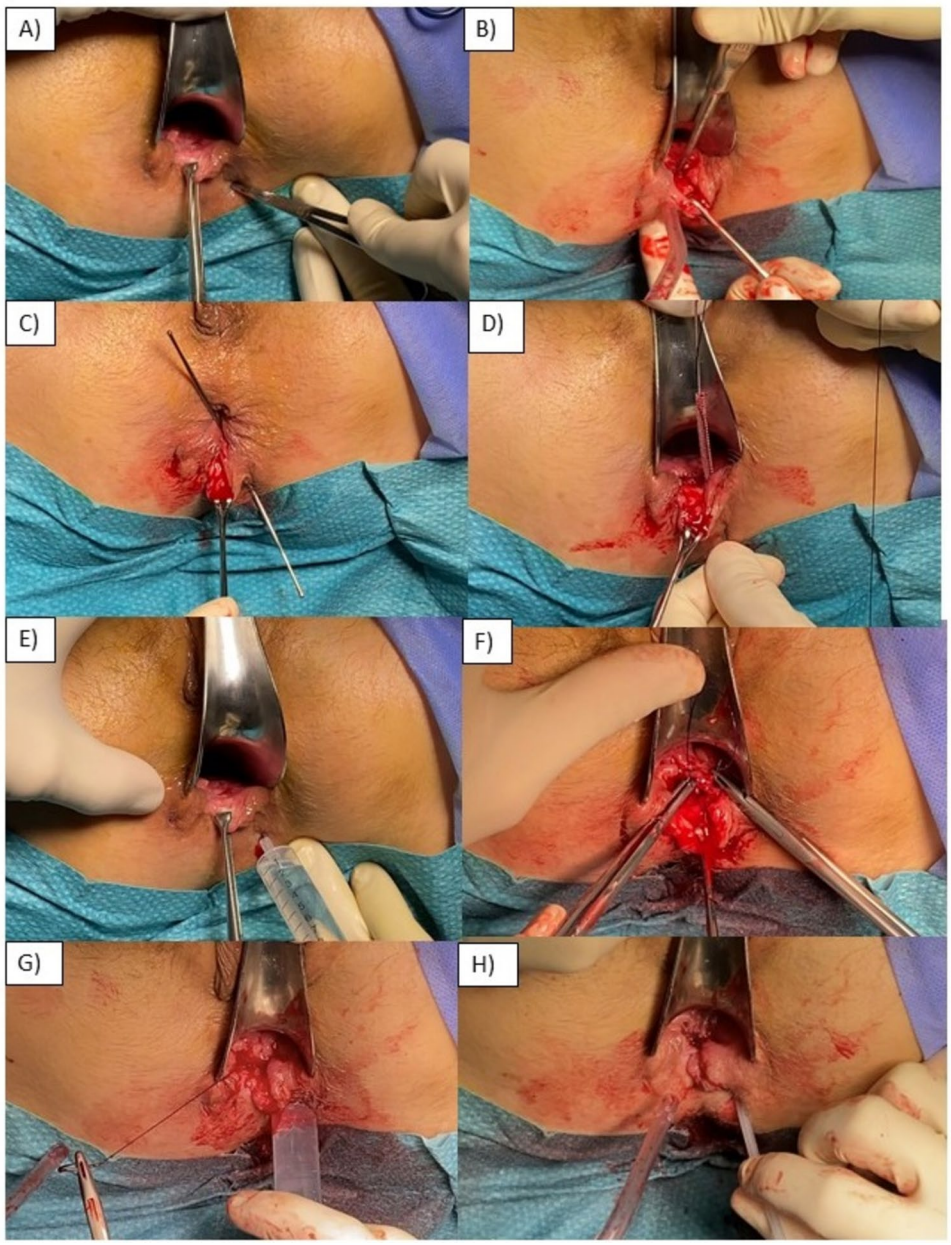

Fig. 1 Surgical procedure. **A** Overview of the fistula tract. **B** Debridement of the internal orifice. **C** Placement of a stylet through the tract. **D** Insertion of a fistula brush to clean and debride fistula tracts with back-and-forth motion (×20). **E** Cleaning the fistula tract with saline solution (37 °C). **F** Application of a Z-suture on the internal orifice. **G** Confirmation of no fluid leakage from the internal orifice and ensuring the suture is securely tightened. **H** Insertion of the RFT applicator from the external orifice to the intraluminal proximal fistula ostium while slowly retracting the catheter

provided that both previous appointments show satisfactory progress. After the first year, follow-up visits are scheduled at 18 and 24 months, with no further appointments thereafter.

All the follow-up and clinical assessment are made by the same surgeon, a specialist in colorectal inflammatory disease surgical treatment in Vall d'Hebron University Hospital.

Ethics

This study adhered to the principles outlined in the Declaration of Helsinki and received approval from the local Ethical Committee. Prior to undergoing the procedure, all patients provided written informed consent.

Statistical analysis

Continuous variables are reported as medians with ranges, while categorical values are expressed as absolute numbers with corresponding percentages.

Results

A total of 31 patients with CAF underwent surgery with RFT in the study period, of whom 17 completed the 6-month follow-up and were included in the analysis (Fig. 2). Among them, nine patients (53%) were women. The median age at the time of surgery was 47 (24–63) years.

Population characteristics and previous procedures

Among the cohort, nine patients (52.9%) presented with a high transsphincteric fistula, while seven (41.2%) had a middle transsphincteric fistula, and one (5.8%) had a rectovaginal fistula. Anterior CAF were observed in 12 patients (70.5%), with the remaining 29.4% presenting posterior CAF ($n=5$). Four patients (23.5%) were current smokers, and one (5.8%) was a former smoker. A summary of patient characteristics is provided in Table 1.

Additionally, eight patients (47%) had an underlying inflammatory bowel disease, with six diagnosed with Crohn's disease and two with ulcerative colitis.

Prior to RFT treatment, patients had undergone various procedures, including abscess debridement ($n=9$), acellular dermal matrix plug (PressFit, Biocablan S.L.) placement ($n=7$), advancement flap ($n=6$), porcine dermal collagen implant (Permacol, Medtronic Inc.) placement ($n=4$), ligation of the intersphincteric fistula tract (LIFT, $n=3$), stem cell treatment ($n=2$), Martius flap ($n=1$), endoluminal vacuum therapy (B. Braun Endo-SPONGE) ($n=1$), and sphincteroplasty ($n=1$). Notably, all patients had had more than one surgical procedure.

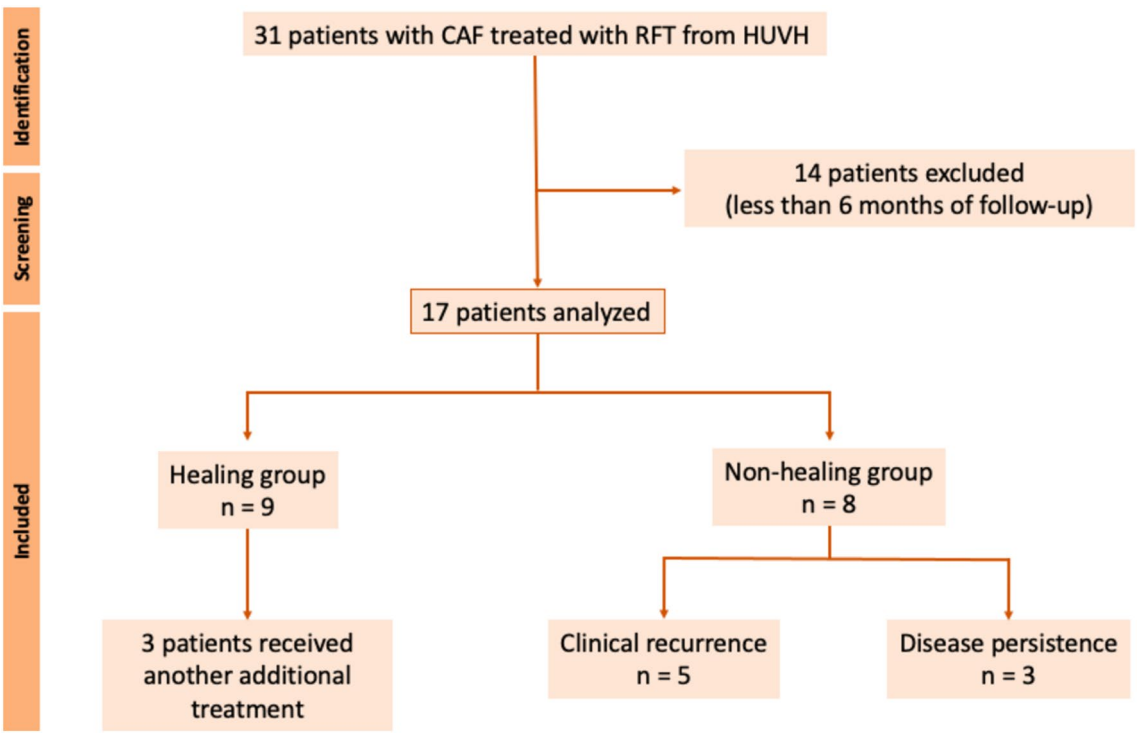

Fig. 2 Flowchart of patients included in the study

Table 1 Patient characteristics

Age, median (range years)	47 (24–63)
Sex, *n* (%)	9 F (53%)
	8 M (47%)
Inflammatory bowel disease, *n* (%)	Crohn's disease: 6 (35%)
	Ulcerative colitis: 2 (11.7%)
Smoking status *n*, (%)	Non-smoker: 12 (70%)
	Active smoker: 4 (23.5%)
	Ex – smoker: 1 (5.8%)
Fistula Park's classification *n*, (%)	Trans-sphincteric, high: 9 (52.9%)
	Trans-sphincteric, middle: 7 (41.2%)
	Rectovaginal fistula: 1 (5.8%)
Fistula location *n*, (%)	Anterior: 12 (70.5%)
	Posterior: 5 (29.4%)
Previous procedures for RFT *n*, (%)	Abscess debridement: 9 (52.9%)
	Pressfit placement: 7 (41.1%)
	Advancement flap: 6 (35.3%)
	Permacol placement: 4 (23.5%)
	LIFT: 3 (17.6%)
	Stem cells placement: 2 (11.7%)
	Martius flap: 1 (5.8%)
	Endosponge: 1 (5.8%)
	Sphincteroplasty: 1 (5.8%)
Additional procedures after RFT *n*, (%)	Loose-seton placement: 4 (23.5%)
	Permacol placement: 2 (11.7%)
	Pressfit placement: 1 (5.8%)
	Abscess debridement: 1 (5.8%)
	LIFT: 1 (5.8%)
	Sphincteroplasty: 1 (5.8%)
	Repeated RFT: 1 (5.8%)
	Advancement flap: 1 (5.8%)

F female, *LIFT* ligation of the intersphincteric fistula tract, *M* male, *RFT* regenerative fistula treatment

The median interval between the "preparation" surgery (seton placement) and RFT was 18.8 months (range 3–57 months). Except for one patient who underwent fistulotomy plus sphincteroplasty 4 months prior to RFT, none of the patients had a seton in place at the time of RFT treatment.

Primary outcome: fistula healing

The median follow-up period was 21.8 (8–36) months. The overall success rate of RFT treatment was 53% (9 patients). However, among the nine patients who achieved healing, three (17.6%) required at least one additional procedure following RFT.

The median time to treatment failure was 6.6 (1–20) months. Of the individuals in whom treatment failed (eight patients, 47%), three (17.6%) never achieved healing (disease persistence), while five (29.4%) experienced clinical recurrence after initially achieving healing.

Secondary outcomes

Following treatment, one patient required emergency drainage of a perianal abscess. However, no further complications were observed during the follow-up period, and there were no recorded deaths.

Eight patients needed at least one additional surgical procedure, including seton placement ($n=4$), porcine dermal collagen implant (Permacol® Medtronic Inc.) placement ($n=2$), acellular dermal matrix plug (PressFit®, Biocablan S.L.) placement ($n=1$), abscess debridement ($n=1$), LIFT ($n=1$), sphincteroplasty ($n=1$), repeated RFT ($n=1$), and an advancement flap ($n=1$). The median interval between RFT and repeated surgery was 9 (3–20) months, with no adverse events recorded during or after these procedures. No deterioration in continence was noted following RFT treatment at last available follow-up.

Baseline and fistula characteristics are compared in Tables 2 and 3.

Table 2 Baseline characteristics according to the outcome

Variable	Healing	No healing
Age, median (range), years	50 (33–61)	43,7 (24–63)
Sex, *n* (%)	6 M (35.3%)–3 F (17.6%)	2 M (11.8%)–6 F (35.3%)
Inflammatory bowel disease, *n* (%)	3 (33%)	5 (62.5%)
Immunosuppression, *n* (%)	3 (33%)	4 (50%)
Active smoker, *n* (%)	1 (11%)	3 (37.5%)
Diabetes mellitus, *n* (%)	2 (22%)	1 (12.5%)
Arterial hypertension, *n* (%)	4 (44%)	2 (25%)

F Female, *M* Male

Discussion

This study assessed the long-term outcomes following the treatment of CAF with RFT and found that the RFT technique has a healing rate of more than 50% at long-term follow-up, with no reported complications of function in the mid- and long-term, even in patients undergoing repeated surgical treatment.

Previous studies have reported healing rates for perianal fistulae ranging from 12.5% to 88% [5, 8, 9, 12–18]. The wide variation in healing rates may be attributed to several factors, including differences in the definition of "healing," the types of fistulae included in the study, and variations in the duration of follow-up (ranging from 1 week to 18 months).

We defined fistula healing as the absence of discharge at last available follow-up visit, with no need for radiological control, except for persistence or recurrence of symptoms. However, other authors suggest performing magnetic resonance imaging (MRI) in all patients after Crohn fistula treatment; in these cases, they defined fistula healing as the absence of a high-signal track on fat saturated T2 sequences, and improvement as a reduction in the number and volume of fistula and > 10% decrease in the MRI signal [24].

In this study, the overall success rate of RFT was 53% at a median follow-up of 21.8 months. Treatment failure, including 17.3% disease persistence and 29.4% clinical recurrence, occurred within a median time of 6.6 months post-treatment. Recurrence rates tended to increase with longer follow-up periods, emphasizing the importance of adequate follow-up duration to accurately assess recurrence rates. This is important because too short a follow-up period contributes to the phenomenon known in clinical medical research methodology as the "honeymoon period": pilot studies often report excellent results that need to be confirmed by studies with longer and more comprehensive follow-up protocols [25].

Owing to the small sample size, no definitive conclusions can be drawn regarding patient and fistula characteristics predictive of treatment failure. However, female sex, inflammatory bowel disease, and smoking habit seemed to impair healing, whereas patient age and cardiovascular disease did not (see Table 2).

Middle transsphincteric fistulae exhibited a slightly higher chance of healing (44.4% in the healing group versus 37.5% in the nonhealing group) compared with high suprasphincteric fistulae (55.6% in the healing group versus 62.5% in the nonhealing group). Additionally, shorter intervals between seton placement and surgery were associated with higher cure rates (14.7 months in the healed group versus 21.2 months in the nonhealed group; Table 3).

Wang et al., in their systematic review and meta-analysis on the use of platelet-rich plasma (PRP) for anal fistula treatment, reported an overall healing rate of 72.11% (95% CI 0.64–0.79). The cure rate of PRP alone was 62.39% (95% CI 0.55–0.69), while the combined cure rate of PRP with other treatments was 83.12% (95% CI 0.77–0.88). The complete cure rate across 8 studies was 66.37% (95% CI 0.52–0.79), with a recurrence rate of 14.84% (95% CI 0.08–0.24) in 12 studies [26]. In the current study, combined treatment modalities included abscess debridement (52.9%), acellular dermal matrix plug (PressFi®, Biocablan S.L.) placement (41.1%), and advanced flap (35.3%) administered as pre-PRF injection treatment. While none of these represent definitive treatment techniques for anal fistulae, their inclusion

Table 3 Comparison of fistula characteristics according to the outcome

Fistula characteristics	Healing group	Non-healing group
Time between seton placement and surgery, median (range) months	14.7 (3–39)	21.2 (4–57)
High trans-sphincteric and rectovaginal fistula, *n* (%)	5 (55.6%)	5 (62.5%)
Middle trans-sphincteric, *n* (%)	4 (44.4%)	3 (37.5%)
Anterior, *n* (%)	7 (77.8%)	5 (62.5%)
Posterior, *n* (%)	2 (22.2%)	3 (37.5%)
First-line treatment, *n* (%)	3 (33.3%)	2 (25%)
Recurrent fistula, *n* (%)	6 (66.6%)	6 (75%)

may lead to an overestimation of RFT success owing to the synergistic effects of combined approaches.

Study limitations and strengths

This retrospective analysis lacks a control group, posing limitations to the study. Additionally, the small sample size makes it challenging to draw definitive conclusions. Another limitation is that all patients in the study group underwent surgical treatment before receiving Obsidian RFT® injections, potentially influencing the outcome.

One major drawback of RFT is its cost, as it is a more expensive option compared with conventional techniques such as fistulotomy, fistulectomy, advancement flap, or LIFT, which do not require special materials or devices. However, RFT was not associated with short- or long-term morbidity. Moreover, the improvement in patient well-being, independent of CAF healing, suggests potential long-term value in reducing secondary costs.

This study has the advantage of being conducted in a group of patients followed by a surgical team specialized in the treatment of perianal pathology, with expertise in minimally invasive CAF treatment. This allowed for the management patients with rigorous and standardized pathways in the perioperative phase and enabled the surgical team to establish an homogeneous and replicable long-term postoperative follow-up.

Conclusions

This study demonstrated that clinical healing can be achieved in over half of patients with CAF using RFT following previous surgical treatment, with no reported adverse events and no impact on continence.

It is essential to conduct follow-up assessments for at least 6 months post-surgery, and future studies should aim for a 12-month follow-up to provide a more comprehensive understanding of treatment outcomes.

While the findings of this study are reassuring and encouraging, they must be interpreted within the context of the high failure rate of any CAF and the significant risk of continence disturbances. Therefore, larger studies with adequate follow-up periods are necessary before definitive conclusions can be drawn. Nonetheless, the information provided here will be invaluable at the time of discussing CAF surgery with patients, allowing the establishment of realistic expectations and providing reassurance regarding the minor long-term impact on function.

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Author contribution Dr. Maya and Dr. Spada made the research and wrote the manuscript. Dr. Cirera translated the manuscript to English. Dr. Maya and Dr. Cirera prepared figures and tables. Dr. Maya recorded the surgical procedure and created the supplementary video. Dr. Pellino, Dr. Espín, and Dr. Martí reviewed the manuscript.

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Data availability No datasets were generated or analyzed during the current study.

Declarations

Conflict of interest The authors declare no conflict of interests in relation with this manuscript.

Ethical approval This study complied with the Declaration of Helsinki. All patients provided written informed consent before undergoing the surgical procedures. The study was approved by the Ethical Committee of the Vall d'Hebron University Hospital.

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