

# Treatment of fistula-in-ano: Outcome comparison between traditional surgery and novel approaches. A retrospective cohort study in a single center

Perianal fistül tedavisi: Geleneksel cerrahi yöntem ile yeni yaklaşımlarının sonuçlarının karşılaştırılması. Tek merkezli bir retrospektif kohort çalışması

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## Abstract

Aim: Fistula-in-ano is a well described disease but no definitive surgical technique has been developed. We conducted a retrospective cohort study in a single center to evaluate patients who underwent surgical treatment of a perianal fistula from 2012 to 2018 in our hospital. The aim of the study was to compare the outcome of different surgical techniques (Fistulotomy/fistulectomy and seton, Video-Assisted Anal Fistula Treatment (VAAFT), Micro-fragmented adipose tissue injection, Lipogems®).

Methods: A cohort of 103 patients with anal fistula who qualified for elective surgery between 2012 and 2018 were recruited at Sant'Anna Hospital in Ferrara. All patients underwent a digital rectal examination and preoperative magnetic resonance imaging (MRI) to identify the fistula tract and internal opening. Patients were divided into 4 groups, one for each type of surgery they underwent: Fistulotomy/fistulectomy and seton, Video-Assisted Anal Fistula Treatment (VAAFT), Micro-fragmented adipose tissue injection, Lipogems®. Numerical rating scale (NRS) was used to assess subjective pain one week after surgery and documented. The scale ranged from 0 to 10, where 0 stands for no pain and 10 stands for worst pain ever faced. Primary end point was fistula recurrence at 1 year of follow-up. Secondary end point was evaluation of post-operative pain.

Results: There were 71 males and 32 females, with a median age of 50 years (range 21-89 years). Among them, 79 patients were newly diagnosed, the other 24 patients had undergone previous surgery and had recurrence. In total, 118 surgical operations were performed for anal fistula. During the follow-up period, anal fistula recurrence was observed in 13 patients after VAAFT, 3 patients after Micro-fragmented adipose tissue injection, 4 after fistulotomy, 12 after fistulectomy, 10 after seton placement and 8 after Lipogems® technique. One week after surgery, pain was evaluated by all patients on a scale from 0 to 10. The mean scores of patients who underwent VAAFT, micro-fragmented adipose tissue injection, fistulotomy, fistulectomy, seton placement and Lipogems® technique were 1 (0-5), 1.5 (0-8), 5 (3-8), 6.8 (5-9), 4.2 (2-6) and 0 (0-2), respectively.

Conclusion: This study presents the difficulties in managing anal fistulas and the variety of surgical options. VAAFT and Micro-fragmented adipose tissue injection appear to be safe and feasible options in the management of anal fistula, and short-term healing rates are acceptable with no sustained effect on continence. There is, however, a paucity of robust data with long-term outcomes. These techniques are thus welcome additions. Lipogems® technique is a safe and reproducible procedure, unfortunately according to our experience, it does not promote fistula healing in patients with recurrent inter-sphincteric anal fistula. We do not suggest the use of this technique as a first-line treatment.

**Keywords:** Anal fistula, Fistulotomy, Fistulectomy, Seton, VAAFT, Lipogems®, Micro-fragmented adipose tissue

## Öz

Amaç: Anal fistül iyi tanımlanmış bir hastalıktır ancak kesin bir cerrahi teknik geliştirilmemiştir. Hastanemizde 2012-2018 yılları arasında perianal fistül nedeniyle cerrahi tedavi uygulanan hastaları değerlendirmek için tek merkezli, retrospektif bir kohort çalışması yürüttük. Çalışmanın amacı, farklı cerrahi tekniklerin (Fistülotomi / fistülektomi ve seton, Video Destekli Anal Fistül Tedavisi (VAAFT), Mikro-parçalanmış yağ dokusu enjeksiyonu, Lipogems®) sonuçlarını karşılaştırmaktır.

Yöntemler: Elektif cerrahi için uygun olan anal fistüllü 103 hastadan oluşan bir kohort, 2012 ve 2018 yılları arasında Ferrara'daki Sant'Anna Hastanesi'nde opere edildi. Tüm hastalara fistül traktını ve iç açıklığı belirlemek için ameliyat öncesi rektal tuşe ve manyetik rezonans görüntüleme (MRI) uygulandı. Hastalar, geçirdikleri her ameliyat için birer tane olmak üzere 4 gruba ayrıldı: Fistülotomi / fistülektomi ve seton, Video Destekli Anal Fistül Tedavisi (VAAFT), Mikro parçalı yağ dokusu enjeksiyonu, Lipogems®). Ameliyattan bir hafta sonra öznel ağrıyı değerlendirmek için sayısal derecelendirme ölçeği (NRS) kullanıldı ve sonuçlar kaydedildi. Puanlar, 0, hiç ağrı yok, ile 10, karşılaşılan en şiddetli ağrı, arasında değişmekteydi. Birincil sonlanım noktası, 1 yıllık takipte fistül rekürrensiydi. İkincil sonlanım noktası, ameliyat sonrası ağrının değerlendirilmesiydi.

Bulgular: Ortanca yaşı 50 olan (aralık 21-89 yaş) 71 erkek ve 32 kadın çalışmaya dahil edildi. Bunlardan 79 hastaya yeni teşhis konulmuş, diğer 24 hasta daha önce ameliyat olmuş ve nüksetmişti. Anal fistül için toplam 118 cerrahi operasyon yapıldı. Takip süresince VAAFT sonrası 13 hastada, Mikro parçalı yağ dokusu enjeksiyonu sonrası 3 hastada, fistülotomi sonrası 4 hastada, fistülotomi sonrası 12 hastada, seton yerleştirme sonrasında 10 hastada ve Lipogems® tekniğinden sonra 8 hastada anal fistül rekürrensisi gözlemlendi. Ameliyattan bir hafta sonra ağrı tüm hastalar tarafından 0 ile 10 arasında bir ölçekte değerlendirildi. VAAFT, mikro parçalı yağ dokusu enjeksiyonu, fistülotomi, fistülektomi, seton yerleştirme ve Lipogems® tekniği uygulanan hastaların ortalama skorları sırasıyla 1 (0-5), 1.5 (0-8), 5 (3-8), 6.8 (5-9), 4.2 (2-6) ve 0'dı (0-2).

Sonuç: Bu çalışma anal fistül yönetimindeki zorlukları ve çeşitli cerrahi seçenekleri sunmaktadır. VAAFT ve Mikro-parçalanmış yağ dokusu enjeksiyonu, anal fistül yönetiminde güvenli ve uygulanabilir seçenekler gibi görünmektedir ve kısa süreli iyileşme oranları, kontinans üzerinde kalıcı bir etki olmaksızın kabul edilebilir. Bununla birlikte, uzun vadeli sonuçları olan güvenilir veri yetersizliği olduğundan, bu teknikler, bu nedenle memnuniyetle karşılanmaktadır. Lipogems® tekniği güvenli ve tekrarlanabilir bir işlemdir, ancak ne yazık ki deneyimlerimize göre, tekrarlayan sfinkterik anal fistüllü olan hastalarda fistül iyileşmesini desteklememektedir. Bu tekniğin birinci basamak tedavi olarak kullanılmasını önermiyoruz.

**Anahtar kelimeler:** Anal fistül, Fistülotomi, Fistülektomi, Seton, VAAFT, Lipogems®, Mikro parçalanmış adipöz doku

## Introduction

Anal fistula is one of the most common conditions in surgical clinics dealing with anorectal diseases. Anal fistula is an epithelized communication of infectious origin between the rectum or anal canal and the perianal region. One of the most widely accepted etiologic factors for the formation of fistulae is when an infected perianal gland develops an abscess and ruptures into anal canal on one side and perianal skin on the other side. Patients with anal fistulae typically complain of pain, drainage of pus or stool, pruritus, and excoriation of adjacent tissue. Though not life-threatening, these symptoms often significantly impact patients' social, intimate, and work lives. There are several types of fistulae with respect to their course through the anal sphincter:

- **Submucosal:** the fistula track passes superficially beneath the submucosa and does not involve any sphincter muscle
- **Inter-sphincteric fistula:** the track passes through the internal sphincter and continues in the inter- sphincteric plane to the perianal skin, not including the external anal sphincter
- **Trans-sphincteric fistula:** the track cross through the internal and external anal sphincter on its exit towards the perianal area.
- **Supra-sphincteric fistula:** the fistulous tract passes through the internal sphincter but traverses the external sphincter below the puborectalis muscle;
- **Extra-sphincteric fistula:** the fistulous track may pass outside the sphincter complex through the ischioanal fossa to the perianal skin [1].

A fistula-in-ano can be "simple" or "complex."

Simple fistulae are inter-sphincteric and low trans-sphincteric, with less than 30% of the external and internal anal sphincter involved.

It is termed "complex" when the tract crosses more than 30% to 50% of the external sphincter (high trans-sphincteric, supra-sphincteric and extra-sphincteric fistulas), is located anteriorly, found in a female, is recurrent, has multiple tracks or the patient has pre-existing incontinence, was exposed to local irradiation or the patient has Crohn's disease. Complex fistulas pose a higher risk of incontinence after surgical management [2].

Fistulotomy/fistulectomy is still considered the gold standard for the treatment of the simple type, but has lot of postoperative pain, takes more time to heal and poses another important problem: Anal sphincter injury which can result in incontinence. On the other hand, the treatment of the complex type is still very challenging, and a gold standard procedure is not available. Studies have shown that complex, branched, or recurrent fistulas are at a higher risk of treatment failure and complications [3].

To date, only a few studies with surgical comparison for treatment of anal fistula are published in the English literature. The aim of our study is to compare outcome and pain control of different surgical procedures for the treatment of anal fistula in a well-defined territorial cohort of a single hospital with dedicated surgeons.

## Materials and methods

This is a retrospective cohort study was designed to compare clinical outcome data on the use of different surgical techniques in the treatment of anorectal fistula.

From 2012 to 2018, a total of 103 patients with anal fistula who qualified for elective surgery were recruited at Sant' Anna Hospital in Ferrara. All patients underwent a digital rectal examination and preoperative magnetic resonance imaging (MRI) to identify the fistula tract and internal opening. Every patient was informed of the procedure and consents were obtained. The plan of the study was approved by the ethical committee of the Province of Ferrara on 14 July 2016 with the number 160597. Prior informed consent was obtained from all patients included in the study.

Patients were divided into 4 groups, one for each type of surgery they underwent:

- **Fistulotomy/fistulectomy and seton**
- **Video-Assisted Anal Fistula Treatment (VAAFT)**
- **Micro-fragmented adipose tissue injection**
- **Lipogems®**

All patients operated with Lipogems technique were affected by simple perianal fistula and all were previously treated unsuccessfully with seton placement.

Some patients operated with the traditional technique (seton with or without fistulectomy) underwent the same or different type of surgery and for this reason they were included in more groups. All patients with first presentation or recurrent fistula were included in the study.

Numerical rating scale was used to assess subjective pain one week after surgery and documented. The scale ranged from 0 to 10, where 0 stands for no pain and 10 stands for worst pain ever faced. After discharge, all patients were followed for one year and any recurrence of the disease was noted. Any complications occurring in the postoperative period and during follow-up were noted. Recurrence was defined as the persistence of fistula at the same site or reappearance of any new fistula at the operated site.

### Surgical procedures performed

#### Traditional surgery

- **Fistulotomy:** To perform fistulotomy, the internal and external sphincters are divided, accessory tracts are excised, and eventually overlapping sphincter reconstruction is performed.
- **Fistulectomy:** A keyhole skin incision is made over the fistulous tract and the external opening is encircled. The incision is deepened through the subcutaneous tissue, and the tract is removed from surrounding tissues.
- **Seton:** There are two types of setons used in treating anal fistulas. A cutting seton is used to slowly cut through the tissue allowing for healing from inside to outside thus minimizing the risk of incontinence. The second type of seton, the non-cutting seton, is used primarily for draining, especially in the acute setting, where it provides rapid and safe relief of the infection, with no compromise to the sphincter complex, providing time for the inflammation to resolve, and better assessment and decision-making. [1] After the removal of the seton, the fistula was closed by performing an anorectal flap.

## VAAFT

Video-assisted anal fistula treatment is performed with a kit which includes a fistuloscope, an obturator, a unipolar electrode, an endobrush and 0.5 mL of synthetic cyanoacrylate glue. The fistuloscope has an 80° angled eyepiece and is equipped with an optical canne and a working and irrigating channel. Its diameter is 3.3 mm × 4.7 mm and its operative length is 18 cm.

The fistuloscope has two channels, one of which is connected to the irrigation fluid and the other which introduces the instruments. VAAFT consists of a diagnostic phase, followed by an operative phase. In the diagnostic phase, after proper cleaning and draping of the anal area, an obturatoris is introduced in the anal canal and fistuloscopy is performed to correctly locate the internal opening of the fistulous tract, secondary tracts, and abscess cavity if any. The running glycine-mannitol solution helps to open the fistulous tract.

The scope is then advanced forward slowly and the tract is straightened by maneuvering the scope. The next step is visualization of the internal opening, which is identified by the exit of the fistuloscope through it. Narrow openings are identified as a beam of illumination through the rectal mucosa or the exit of irrigating fluid through them. Both primary and secondary os and tracts are explored via fistuloscope. After the internal opening is located, absorbable sutures are put at its site in the rectum or anal canal for traction.

During the next operative phase, the aim is to destroy the fistula tract from the inside, curette it and close the internal opening. For this purpose, the electrode replaces the obturator from the external opening, under direct vision. The fistula wall is cauterized, and all wasted material is eliminated into the rectum through the internal opening. The internal opening is then closed with an anorectal flap. [4]

## Micro-fragmented adipose tissue injection

Adipose tissue is collected via liposuction. Collected adipose tissue is centrifuged, and the aqueous fraction is subsequently expelled. The remaining adipose tissue is homogenized by shifting it between 2 connected syringes.

Epithelium and granulation tissue are removed by curettage, and a thin catheter is placed through the fistula. The mucosal edges are lifted before closing the internal opening, including the internal anal sphincter and the mucosa. The adipose tissue is injected around the internal opening and the fistula tract, creating a doughnut shape, until a firm swelling surrounds the fistula tract. [5]

## Lipogems®

The initial procedure includes two phases: Liposuction (harvesting) and processing. Lower or lateral abdomen are chosen as the donor site. Before harvesting the fat, the area is injected with a local anesthetic (20 ml lidocaine 20 mg/ml and diluted with 1 ml adrenaline for vasoconstriction). After infiltration, the adipose tissue is harvested using standard liposuction technique, a 19cm 13G blunt cannula is used to prevent additional trauma to cells during the aspiration process. The harvested fat is then processed in the Lipogems® processing kit, a disposable device that gradually reduces the size of the adipose tissue clusters while eliminating oily substances and blood residues with pro-inflammatory properties. The entire

process is performed in complete immersion in saline solution minimizing any traumatic action on cell products. The resulting microfragmented adipose tissue is collected in a 10-ml syringe and positioned to empty the excess of saline solution. At the end, the product is transferred to several 1-ml syringes with a 22G and 30-mm length needle to be injected into the patient. The entire process takes between 15-20 minutes.

The first step of the surgical procedure is the debridement of the internal opening, and then, the closure of the muscular layer is carried out with 2/0 polydioxanone (PDS) stitches after undermining the mucosal edges in order to raise an amount of tissue 1 cm wider than the size of the enlarged tract. The product is injected into the submucosal layer surrounding the inner orifice and along the walls of the fistula's tract. [6]

## Statistical analysis

Based on the size of the patient sample we performed a descriptive statistical analysis of the data collected. A total of 103 patients with anal fistulae were included in this study. There were 71 males and 32 females, with a median age of 50 years (range 21-89 years). Among them, 79 patients were newly diagnosed, the other 24 patients had undergone previous surgery and had recurrent conditions. In total, 118 surgical operations for anal fistula treatment were performed.

## Results

Most of the perianal fistulas treated in our study were of the trans-sphincteric type 36 (35%), of which 25 were firstly diagnosed and 11 were recurrences (Table 1, figure 1).

Table 1: Types of fistula in ano

Type of fistula	First Diagnosis	Recurrent Fistula	Total
Complex fistula	3	2	5
Extrasphincteric	9	6	15
Transsphincteric	25	11	36
Intersphincteric	18	1	19
Submucosal	10	1	11
Not classified	14	3	17
Total	79 (77%)	24 (23%)	103

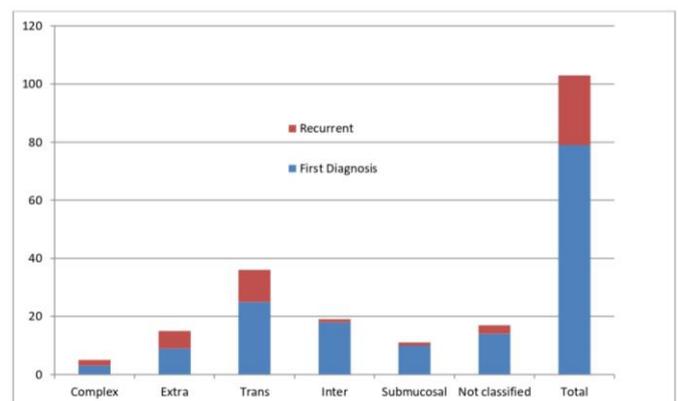


Figure 1: Groups of perianal fistulas, classified by type and first diagnosis/recurrence. Complex, Extra (extrasphincteric fistula), Trans (trans-sphincteric fistula), Inter (intersphincteric fistula), Submucosal, Not classified, Total (total of cases). First diagnosis of fistula in ano are blue and Recurrent fistula are red. Sant' Anna Hospital, Ferrara (2012-2018)

Video-Assisted Anal Fistula Treatment (VAAFT) group consisted of 24 patients, constituting 20% of surgeries. Micro-fragmented adipose tissue injection was performed in 25 patients, 21% of surgeries. Fistulotomy was performed in 21 patients, 18% of surgeries, fistulectomies were performed in 19 patients, 16% of surgeries and Setons were placed in 21 patients, making up 18% of all surgeries. Lipogems® technique was performed in 8 patients, adding up to only 6% of the total

number of surgeries. The outcomes of surgeries are summarized in Table 2 and Figure 2. During the follow-up period, anal fistula recurrence was observed in 13 (54%) patients after VAAFT, 3 (12%) patients after Micro-fragmented adipose tissue injection, 4 (19%) after fistulotomy, 12 (63%) after fistulectomy, 10 (48%) after seton placement and 8 (100%) after the Lipogems® technique. 3 cases who underwent fistulotomy and 1 patient who underwent seton application developed fecal soiling after the treatment. One week after surgery, pain was assessed by all patients on a scale (NRS) ranging from 0 to 10. One week after surgery, pain was evaluated by all patients on a scale from 0 to 10. The mean scores of patients who underwent VAAFT, micro-fragmented adipose tissue injection, fistulotomy, fistulectomy, seton placement and Lipogems® technique were 1 (0-5), 1.5 (0-8), 5 (3-8), 6.8 (5-9), 4.2 (2-6) and 0 (0-2), respectively.

Table 2: Outcomes of surgeries

Prognosis at 12-months follow-up	Healing	Recurrences	Total
VAAFT	11 (46%)	13 (54%)	24
Micro-fragmented adipose tissue injection	22 (88%)	3 (12%)	25
Fistulotomy	17 (81%)	4 (19%)	21
Fistulectomy	7 (37%)	12 (63%)	19
Seton	11 (52%)	10 (48%)	21
Lipogems	0 (0%)	8 (100%)	8
Total	68 (58%)	50 (42%)	118

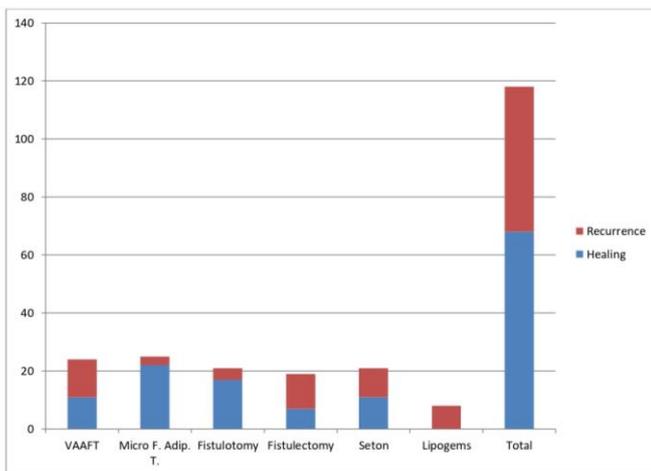


Figure 2: Type of surgery and outcomes (healing in blue and recurrence in red), Sant'Anna Hospital, Ferrara (2012-2018)

## Discussion

The treatment of anal fistula is still challenging, although many attempts with new minimally invasive techniques have been made over the decades, it continues to be one of the most complex clinical problems in anorectal surgery [7].

The success rate of each technique varies, as reported in recent systemic reviews [8,9]. Fistulotomy remains the best option when solely addressing the chance of cure, although a third to a quarter of patients will experience mild leakage of flatus and mucus or fecal incontinence [10,11].

The goal of curing the disease whilst minimizing the risk of functional impairment has fueled the development of sphincter-preserving techniques.

### VAAFT technique

VAAFT provides a minimally invasive technique with the ability to view the fistula from the inside so that all extensions can be identified and eradicated under direct vision using a fistuloscope [12]. Review demonstrates variable success rates with short-term (< 1 year) healing rates ranging from 67% [13] to 100% [14].

In our VAAFT group the recurrences were 13 (54%) out of 24. However, out of the total of 13 recurrences after VAAFT, 8 were trans-sphincteric fistulas. Some of the patients who had recurrence after VAAFT underwent autologous micro-fragmented adipose tissue injection. Only 1 patient out of 7 had another recurrence at 12 months of follow-up.

### Micro-fragmented adipose tissue injection

It is well known that, besides being multipotent, mesenchymal stem cells (MSCs) can promote tissue repair through the release of bioactive [15] and immunomodulatory molecules [16]. Adipose tissue is an optimal source of MSCs because of easier access and greater abundance than other sources such as the bone marrow. Panès and colleagues reported a 50% combined remission rate in the intention-to-treat group treated with MSCs, compared to 34% success rate in those who received placebo in a randomized, double-blind, parallel group, placebo-controlled study. The treatment-related adverse events rate was 17% in the group treated with MSCs versus 29% in those treated with placebo [17].

In our experience Micro-fragmented adipose tissue injection had the lowest number of recurrences. Out of 25 patients treated with autologous micro-fragmented adipose tissue injection, 12 had trans-sphincteric fistulas (48%), 9 patients had recurrences (5 trans-sphincteric, 2 complex fistulas, 1 extra-sphincteric and 1 submucosal). 3 recurrences were recorded in patients injected with autologous micro-fragmented adipose tissue, 2 were complex fistulas and 1 was inter-sphincteric. All-trans sphincteric fistulas had healed at the 12-month follow-up visit.

### Lipogems technique

Based on our experience, patients treated with Lipogems® do not require numerous post-operative medications. Postoperative pain and discomfort reported by our patients was limited when compared with patients treated with other techniques like seton with and without fistulectomy.

Furthermore, using autologous adipose tissue always allows compatible material to be available and ready to be used without major complications or adverse events.

The reduced amount of adipose tissue needed for each patient does not limit the use of this technique to patients with high BMI only. However, the high recurrence rate that occurred in our experience and the high cost of the product doesn't allow us to suggest its use as a first-line treatment for anal fistula. However, it could be taken into consideration as a possible second-line treatment after informing the patient about the advantages and risks. The high recurrence rate after treatment with Lipogems® technique could be explained by the type of fistula treated. In fact, all patients had already been treated with seton placement unsuccessfully.

Despite the limited cases in our study, the distribution of type of surgery within the individual arms of the study is homogeneous. The percentage of total recurrences in our hospital is 42%. As reported in literature, as well as in our study, the treatment of simple fistulas resulted in less recurrences (1 sub-submucosal; 1 inter-sphincteric). It is interesting to note that the only recurrences of this type of fistula were those treated with non-traditional surgery (1 submucosal recurrence after VAAFT; 1 inter-sphincteric recurrence after lipoaspirate). The surgical

procedure that had the highest number of recurrences was Fistulectomy (63%) followed by Seton application (48%). However, these groups of patients were not selected by type of fistulas; therefore, it is possible that many complex fistulas were subjected to this surgery. Furthermore, these types of interventions have been proposed to some patients who already underwent surgery.

The present study has several limitations. Firstly, there is significant heterogeneity in the population studied, fistula morphology and etiology, with no standardized population. Follow-up times is relatively short; high initial success rates (many lacking radiological assessment) may be misleading, and recurrences may develop more than a year after surgery.

However, the choice made by our center was to have all the operations performed by a single experienced surgeon, to standardize the surgical procedure as much as possible, reducing any bias. The paucity of patients on VAAFT and Micro-fragmented adipose tissue injection makes it difficult to comment accurately on success rates, but early results are promising. Notable advantages of these techniques are their avoidance of sphincter injury, minimal morbidity, and the ability to repeat them or perform other surgical techniques following failure.

Despite many treatment modalities, anal fistula disease remains an important problem. High recurrence rates have been reported in the surgical treatment of complicated anal fistulas [18].

The cost of the procedures is an important consideration. All new techniques involve the use of novel medical devices with an associated cost which is not a consideration when performing procedures like fistulotomy. No studies assessed cost-effectiveness. This needs to be further investigated.

### Conclusion

This study is a picture of the difficulties in managing anal fistulas and of the variety of surgical options. VAAFT and Micro-fragmented adipose tissue injection appear to be safe and feasible options in the management of anal fistula, and short-term healing rates are acceptable with no sustained effect on continence. There is, however, a paucity of robust data with long-term outcomes. These techniques are thus welcome additions.

Lipogems® technique is a safe and reproducible procedure; unfortunately, according to our experience, it does not promote fistula healing in patients with recurrent intersphincteric anal fistula. We do not suggest the use of this technique as a first-line treatment.

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