Digestive Surgery

Historical Review

Dig Surg 2021;38:104–119
DOI: 10.1159/000512652

Received: April 30, 2020
Accepted: October 25, 2020
Published online: January 27, 2021

Surgical Management of Idiopathic Perianal Fistulas: A Systematic Review and Meta-Analysis

Xinyi Cherry Cheung[a] Tom Fahey[b] Ailin C. Rogers[b]
John Hogeland Pemberton[c] Dara Oliver Kavanagh[a, d]

[a]Department of Surgery, Tallaght University Hospital, Dublin, Ireland; [b]Department of Postgraduate Studies, RCSI, Dublin, Ireland; [c]Division of Colon & Rectal Surgery, Mayo Clinic, Rochester, MN, USA; [d]Department of Surgical Affairs, RCSI, Dublin, Ireland

Keywords
Fistula · Plug · Fibrin glue · Crohn's disease · Cryptoglandular fistula

Abstract
Background: Perianal fistula is a common colorectal condition with an incidence of 9 per 100,000. Many surgical treatments exist, all aiming to eliminate symptoms with minimal risk of recurrence and impact upon continence. Despite extensive evaluation of the therapeutic modalities, no clear consensus exists as to what is the gold standard approach. This systematic review aimed to examine all available evidence pertaining to the surgical management of perianal fistulas. Primary outcomes examined were recurrence and incontinence. ***Summary:*** This study was conducted according to PRISMA guidelines. Primary outcomes were analyzed for each group and expressed as pooled odds ratio with confidence intervals of 95%. 687 studies were identified from which 28 relevant studies were included. There was no significant difference in rates of incontinence identified between various surgical approaches. Glues and plugs show higher recurrence rates. Newer treatments continue to emerge with promise but lack supporting evidence of benefit over conventional therapies. ***Key Messages:*** While we await more robust randomized data, we will continue to proceed cautiously trying to offset the benefits of fistula healing against the inherent risk of altered continence.

Introduction

Perianal fistula is one of the most common colorectal conditions impacting significantly on patients' quality of life with a reported incidence of 9 per 100,000 [1]. It is a very common initial manifestation of perianal Crohn's disease (CD) (~30%). Several authors have proposed the cryptoglandular theory as the likely aetiology in the absence of perianal CD [2–4]. This is the most plausible explanation although it lacks supporting evidence. While fistulas are rarely life threatening, they can be very debilitating and socially embarrassing.

Various treatment options are available with the aim of eliminating the tract while achieving low recurrence rates and having minimal impact upon continence. Incontinence is a spectrum of illness ranging from sporadic flatus incontinence to overt soiling with social isolation

karger@karger.com
www.karger.com/dsu

Dara Oliver Kavanagh
Department of Surgical Affairs
RCSI, Royal College of Surgeons in Ireland
123 St Stephens Green, IE Dublin 2 (Ireland)
darakavanagh@rcsi.com

and severe impact on quality of life. Setons are one of the oldest means of treating perianal fistulas with cutting setons to externalize trans-sphincteric fistula tracts and draining setons to control sepsis within fistula tracts especially in patients with CD [5]. A variety of materials have been used including non-absorbable silk sutures or rubber vascular loops [4, 6, 7]. The latter rarely induce healing (<10%). While relatively easy to perform, setons are associated with a reported incontinence rate of 20–67% [8, 9]. Advancement flaps – mucosal or endorectal – involve complete excision of the tract and the closure of the subsequent defect with a raised rectal mucomuscular flap. Endorectal flaps are variations in which the mucosal flap is raised in a submucosal plane superior to the internal defect. Reported success rates for endorectal flaps range from 55 to 98% [6].

Fistulotomy involves laying open of the fistula tract by incising onto the tract. Success rates of 90% have been reported, but a variable incontinence rate of 5–30% is also described [7]. The addition of marsupialization has expedited healing times in select series. Fistulectomy involves complete excision of the fistula tract including its openings. Wound sizes are larger with fistulectomy, and hence healing time is prolonged [6]. Marsupialization can expedite healing. Ligation of intersphincteric fistula tract (LIFT) procedure is a relatively novel therapy first introduced in 2007 [10]. It involves accessing the fistula tract through the intersphincteric space and interrupting and ligating both ends of the fistulous tract. Modifications of this include the addition of a mucosal advancement flap, plug, or biograft mesh following interruption of the tract [6, 7]. This approach has reported success between 50 and 80% [6].

Different types of glues to obliterate the fistula tract have been tried. The main issue with glues is high recurrence rates. Successful healing rates vary between 31 and 85% [11, 12]. Similar to glues, fistula plugs work by obliterating the tract [4, 6]. Incontinence rates are low, but results are variable with success rates of 14–87% [13]. Autologous stem cells derived from adipose tissue have recently been utilized in the treatment of perianal fistulas. Stem cells are extracted and purified from adipose tissue obtained by liposuction [14].

Despite continuing research and novel therapies, there remains a lack of consensus as to what is the best management plan for patients with perianal fistulae not related to CD. The strongest evidence to date is presented by the most recent Cochrane review in 2010 which concludes that there is no difference in recurrence rates between the various treatments, but flaps and glues may have lower incontinence rates [15]. Novel treatments such as LIFT and stem cell injection have shown promise based on early data but were not included in the 2010 Cochrane review. The aim of this study is to conduct a systematic review of all the current available evidence on the surgical management of non-Crohn's-related perianal fistulas, comparing their outcomes based on rates of recurrence and incontinence.

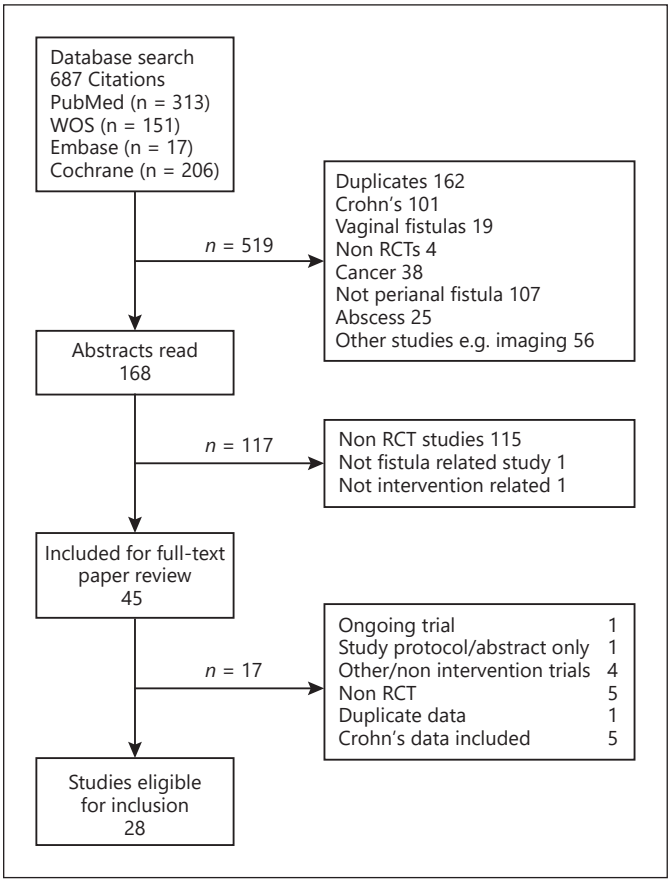


Fig. 1. Flowchart of eligible studies including included and excluded trials.

Methods

This meta-analysis was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (see online suppl. Appendix; for all online suppl. material, see www.karger.com/doi/10.1159/000512652). Approval from an ethics committee was not required for this study. An extensive search strategy was devised in order to maximize the capture of relevant studies and perform a highly sensitive search (online suppl. Appendix). The search strategy was applied to 4 major online databases: PubMed, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials. Reference lists of included studies were also reviewed to identify any other potential studies.

Dig Surg 2021;38:104–119
DOI: 10.1159/000512652

Table 1. Characteristics of included studies

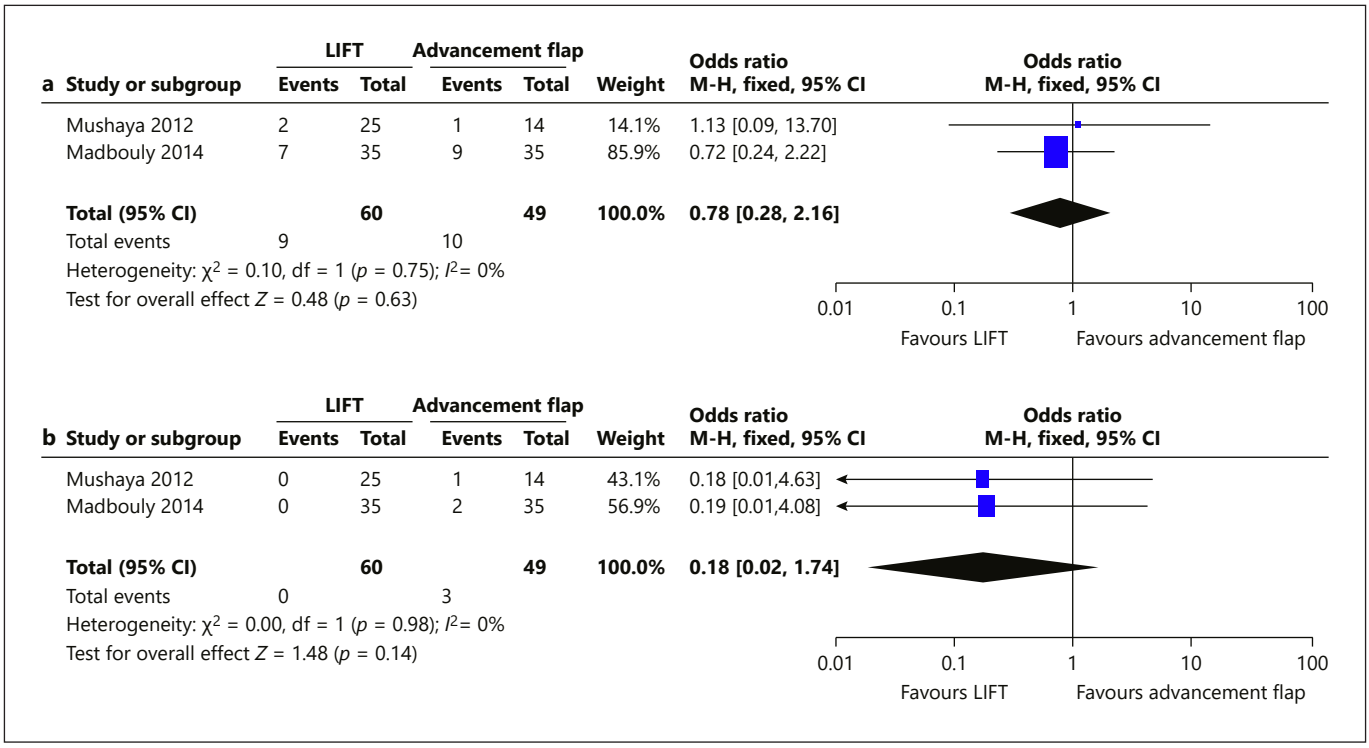
Study	Date published	Design	Population		*N*	Intervention	Control	Outcomes reported
			inclusion	exclusion				
Mushaya et.al. [19]	2012	Randomized control trial – EAUS and MRI performed initially, procedure is after initial seton drainage in both groups	Cryptoglandular origin, trans-sphincteric, complex fistulas = >30%, external sphincter, anterior fistula in women, multiple tracts, recurrent, incontinence	Crohn's fistulas – colonoscopy performed first	39	LIFT	Advancement flap	Recurrence, continence, manometry, procedure time
Madbouly et al. [20]	2014	Single centre prospective randomized control trial, 80 screened – 70 randomly assigned	High trans-sphincteric fistulas involving upper third of complex, above 18, cryptoglandular origin	Crohn's fistulas, malignancy, TB	70	LIFT	Advancement flap	Recurrence, closure, incontinence, pain, QOL
Ho et al. [30]	1998	Randomized control trial	Uncomplicated intersphincteric or trans-sphincteric	Complex fistulas with multiple openings, horse-shoe tracts, suprasphincteric and extrasphincteric fistulas, recurrent fistulas	103	Fistulotomy + marsupialization	Fistulotomy	Healing time, manometry, incontinence, recurrence
Sahakitrungruang et al. [29]	2011	Randomized control trial	Uncomplicated simple fistula – depth not beyond subcutaneous external sphincter	Complex fistulas, recurrent, prior incontinence, immunocompromised, bleeding tendency	50	Fistulotomy with marsupialization	Fistulotomy	Pain, analgesia, recurrence, complications
Pescatori et al. [28]	2006	Prospective randomized clinical trial	High fistula, recurrent, horseshoe	Intersphincteric/ superficial fistulas normally treated at outpatients	46	Fistulotomy/ fistulectomy with marsupialization	Fistulotomy/ fistulectomy	Wound size, complications: pain bleeding, recurrence, incontinence
Chalya et al. [31]	2013	Prospective randomized clinical trial	Low fistula in ano, single internal and external opening, absence of secondary tract	Recurrent fistula, comorbid fissure, haemorrhoids, chronic colitis, patient refusing consent	162	Fistulotomy with marsupialization	Fistulectomy	Healing time, pain, recurrence, infection, incontinence, size of wound, operating time, patient satisfaction
Jain et al. [32]	2011	Prospective randomized 2-arm open-label controlled pilot clinical trial	Low trans-sphincteric/inter/ subcutaneous fistula, single tract, one internal/external opening	Recurrent, comorbid fissures, haemorrhoids, colitis	40	Fistulotomy with marsupialization	Fistulectomy	Healing time, operating time, infection, incontinence, recurrence, patient satisfaction
Nazeer et al. [26]	2012	Prospective randomized clinical trial	Perianal fistula, over 18 years of age, single tract	Perianal abscess, pilonidal sinus, IBD, TB	150	Fistulotomy	Fistulectomy	Healing time, pain, recurrence, bleeding, incontinence, LOS
Kronborg [27]	1985	Prospective randomized trial, balanced randomization	Single track anal fistula below anal ring	IBD, DM	47	Fistulotomy (lay open)	Fistulectomy	Healing times/ recurrence

Table 1 (continued)

Study	Date published	Design	Population		*N*	Intervention	Control	Outcomes reported
			inclusion	exclusion				
Filingeri et al. [37]	2004	Randomized clinical trial following CONSORT	Submucosal fistula with posterior internal and external orifices	Associated inflammatory colorectal diseases, previous proctologic surgery, multiple orifices, non-submucosal, anterior fistulas, pregnant, ASA III/IV	20	Radiofrequency fistulotomy	Fistulotomy	Pain, bleeding, operative time, complications, incontinence, recurrence
Gupta et al. [38]	2003	Prospective randomized clinical trial	Low anal fistula – does not extend beyond anal crypts	High trans-sphincteric fistulas with or without high blind tract, associated IBD, supra/extrasphincteric fistulas, horseshoe fistula	100	Radiofrequency fistulotomy	Fistulotomy	Time, recurrence, bleeding, pain, return to work time, complications
Gupta et al. [39]	2003	Prospective randomized clinical trial – using RF high-frequency wave 4 MHz	Low fistulas with opening below anal ring	High trans-sphincteric fistulas with or without high blind tract, associated IBD, supra/extrasphincteric fistulas, horseshoe fistula	50	Radiofrequency fistulotomy	Fistulotomy	Time, recurrence, bleeding, pain, return to work time
Indian Council of Medical Research [24]	1991	Multicentre randomized control trial – 4 centres	Patients with evidence of anal fistula willing to be hospitalized 2–6 wks, report weekly for thread change, and regularly for follow-up	DM/cellulitis/CVD/renal disease (data included in non-randomized data)	502	Kshaarasoota seton	Fistulectomy	Healing time, complications, recurrence
Ho et al. [25]	2001	Randomized control trial	Trans-sphincteric or intersphincteric fistulas confirmed on US	High fistulas not suitable for fistulotomy	100	Ayurvedic cutting seton	Fistulotomy	Wound healing, complications, continence
Zbar et al. [22]	2003	Prospective randomized trial, anal manometry compared with normal age-matched volunteers	Cryptogenic high trans-sphincteric fistula	Crohn's, anovaginal fistula	34	IAS preserving seton	Cutting seton	Fistula eradication, recurrence, continence
Lu et al. [21]	2006	Multicentre randomized control trial – 3 centres	High and low simple fistulas, 18–65, disease duration <5 y, consenting to treatment	History of trauma and previous surgery in anorectum, acute/chronic diarrhoea, perianal eczema, IHD, DM, haematological disorders, malignancy, psychiatric disorders, pregnant, breastfeeding	244	Cutting seton	Fistulotomy ± draining	Healing time and rate, QOL scores, symptom evaluation scores

LIFT, ligation of intersphincteric fistula tract; IAS, internal anal sphincter.

Dig Surg 2021;38:104–119
DOI: 10.1159/000512652



Color version available online

Fig. 2. Comparison of LIFT versus advancement flap in relation to the primary outcomes recurrence (**a**) and faecal incontinence (**b**) with funnel plots. LIFT, ligation of intersphincteric fistula tract.

Eligibility Criteria

The target population of this study was adult patients (over 18 years of age) with perianal fistulas. We focussed upon perianal fistulas, the aetiology of which is cryptogenic in nature. All randomized control trials on surgical management of cryptogenic perianal fistulas were included. The search was not confined to English-language articles.

Fistulas related to inflammatory bowel disease, in particular CD, have been excluded as concomitant medical management with immunomodulatory therapies form the mainstay of treatment for these types of fistulas [16]. Fistulas associated with malignancy or hidradenitis suppurativa together with rectovaginal fistulas are considered separate entities with different treatment modalities and are also excluded from this study (online suppl. Appendix).

Search

Two independent reviewers applied the inclusion/exclusion criteria to the citation list (C.C. and A.R.). Any disagreement was resolved by a third independent reviewer (D.K.). We appraised 46 full-text manuscripts after initial exclusion, and 28 were eligible for inclusion. Abstracts and full manuscripts that were in a foreign language were translated by an online translating tool (Google Translate) by one of the reviewers (C.C.) [17].

Dataset

Data from included studies were extracted and inputted onto an electronic spreadsheet in excel format. Defined outcome measures were extracted for meta-analysis. Data were grouped according to the comparative groups in each study to allow pooling of data from studies examining the same comparative groups.

Outcomes

The primary outcomes for meta-analysis in this study were fistula recurrence and faecal incontinence. Raw data for each outcome were extracted and analyzed. Rates of recurrence and incontinence were examined by recording the total number of patients in each comparison group (intervention and control) and the total events in each group.

Statistical Analysis

RevMan version 5.3.5 (Cochrane Collaboration, Copenhagen, Denmark) was used to complete statistical analyses for the dataset. For each comparison group, odds ratio of the dichotomous outcomes of (1) recurrence and (2) incontinence were pooled where possible. Mantel-Haenszel fixed-effects models were used in all comparison groups. Odds ratios of compared outcomes were described with p values <0.05 as statistically significant. We accepted a confidence interval of 95% for all outcomes. Forest plots were drawn for each analysis. The I^2 statistic was used to assess statistical heterogeneity objectively. The potential for publication bias was evaluated by visually inspecting funnel plots where possible. Quality of the included studies was measured using the Jadad scale for the assessment of quality of reports in randomized clinical trials [18] (online suppl. Appendix). A score of >2 indicates good methodological quality [18].

Table 2. Characteristics of included studies (continued)

Study	Date published	Design	Population		*N*	Intervention	Control	Outcomes reported
			inclusion	exclusion				
Wang et al. [23]	2012	Randomized control trial	Intersphincteric or trans-sphincteric anal fistulae with secondary tracks and abscess	Chronic inflammatory bowel disease, dermatitis, diabetes, tumours, and pregnant or lactating women	60	Suture dragging + pad compression	Fistulotomy	Healing time, pain, recurrence, patient satisfaction, incontinence, anorectal manometry
Ortiz et al. [40]	2009	Prospective randomized clinical trial – learning curve effect avoided: first 5 AFP (I) excluded from data	High fistula in ano of cryptoglandular – upper two-thirds of the external sphincter complex	Patients with secondary tracts, horseshoe fistulas, anovaginal fistulas or rectourethral fistulas, associated CD, evidence of infection, anorectal abscess formation, a persistent cavity and fistulas with induration or purulent drainage	32	Fistula plug	Advancement flap	Fistula healing, recurrence
van Koperen et al. [41]	2011	Multicentre double blinded RCT – 6 centres	Age above 18 years, high perianal fistulas, cryptoglandular, trans-sphincteric, upper two-thirds of the sphincter complex that was confined by the puborectal sling and the end of the anal canal	No internal opening found, HIV positive, CD, malignancy, or other causes	60	Fistula plug	Advancement flap	Morbidity recurrence, incontinence, postoperative pain, quality of life
Altomare et al. [42]	2011	Prospective randomized crossover trial – human fibrin glue Tissucol used	Medium/high trans-sphincteric fistulae of cryptoglandular origin	Crohn's complex fistula, age <18 and >70, immunosuppression, DM, fissures, pregnancy, anticoagulants, allergy to glue components	64	Fibrin glue	Seton	Healing rate, pain, incontinence, hospital stay, healing time
van der Hagen et al. [43]	2011	Prospective randomized clinical trial	Complex fistulas – trans-sphincteric, suprasphincteric, and extrasphincteric fistula tracts originating from the middle third or upper part of the anal sphincter, cryptogenic origin	Rectovaginal fistulas, CD, patients younger than 18 years, malignancy, or HIV	30	Fibrin sealant	Advancement flap	Recurrence/ incontinence/QOL
Ellis et al. [44]	2004	Prospective randomized clinical trial	Complex fistulas – tract involved, >30–50 percent of the sphincter mechanism was located anteriorly in a female, or the patient had a history of pre-existing incontinence	Fistulotomy inappropriate, or whose fistula was rectovaginal or associated with a history of radiation or Crohn's	58	Flap plus fibrin glue	Advancement flap alone	Recurrence
Ho et al. [33]	2005	Randomized control trial	Trans-sphincteric fistula	Not specified	20	Island flap anoplasty (AF)	Fistulotomy	Pain, incontinence, complications, healing, recurrence rates

Dig Surg 2021;38:104–119
DOI: 10.1159/000512652

Table 2 (continued)

Study	Date published	Design	Population		*N*	Intervention	Control	Outcomes reported
			inclusion	exclusion				
Khafagy et al. [34]	2010	Prospective randomized clinical trial	Trans-sphincteric anal fistula	Acute sepsis, specific cause of fistula, strictured anorectum, any degree of incontinence	40	Partial rectal wall advancement flap	Mucosal advancement flap	Fistula closure rate, continence, morbidity, post-operative pain, hospital stay, and quality of life
Perez et al. [35]	2006	Prospective randomized clinical trial	Primary fistulas with high trans-sphincteric and suprasphincteric tracks	Acute anal sepsis non-cryptoglandular fistulas, inflammatory bowel disease Recurrent complex fistulas. Prior anal or rectal surgery, faecal incontinence ranging >2 points (on the WCGS)	60	Fistulotomy and recon	Advancement flap	Recurrence, continence, manometry
Gustafsson et al. [36]	2006	Prospective randomized clinical trial, intention to treat	Intersphincteric or higher anal fistula Unsuitable for division of sphincter muscle	CD or ongoing preoperative antibiotic treatment or fistula, >1 internal opening	83	Gent-collagen + flap	Advancement flap alone	Healing, factors affecting healing
A ba-bai-ke-re et al. [45]	2010	Single-centre, randomized, prospective, single-blinded, controlled trial	Patients at the age of 12–60 years with 2–6 cm long intrasphincteric and trans-sphincteric anorectal complex fistulae identified with a fistula probe during surgery	No internal opening found during surgery, and those with positive human immunodeficiency virus CD, malignant cause, tuberculosis, hidradenitis suppurativa, severe cardiovascular state, diabetes, pregnancy, and sepsis	90	Acellular dermal matrix	Advancement flap ERAF	Success rate, incontinence, deformity, pain, closure time, QOL, recurrence
Herreros et al. [46]	2012	Phase III randomized clinical trial – multi-centred single-blinded, 3 parallel groups	(1) No identifiable fistula tract under the perianal skin and/or the fistula tract parallel to the rectum. (2) Faecal incontinence in trans-sphincteric fistulas. (3) Risk factors for anal incontinence. (4) At least 1 previous operation due to fistulous disease (fistulectomy or advancement flap). (5) Suprasphincteric tracts shown by the MRI. Seton presence was allowed until the therapy was applied	(1) Patients diagnosed with IBD, rectovaginal fistula, or acute sepsis. (2) Liposuction not technically possible. (3) Perianal surgery needed for reasons other than fistulas. (4) Presence of two or more perianal fistulas or collections >2 cm. (5) Allergy to local anaesthetics or gadolinium. (6) Alcohol or other addictive substance abuse within last 6 months. (7) HIV, HBV, or HCV active or latent infection. (8) Major surgery within 28 days of recruitment. (9) Presence of a malignant tumour in the past 5 years. (10) Immunomodulatory treatment for reason	200	1 = stem cells; 2 = SC + glue	3 = glue	Fistula healing at 24/26 wks and 1 year, QOL scores, adverse events

CD, Crohn's disease.

Results

We identified 687 studies. Figure 1 (flowchart) summarizes the results of the search. A total of 28 studies were included in this review. As the topic of perianal fistulas and its surgical treatment is so diverse, we found that the 28 included studies had a range of different comparison groups, and thus pooling of data from all 28 studies was not possible. We divided the 28 studies into 9 different sections with similar comparison groups in order to analyze pooled data where possible. The characteristics of the 28 included studies are shown in Tables 1 and 2, and the main results from the studies are presented in Tables 3 and 4.

Twenty six out of 28 included studies reported on recurrence rates with 7 out of 26 reporting no recurrence in either intervention or control intervention groups (online suppl. Tables 1, 2). Data from 19 studies were suitable for analysis. Seventeen comparative groups were analyzed. Twenty out of 28 studies reported on incontinence as a primary outcome. Fifteen of these studies provided data for possible analysis (online suppl. Tables 1, 2). In all studies that reported on incontinence, clinical follow-up occurred at the outpatient setting. There was no objective measurements of continence performed.

LIFT Procedure

Two RCTs were included in our analysis [19, 20]. Both used advancement flap as a control group and found no statistically significant difference in recurrence rates. Pooled odds ratio for recurrence is 0.78 with a 95% confidence interval of 0.28–2.15, $p = 0.63$ (Fig. 2a). There was no significant heterogeneity evident with an I^2 of 0%. Comparison between the groups for post-operative incontinence also showed no significant difference. Pooled odds ratio for incontinence is 0.18, 95% CI: 0.02–1.74, $p = 0.14$. There is no significant heterogeneity evident with an I^2 of 0% (Fig. 2b). Pain scores in the LIFT group, 0 and 3.1, were significantly lower than in the advancement flap group, 1 and 4.8 ($p = 0.017$, $p = 0.002$).

Setons

Six included studies examined the use of different types of setons for treating perianal fistulas. Three studies examined the use of different cutting setons in transsphincteric fistulas [22, 23]. There was a single RCT, and hence meta-analysis of pooled data was not possible.

Internal anal sphincter (IAS) preserving seton involves rerouting of the fistula tract in the intersphincteric space. In a study that compared IAS preserving seton versus conventional cutting seton [22], there was no difference in recurrence rates (OR 1.88, 95% CI: 0.15–22.88, $p = 0.62$). Incontinence rates between IAS preserving seton and conventional cutting seton were not shown to be significant (OR 0.41, 95% CI: 0.03–5.03, $p = 0.49$) [22].

Fistulotomy versus Fistulectomy

Two studies compared fistulotomy with fistulectomy in simple low fistulas [26, 27]. Nazeer et al. [26] reported no recurrence or incontinence in both groups after a 10-month follow-up (no statistics were provided). Data from the study by Kronborg [27] alone were analyzed here. Three out of 24 from the fistulotomy group recurred compared to 2 out of 21 from the fistulectomy group, giving an OR of 1.36 (95% CI: 0.20–9.02, $p = 0.75$). This difference is not statistically significant (online suppl. Fig. 1a). A single case of post-operative incontinence occurred in the fistulotomy group ($n = 24$) compared to 3 cases in the fistulectomy group ($n = 21$). There was no significant difference in incontinence between the groups with an OR of 0.26 (95% CI: 0.02–2.72, $p = 0.26$) (online suppl. Fig. 1b). Kronborg [27] also reported a significant decrease in healing time in the fistulotomy group with a median healing time of 34 days versus 41 days in the fistulectomy group ($p < 0.02$).

Marsupialization of the Fistula Wound

Fistulotomy and marsupialization ultimately results in a decreased wound size. Five studies examining marsupialization were included in our analysis [28–32]. Two studies compared it with fistulotomy alone [29, 30]. Two studies used fistulectomy as controls [31, 32]. One study used fistulotomy and/or fistulectomy as the control group [28].

Marsupialization versus Fistulotomy Alone

Three studies were included [28, 30]. There was no difference in recurrence rates. Pooled OR is 0.84, 95% CI: 0.21–3.34, $p = 0.80$ (online suppl. Fig. 2a). There is no evidence of significant heterogeneity (I^2 0%). Analysis of incontinence in these groups gave an OR of 0.5 (95% CI: 0.14–1.72, $p = 0.27$; online suppl. Fig. 2b). Post-operative continence is not significantly different between the comparison groups. Heterogeneity is insignificant with an I^2 of 0%.

Marsupialization versus Fistulectomy

Three studies examined marsupialization versus fistulectomy [28, 31, 32]. Two studies reported no cases of recurrence or incontinence. Data from the study by Pesca-

Table 3. Summary of overall results

Study	Procedures compared	Control group	Results		Main findings
Mushaya et al. [19]	LIFT	Advancement flap	Operative time: LIFT median 10 min; AF 42.5, $p < 0.0011$ Satisfaction scores: LIFT 9.5; AF 8.07, $p = <0.001$ Pain score: LIFT 0, AF 1, $p = 0.017$	Time to *N* activities: LIFT 1.0 wks, AF 2.0 wks, $p = 0.16$ Recurrence: AF 1/14, LIFT 2/25 Incontinence: AF 1/14, LIFT 0/25	LIFT is safe and simple Shorter to perform and patients return to work sooner No difference in recurrence and incontinence with AF
Madbouly et al. [20]	LIFT	Advancement flap	Operative time: LIFT 22.6 min, AF 36.5 min, $p = 0.0001$ Pain scores at 1 week: 4.8±2.8 LIFT 3.1±1.3, $p = 0.002$		In high trans-sphincteric fistulas, LIFT and AF have similar healing rate, recurrences, continence, QOL LIFT has less pain
Ho et al. [30]	Fistulotomy with marsupialization	Fistulectomy	Mean operating time: C 28.47±6.7 min, I 29.2±8.4, ns Mean wound size: C 2.4± 0 cm^2, I 1.2±0.1 cm^2, $p = 0.542$ Duration of discharge: C 4.3±1.4 wk, I 2.6±1.2 wk, $p = 0.012$ Pain mean VAS higher in I but ns	Infection rate: C 32.6%, I 34.9%, ns LOS mean: C 3.9±0.9 d, I 4.2±1.6 d Mean healing time: C 36.4±12.8 d, I 28.6±16.3 d, $p = 0.002$	Marsupialization significantly heals wound quicker and may improve anal continence by preserving anal squeeze pressures with the disadvantage of lengthening surgery time
Sahaki-trungruang et al. [29]	Fistulotomy with marsupialization	Fistulectomy	Mean operating time: C 28±6.35 min, I 28.2±6.57, $p = 0.92$, ns Mean wound size: C 2.06±1.90 cm^2, I 1.23±0.87 cm^2, ns	Duration of discharge: C 4.1±1.9 wk, I 2.75±1.71 wk, $p = 0.035$ Pain: no diff in pain scores. Mean healing time: C 6.75±1.83 wk, I 4.85±1.39 wk, $p = 0.003$	No significant difference in pain scores and complications although sig diff in pethidine usage suggests the advantage of marsupialization in reducing acute pain post-operatively
Pescatori et al. [28]	Fistulotomy/ fistulectomy with marsupialization	Fistulotomy/ fistulectomy	Median operative time for marsupialization = 8 min No significant difference between both groups VAS pain score after 12 and 24 h Bleeding rate: C 46%, I 36%, $p < 0.05$	Sepsis rate: C 23%, I 14%, ns Wound size: I 1,749±66 mm^2 to 819±38 mm^2, $p < 0.001$, to 217±15 mm^2 at 4 wks, $p < 0.01$; C 1171±31 mm^2 to 543±19 mm^2 at 4 wks, ns Six in each group had incontinence post-op: 2 in each new	Marsupialization significantly decreased wound size and risk of bleeding. No increase in sepsis or pain
Chalya et al. [31]	Fistulotomy + marsupialization	Fistulotomy	I: faster healing 6·0 (0·4) versus 10·0 (0·5) wks for C group; p 0·001 Two marsupialized wounds (4 percent) broke down at follow-up, only 1 (2 percent) patient in the I group complained of incontinence (to liquid stools and flatus) compared with 6 (12 percent) in the C group, ns	Recurrence: I 1/51, LO 2/52 Operative time: I 10 (0·7) versus 8·0 (0·5) min for C group; p 0·05. The postoperative hospital stay was similar between the 2 groups C 2·0 (0·2) days; I 1·0 (0·1) days Manometry: significant drop in MSP at 3 months in the C group compared with the I group; p 0·05	Significantly shorter healing time and duration of wound discharge with marsupialization
Jain et al. [32]	Fistulotomy with marsupialization	Fistulotomy	Healing time: I 4.85±1.39 wks, C 6.75±1.83, $p = 0.003$ Operating time – no difference between groups Time to cessation of ooze: I 2.75±1.71 wks, C 4.10±1.91, $p = 0.035$	Wound size: I 1.23±0.87 cm^2, C 2.06±1.90 cm^2, ns No difference in QOL measures between both groups	Significantly shorter healing time and duration of wound discharge with marsupialization, no increase in OT time
Nazeer et al. [26]	Fistulotomy (lay open)	Fistulectomy	Median healing time: I 34 d, C 41 d	Recurrence: I 3/24, C 2/21, *n* = 5 needed decisional surgery (I 2; C 3) before healing, exclusion of these still resulted in sig shorter healing time in I	Fistulotomy gave shorter LOS, less pain, shorter healing time

Table 3 (continued)

Study	Procedures compared	Control group	Results		Main findings
Kronborg et al. [27]	Fistulotomy	Fistulectomy	LOS: I 2 d; C 3.5 d Pain (analgesics, *n*): I 9; C 15	Bleeding: I 1; C 5 Healing time: I 38 d; C 40 d	Shorter healing time in fistulotomy group, need study to compare with excision with primary suture
Filingeri et al. [37]	Radiofrequency fistulotomy	Fistulotomy	Op time mean: I 18.3 min, C 17.9 min, $p = 0.05$ Pain VAS day 1 mean: I 2.8, C 4.1, $p = 0.05$	Healing time mean: I 3.5 wks, C 5.9 wks, $p = 0.025$; no complications, no recurrence (new anterior fistula not recorded as recurrence)	Radiofrequency gives less post-op pain and faster wound healing
Gupta et al. [38]	Radiofrequency fistulotomy	Fistulotomy	Average time of procedure: C 37 min, I 22 min, p 0.001 Average bleeding during procedure: C 134 mL, I 47 mL, p 0.0002 Intensity of postoperative pain (first 24 h) VAS: C 2–5, I 0–3, p 0.2995 Period of postoperative pain: C 9 days, I 5 days, p 0.0121 Period of hospital stay: C 56 h, I 37 h, p 0.0015	Impairment of continence for flatus (patients, *n*): C 6, I 2, p 0.004 Time off work: C 11 days, I7 days; p 0.0121 Average healing time: C 64 days, I 47 days, p 0.0009 Recurrence or failure: C 3, I 1, p 0.0198	Radiofrequency fistulotomy sig quicker with less bleeding than conventional with less pain and faster healing without compromising recurrence rates
Gupta et al. [39]	Radiofrequency fistulotomy	Fistulotomy	Average time of procedure: C 41 min, I 24 min, p 0.001 Average bleeding during procedure: C 84 mL, I 47 mL, p 0.0004 Period of postoperative pain: C 9 days, I 5 days, p 0.029 Period of hospital stay: C 36 h, I 21 h, p 0.0022	Impairment of continence for flatus: C 12%, I 4%, p 0.0077 Time off work: C 11 days, I7 days, p 0.029 Wound healing time: C 64 days, I 47 days, p 0.0017 Recurrence or failure: C 1, I 0, ns	Radiofrequency fistulotomy had significantly shorter procedure time and wound healing, less bleeding, and patients returned to work sooner
Indian Council of Medical Research [24]	Kshaarasoota seton	Fistulectomy	Time to healing: at 12 wks: I 68% healed, C 89%; at 40 wks: I 92%, C 98% Time to healing varied according to fistula type (In wks): subcut: I 5, C 2: low: I 8, C 4.5; high: I 15, C 8	Incontinence at 1 year: I 8, C 13 Impact of previous surgery on recurrence: I 6 versus 3%, C 24 versus 7%; recurrence: I 6/155, C 16/142	Medicated seton (Kshaarasootra) offers an effective and safe alternative for the treatment of perianal fistulas with better recurrence rates than fistulectomy but initial healing time is longer
Ho et al. [25]	Ayurvedic cutting seton	Fistulotomy	LOS: median of 1 in both groups, p 0.09 Median time to heal: I 54 d, C 45 d, $p = 0.1682$ Pain (VAS score) significantly more pain on DOS, day 1, 2, 4	No difference in resting and max squeeze pressures between 2 groups No difference in complication and incontinence rates	Increased pain in the acute post-operative period with chemical setons. No difference in healing time, complication, or functional outcomes
Zbar et al. [22]	IAS preserving seton	Cutting seton	Incontinence = I $n = 1$ (flatus), C $n = 2$ (1 flatus and 1 faecal leakage) Recurrence: I 2/18, C 1/16 Healing time: (mean) I 14 wks, C 12 wks	No preoperative differences between patients and controls in resting manometric parameters and squeeze parameters. Difference AUIC of rectoinhibitory reflex at all levels between 2 operative groups significant $p < 0.05$	No difference in post-operative continence scores, recurrence, and healing times between IAS preserving seton and cutting seton. Need for a larger prospective RCT to evaluate
Lu et al. [21]	Cutting seton	Fistulotomy ± draining	Healing time in days: (high) I 24.73±8.15, C 32.20±12.6, $p < 0.01$; (low) I 22.26±8.67, C 31.41±11.39, $p < 0.01$ Healing rate: High I 54/56, C 53/53; low I 63/64, C 61/63; not significant between groups No difference in integral calculus pain scores, and QOL scores	Confidence in treatment scores better in I than C, $p < 0.05$ Hospital expenses significantly lower in I, $p < 0.01$ Max anal squeeze signif lower in controls Anal sphincter function at 3 month f/u less than C both in low $p = 0.03$ and high 0.02	Benefits of thread dragging through fistula method in simple fistulas: Shorter course, lower cost, better QOL, and protects anal function

LIFT, ligation of intersphincteric fistula tract; IAS, internal anal sphincter.

Dig Surg 2021;38:104–119
DOI: 10.1159/000512652

Table 4. Summary of overall results (continued)

Study	Procedures compared	Control group	Results		Main findings
Wang et al. [23]	Suture dragging + pad compression	Fistulotomy	Time of healing (d): I 24.33±4.44, C 31.57±5.30, $p < 0.001$, significantly shorter in I Pain: postoperative pain scores: I 5.83±2.50, C 6.37±2.33, p 0.373 Oral analgesics, n: I 10, C 14, p 0.292 Parenteral analgesics, n: I 0, C 1, p 0.313, I group did not require IV analgesia Incontinence score: Wexner score after treatment of trans-sphincter fistulae was 0.13±0.45 in I group and 0.56±1.35 in the C group ($p = 0.071$)	Manometry: MRP and MSP reduced in both after treatment but did not reach significance in both inter-group difference and pre/post-procedure difference Mean satisfaction score was significantly higher in the I group (4.07±0.94 in I vs. 3.37±1.45 in C), p 0.031 Recurrence rate, %: I 3.33, C 0, p 0.313, ns	Traditional Chinese surgical treatment with SDPC is safe, comparable to conventional fistulotomy in recurrence, incontinence, and complication rates but offer a sig shorter course with better patient satisfaction
Ortiz et al. [40]	Fistula plug	Advancement flap	Recurrence: I 12/15, C 2/16, $p < 0.001$ Three patients plug was extruded at 2 wks and 1 at 4 wks all detected within 3 months	In C group, 2 recurrence had abscess at previous site. Of 16 who had previous sx, 9 recurred of which 8 had plug Of recurrences, 7 healed after second procedure – 6 ERAF and 1 AFP	Plugs associated with a low healing rate/high recurrence rate especially in patients with previous history of fistula surgery
van Koperen et al. [41]	Fistula plug	Advancement flap	Recurrence rate: I 71% (n 22), C (n 15), $p = 0.126$ Pain d1 VAS: I 3±3, C 4±2.5, p 0.143 4/31 I plugs fell out within 10 days Continence: no significant diff between group	I: Wexner score was 5.50 (range, 0–16) before surgery and was 5.50 (range, 0–14) after surgery C: Wexner score was 7.00 (range, 0–12) before surgery and 6.50 (range, 0–16) after surgery, ns No difference in QOL scores	No significant differences between AF and plug in recurrence, functional outcome, and QOL
Altomare et al. [42]	Fibrin glue	Seton	% healed in 3 months: I 38%, C 87.5% Recurrence: I 23/38, C 3/24 Of the recurred I 4/8 failed second, C 8/18 failed second Pain scores median: I 0, C 5, $p < 0.0001$	LOS median I 24 h, C 48 h, $p < 0.0001$ Wexner score for incontinence increased significantly in C 1.79±4.4–5.1±5.9, $p = 0.0017$, I 0.67–0.49, $p = 0.07$ Manometry: resting and anal squeeze pressures decreases significantly in C	Fibrin glue is a good alternative in patients with poor anal tone or other comorbidities but has higher failure rates compared to seton. Seton has higher risk of incontinence than glue
van der Hagen et al. [43]	Fibrin sealant	Advancement flap	Recurrence: C: 3 (20%), I: 9 (60%), $p = 0.06$ Nine (64%) of all the smoking patients ($n = 14$) and 3 (18%) of the non-smoking patients ($n = 16$) had a recurrent fistula ($p = 0.02$) I: 8 patients (100%) of the tobacco smokers developed a recurrent fistula, C: 1 patient (17%) of the tobacco smokers developed a recurrent fistula ($p < 0.001$)	No difference in quality of life (EuroQuol-5D) was found at 6 and 12 months after treatment between both groups Previous surgical attempts, sex, and age – no significance impact on outcomes	Fibrin sealant has lower success rate than staged flap
Ellis et al. [44]	Flap plus fibrin glue	Advancement flap alone	C – 6/30 recurred, V I – 13/28, $p < 0.05$ Subset analysis of 6 in control: 3 = anodermal and 3 = mucosal Combined treatment group: 10 mucosal and 3 anodermal recurred – ns		Fibrin sealant with flap repair does not offer improved outcomes
Ho et al. [33]	Island flap anoplasty (AF)	Fistulotomy	There were no differences in the postoperative pain score, incontinence score, complications, wound healing, and recurrence rates between the 2 groups	LOS mean I 2.1 d, C 1.8 d Zero recurrences in both groups at mean f/u 63.3 wks	IFA is a safe and useful method for treating trans-sphincteric fistula. Long-term results required

Table 4 (continued)

Study	Procedures compared	Control group	Results		Main findings
Khafagy et al. [34]	Partial rectal wall advancement flap	Mucosal advancement flap	Operative time: I 31.6± 6.8 min, C 29.4±4.7 min ($p = 0.783$) Hospital stay more in C (I 96.35±9.5 vs. C 105.8±13.23) ($p = 0.014$) Incontinence: I 2, C 0, $p = 0.15$ Recurrence: I 2, C 8, $p = 0.03$ Disruption of flap: I 1, C 6, p 0.04	Manometry I – decreased MRP 68.4±8.55 to 62.15±7.62 and MSP 162.15±14.51 to 160.70±14.17, $p < 0.001$. C – decreased MRP 65.4±8.17 to 63.4±7.38 ($p < 0.001$) but no significant decrease in MSP 161.35±14.10 to 155.40±18.73, $p > 0.05$	Pa thickness, AF significantly decrease LOS, and complications such as flap disruption and recurrence
Perez et al. [35]	Fistulotomy and recon	Advancement flap	No diff in LOS Continence: C – 6/27 altered continence preop, of these 2 worse post-op, 2 developed incontinence Wexner score 1.5 mean 0.26 to 0.48, ns I – 5/28 altered continence preop of these 1 worsened post-op Four developed incontinence Wexner score, 2 mean WCGS 0.36–0.64, ns	Manometry: C: signif decrease in MRP and MSP post-op, I: signif decrease in MRP only. No diff between the groups Recurrence C 2/27, I 2/28	FSR comparable to AF incontinence and recurrence
Gustafsson et al. [36]	Gent-collagen + flap	Advancement flap alone	Median operating time: C 55 min, I 55 min At 12 months: – I 26/42, C 21/42, ns	Prognostic factors for healing did not demonstrate any difference with gender/BMI/ operation time Healing rate tended to be lower with previous fistula surgery and younger patients but ns	Recurrence rates in AF±antibiotics. Healing not improved with the addition of collagen gent
A ba-bai-ke-re et al. [45]	ADM	Advancement flap ERAF	Recurrence: ADM (I) $n = 2$, ERAF $n = 13$, $p = 0.0047$ Healing rate: ADM 37 (82.22%) and ERAF 29 (64.44%) of the 45 patients The life quality score was higher, the fistula healing time and postoperative pain time were shorter in the ADM group than in the ERAF group ($p < 0.05$) Faecal incontinence: ADM 1 (2.22), ERAF4 (8.89), p 0.3574	Anal deformity: ADM 0 (0), ERAF 3 (6.67), p 0.2402 Postoperative pain time, d: ADM 1.5±0.5, ERAF7.5±1.8, p 0.0000 Healing time, d: ADM 7.5±3.5, ERAF 24.5±5.5, p 0.0000 Subset analysis (fistula type): recurrence rate of trans-sphincteric fistula was significantly lower in the ADM group than in the ERAF group; recurrence: ADM 2 (7.69), ERAF10 (35.71), p 0.0318	Success rate, post-operative pain time, and closure time are significantly higher in ADM group compared to ERAF and should be used in complex fistulas No significant difference in the incontinence and anal deformity rate between groups
Herreros et al. [46]	1 = stem cells; 2 = SC + glue	Glue	Fistula healing rates at week 12 were 26.56, 38.33, and 15.25% in arms A, B, and C ($p = 0.01$) A total of 61.75% ($n = 113$) patients received 2 doses of treatment The fistula healing after the second dose was 39.1% ($n = 25$), 43.30% ($n = 26$), and 37.29% ($n = 22$) ($p = 0.79$), ns Time to healing was similar in all groups Recurrence at 24 to 26 was 25.00, 14.29, and 11.11% ($p > 0.5$) A = B (ASC with/without fibrin) versus C (fibrin alone) healing rate double in ASC group (p 0.048)	The results indicated that "centre" (pioneer) and "fistula complexity score" were significant factors in closure rate ($p = 0.024$); continence: decreased scores in group A (0.86±2.71 to 0.64±2.52) and in group B (1.55±3·43 to 0.95±2·84), whereas the score increased in group C (1.09±2.48 to 1.48±3·11) ($p = 0.09$) Healing 24–26 wk, n (%): 20 (47.6), 23 (54.8), and 18 (35.3), p 0.16 Healing rate at 1 y: 57.1, 52.4, and 37.3% in arms A, B, and C ($p = 0.13$)	No statistically significant difference between the 3 arms Healing rate of patients treated with stem cells × 2 times higher compared with fibrin alone, $p = 0.048$

ADM, acellular dermal matrix.

tori et al. [28] generated an OR of 1.11 for recurrence (95% CI: 0.02–6.15, $p = 0.91$; online suppl. Fig. 3) and an OR for incontinence of 1.10 (95% CI: 0.14–8.56, $p = 0.93$; online suppl. Fig. 3).

Advancement Flaps

Four studies included in our review examined advancement flaps [33–36]. Meta-analysis was not possible due to a single RCT. Island flap anoplasty was compared with fistulotomy. Sample size was small, and the authors reported no recurrence. Incontinence rates between island flap anoplasty and fistulotomy were also not significant (OR 0.64, 95% CI: 0.10–4.10, $p = 0.64$). Khafagy et al. [34] compared partial rectal wall advancement flap to conventional mucosal advancement flap. They found that recurrence is lower in the partial rectal wall advancement flap group with an OR of 0.17 (95% CI: 0.03–0.92, $p = 0.04$). Incontinence rates are comparable between partial rectal wall advancement flap and conventional mucosal advancement flap with no significant difference (OR 5.54, 95% CI: 0.25–123.08, $p = 0.28$). Perez et al. [35] reported on recurrence rates from the comparison of fistulotomy with sphincter reconstruction with advancement flap [35]. There was no significant difference in recurrence on incontinence rates (recurrence: OR 0.96, 95% CI: 0.13–7.36, $p = 0.97$; incontinence: OR 2.0, 95% CI: 0.33–12.55, $p = 0.45$).

Radiofrequency Fistulotomy versus Conventional Fistulotomy

Three studies included examined radiofrequency fistulotomy versus conventional fistulotomy [37–39]. Analysis of pooled data gave an OR for recurrence of 0.33 (95% CI: 0.05–2.14, $p = 0.24$). There is no evidence of significant heterogeneity between groups (I^2 0%). There was no significant difference in recurrence rates (online suppl. Fig. 4a). There were improved post-operative incontinence rates in the radiofrequency group. This did not reach statistical significance in pooled data analysis. OR for incontinence is 0.31 (95% CI: 0.08–1.21, $p = 0.09$; online suppl. Fig. 4b) ($I^2 = 0\%$).

Fistula Plugs

Two studies compared fistula plug with advancement flap as a control group [40, 41] and found a higher recurrence rate in the plug group. In the study by Ortiz et al. [40] recruitment stopped after 3 months due to high recurrence rate in the plug arm at preliminary analysis. Van Koperen et al. [41] showed no difference between recurrence rates which were high in both groups. Pooled data analysis on recurrence showed an OR of 4.22 favouring advancement flap (95% CI: 1.76–10.13, $p = 0.03$; online suppl. Fig. 5). They reported no difference in incontinence scores in either groups.

Fibrin Glue

Three studies compared the use of fibrin glue with 3 different controls: seton, advancement flaps, and glue as an adjunct to flaps versus flap alone [42–44]. Altomare et al. [42] compared fibrin glue with the seton group (cutting or loose). Recruitment was stopped after 3 months as preliminary data showed clear advantage in the control arm. A minimum follow-up period of 1 year was noted. The authors found that the glue group had significantly increased recurrence (23/38 in the glue group vs. 3/24 in the seton group, OR 10.73, 95% CI: 2.72–42.39, $p = 0.0007$). There was an increase in incontinence from 6/24 to 15/24 in the seton group at completion of follow-up ($p = 0.0017$). Van der Hagen et al. [43] compared glue with advancement flap. Recruitment stopped after a total of 30 patients were enrolled due to high recurrence rate in the glue arm. Nine out of 15 of the glue group recurred versus 3 out of 15 in control (OR 6.00, 95% CI: 1.17–30.72, $p = 0.03$).

Others

Acellular Dermal Matrix versus ERAF

A novel bioprosthetic matrix used to close the fistula tracts was compared to endorectal advancement flap [45]. This study showed promising results for this bioprosthetic acellular dermal matrix (J-I ADM; J.Y. Life Tissue Engineering Co., Ltd., China) with a recurrence rate of 2 out of 45 compared to 13 out of 45 in the advancement flap control group (OR 0.11, 95% CI: 0.02–0.54, $p = 0.006$). There was no significant difference in incontinence (OR 0.23, 95% CI: 0.02–2.17, $p = 0.2$).

Stem Cells

Stem cells in the treatment of perianal fistulas were investigated in a single blinded multi-centred clinical trial with 3 parallel groups: stem cells alone, stem cell + fibrin glue, and fibrin glue alone [46]. This study did not show any significant difference in healing rates, recurrence, and incontinence rates between the 3 groups. The healing rate was 2 times higher in the stem cell group (RR 2.039, 95% CI: 1–4.15, $p = 0.048$).

Video-Assisted Anal Fistula Treatment

Video-assisted anal fistula treatment is another novel treatment that shows some promise. It is unclear which

part of the treatment is important and whether the video element is vital to its success or whether thorough cleaning of the track and secure closure of the internal opening is equally beneficial [47, 48]. Success rates of >75% fistula healing with no impact upon continence have been reported in single series.

Discussion

Perianal fistulas form a significant part of the workload of a colorectal surgeon. While there are many different types of treatment, there is no current gold standard. Clinicians tend to utilize one treatment or another depending on their own anecdotal experiences. It is a very distressing condition for the patient and can have a very negative impact on the patients' quality of life. A Cochrane review in 2010 concluded that there is no major difference between the various techniques with regards to recurrence rates, and fibrin glue and advancement flaps have lower incontinence rates [15]. At that time, evidence for the LIFT procedure was not yet available. Since then, the literature pertaining to anal fistula has expanded significantly. With this in mind, we embarked on the current study to establish the optimal surgical intervention for idiopathic (cryptoglandular) perianal fistula.

Recurrence rates ranging from 0 to 80% have been reported across all the examined surgical techniques. Many comparative groups have a single randomized control trial, and hence meta-analysis was not possible. Despite updates on newer interventions, we found that in terms of recurrence, the majority of interventions showed no significant difference compared to a specific control treatment. Our review shows that although the LIFT procedure has a reported success rate of 70% [47], there is no statistically significant difference in both recurrence and incontinence rates when compared with advancement flap.

Early results for fibrin plugs report favourable success rates of up to 80%, and it was postulated that it could reduce overall recurrence. A multi-centre randomized control trial (PLUG Trial) found no difference in recurrence rates between fibrin plugs and advancement flaps. However, when we pooled data incorporating the results of the PLUG Trial, meta-analysis of 2 studies showed that fistula plugs have significantly higher recurrence rates when compared to advancement flaps with an odds ratio of 4.22 favouring advancement flap (95% CI: 1.76–10.13, p = 0.03; online suppl. Fig. 5) [49]. We also found no significant difference in overall incontinence rates.

The other most commonly reported outcomes in the included studies are pain, healing time, and operative time. Pain scores were found to be reduced in novel treatments such as the LIFT procedure and acellular dermal matrix. Radiofrequency fistulotomy is reported to have less pain scores and reduced bleeding. This has been postulated to be due to the coagulation of blood vessels and sealing of nerves by radiofrequency waves.

Having considered the evidence including the novel (previously not evaluated) interventions, our results mirror those of the Cochrane 2010 review and that there is no difference in recurrence between the majority of interventions. However, fibrin glue and plugs show higher recurrence in the RCT setting. In the absence of favourable incontinence rates, these findings question the continual inclusion of glues and plugs in the armamentarium for the treatment of perianal fistulas. Without further evidence, from the results of this study, we are unable to make specific recommendations regarding a more robust treatment algorithm for the management of perianal fistulas. We postulate that specific treatments applied to a specific fistula subtype may generate more favourable outcomes, but we await with interest the outcomes of future trials to support this hypothesis.

With ongoing evidence that surgical interventions have no difference in terms of recurrence and incontinence, it may be useful to analyze these outcomes in different subgroups, for example, female gender, anterior fistulas, and recurrent fistulas, that is, high risk for incontinence or recurrence groups, in order to develop more patient-specific treatment guidelines rather than looking for a single best fit for all. This may be difficult as numbers in these specific subgroups are likely low and therefore difficult to perform a well-powered study. Multi-centre international-based collaborative RCTs may generate sufficient patient numbers and follow-up duration to facilitate this subset analysis.

The main strength of our review is our exhaustive search strategy which yielded a large number of eligible studies. All studies included are randomized control studies, which offer a high level of evidence (grade IB). We provided updated evidence on a range of novel interventions. This is a very broad topic with multiple comparison groups rather than a more conventional intervention versus control scenario. This is one of the major limitations as there was a limited number of RCTs available in each of the comparisons, and hence pooled data was not possible in all comparison groups. In many cases, results from 1 study are analyzed rather than full meta-analysis. Most of the studies are scored as low (<2) or av-

erage (3) on the Jadad quality assessment scale with a mean of 2.46, just below average for good-quality studies. Funnel plots could not show meaningful conclusions on bias due to the small number of studies in each comparison group, and shape of the funnel plot is not apparent (online suppl. material).

Conclusion

Current evidence failed to demonstrate an optimal surgical strategy for the management of non-Crohn's related perianal fistulas. There is a need for further assessment of the benefit of stem cells compared to other conventional treatments. In the interim, in absence of convincing evidence, it is likely that individual clinicians will continue to utilize treatment options based on patient factors, their personal experience, and often influenced by enthusiasm for novel as yet unproven therapies which require further evaluation within robust study designs.

Acknowledgements

We would like to acknowledge the help of the RCSI library in supporting our electronic searches.

Statement of Ethics

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. Approval from an ethics committee was not required for this study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

There was no funding.

Author Contributions

X.C. developed the search and wrote the initial draft. T.F. reviewed the methodology and thoroughly reviewed the manuscript. A.R. did the searches along with X.C. and reviewed the manuscript. J.P. reviewed the manuscript and provided suitable modifications which enhanced the manuscript. D.K. developed the idea, supported X.C. in the methods, and reviewed, submitted, and revised the manuscript.

References

1 Williams NS, O'Connell PR. The anus and anal canal. In: Williams NS, editor. Bailey & Love's short practice of surgery. 25th ed. London: Hodder Arnold; 2008. p. 1240–72.
2 Hermann GDL. Sur la muquese de la region cloacale du rectum. C R Acad Sci. 1880;(90):1301–2.
3 Kelly ME, Heneghan HM, McDermott FD, Nason GJ, Freeman C, Martin ST, et al. The role of loose seton in the management of anal fistula: a multicenter study of 200 patients. Tech Coloproctol. 2014;18(10):915–9.
4 Akhtar M. Fistula in ano: an overview. JIMSA. 2012;25(1):53–5.
5 Hippocrates. On Fistulae. Available from: http: //classics.mit.edu//Hippocrates/fistulae.html.
6 Gupta PJ, Gupta SN, Heda PS. Which treatment for anal fistula? Cut or cover, plug or paste, loop or lift. Acta Chir Iugosl. 2012;59(2):15–20.
7 Nicholls RJ. Fistula in ano: an overview. Acta Chir Iugosl. 2012;59(2):9–13.
8 Subhas G, Singh Bhullar J, Al-Omari A, Unawane A, Mittal VK, Pearlman R. Setons in the treatment of anal fistula: review of variations in materials and techniques. Dig Surg. 2012;29(4):292–300.
9 Ritchie RD, Sackier JM, Hodde JP. Incontinence rates after cutting seton treatment for anal fistula. Colorectal Dis. 2009;11(6):564–71.
10 Rojanasakul A, Pattanaarun J, Sahakitrungruang C, Tantiphlachiva K. Total anal sphincter saving technique for fistula-in-ano; the ligation of intersphincteric fistula tract. J Med Assoc Thai. 2007;90(3):581–6.
11 Ratto C, Grillo E, Parello A, Costamagna G, Doglietto GB. Endoanal ultrasound-guided surgery for anal fistula. Endoscopy. 2005;37(8):722–8.
12 Sentovich SM. Fibrin glue for anal fistulas: long-term results. Dis Colon Rectum. 2003;46(4):498–502.
13 Sentovich SM. Fibrin glue for all anal fistulas. J Gastrointest Surg. 2001;5(2):158–61.
14 Garcia-Olmo D, Herreros D, Pascual I, Pascual JA, Del-Valle E, Zorrilla J, et al. Expanded adipose-derived stem cells for the treatment of complex perianal fistula: a phase II clinical trial. Dis Colon Rectum. 2009;52(1):79–86.
15 Jacob TJ, Perakath B, Keighley MR. Surgical intervention for anorectal fistula. Cochrane Database Syst Rev. 2010;(5):CD006319.
16 Yassin NA, Askari A, Warusavitarne J, Faiz OD, Athanasiou T, Phillips RK, et al. Systematic review: the combined surgical and medical treatment of fistulising perianal Crohn's disease. Aliment Pharmacol Ther. 2014;40(7):741–9.
17 Google Translate. Available from: https://translate.google.ie.
18 Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1–12.
19 Mushaya C, Bartlett L, Schulze B, Ho YH. Ligation of intersphincteric fistula tract compared with advancement flap for complex anorectal fistulas requiring initial seton drainage. Am J Surg. 2012;204(3):283–9.
20 Madbouly KM, El Shazly W, Abbas KS, Hussein AM. Ligation of intersphincteric fistula tract versus mucosal advancement flap in patients with high transsphincteric fistula-in-ano: a prospective randomized trial. Dis Colon Rectum. 2014;57(10):1202–8.
21 Lu JG, Cao YQ, He CM, Guo XT, Huang HX, Yi J, et al. Clinical research of thread-dragging through fistula method in treating patients with simple anorectal fistula. Zhong Xi Yi Jie He Xue Bao. 2006;4(2):140–6.

22 Zbar AP, Ramesh J, Beer-Gabel M, Salazar R, Pescatori M. Conventional cutting vs. internal anal sphincter-preserving seton for high trans-sphincteric fistula: a prospective randomized manometric and clinical trial. Tech Coloproctol. 2003;7(2):89–94.
23 Wang C, Lu JG, Cao YQ, Yao YB, Guo XT, Yin HQ. Traditional Chinese surgical treatment for anal fistulae with secondary tracks and abscess. World J Gastroenterol. 2012; 18(40):5702–8.
24 Multicentric randomized controlled clinical trial of Kshaarasootra (Ayurvedic medicated thread) in the management of fistula-in-ano. Indian Council of Medical Research. Indian J Med Res. 1991;94:177–85.
25 Ho KS, Tsang C, Seow-Choen F, Ho YH, Tang CL, Heah SM, et al. Prospective randomised trial comparing ayurvedic cutting seton and fistulotomy for low fistula-in-ano. Tech Coloproctol. 2001;5(3):137–41.
26 Nazeer MA, Saleem R, Ali M, Ahmed ZN. Better option for the patients of low fistula in ano: fistulectomy or fistulotomy. Pak J Med Health Sci. 2012;6(4):885–7.
27 Kronborg O. To lay open or excise a fistula-in-ano: a randomized trial. Br J Surg. 1985; 72(12):970.
28 Pescatori M, Ayabaca SM, Cafaro D, Iannello A, Magrini S. Marsupialization of fistulotomy and fistulectomy wounds improves healing and decreases bleeding: a randomized controlled trial. Colorectal Dis. 2006;8(1):11–4.
29 Sahakitrungruang C, Pattana-Arun J, Khomvilai S, Tantiphlachiva K, Atittharnsakul P, Rojanasakul A. Marsupialization for simple fistula in ano: a randomized controlled trial. J Med Assoc Thai. 2011;94(6):699–703.
30 Ho YH, Tan M, Leong AF, Seow-Choen F. Marsupialization of fistulotomy wounds improves healing: a randomized controlled trial. Br J Surg. 1998;85(1):105–7.
31 Chalya PL, Mabula JB. Fistulectomy versus fistulotomy with marsupialisation in the treatment of low fistula-in-ano: a prospective randomized controlled trial. Tanzan J Health Res. 2013;15(3):193–8.
32 Jain BK, Vaibhaw K, Garg PK, Gupta S, Mohanty D. Comparison of a fistulectomy and a fistulotomy with marsupialization in the management of a simple anal fistula: a randomized, controlled pilot trial. J Korean Soc Coloproctol. 2012;28(2):78–82.
33 Ho KS, Ho YH. Controlled, randomized trial of island flap anoplasty for treatment of transsphincteric fistula-in-ano: early results. Tech Coloproctol. 2005;9(2):166–8.
34 Khafagy W, Omar W, El Nakeeb A, Fouda E, Yousef M, Farid M. Treatment of anal fistulas by partial rectal wall advancement flap or mucosal advancement flap: a prospective randomized study. Int J Surg. 2010;8(4):321–5.
35 Perez F, Arroyo A, Serrano P, Sánchez A, Candela F, Perez MT, et al. Randomized clinical and manometric study of advancement flap versus fistulotomy with sphincter reconstruction in the management of complex fistula-in-ano. Am J Surg. 2006;192(1):34–40.
36 Gustafsson UM, Graf W. Randomized clinical trial of local gentamicin-collagen treatment in advancement flap repair for anal fistula. Br J Surg. 2006;93(10):1202–7.
37 Filingeri V, Gravante G, Baldessari E, Casciani CU. Radiofrequency fistulectomy vs. diathermic fistulotomy for submucosal fistulas: a randomized trial. Eur Rev Med Pharmacol Sci. 2004;8(3):111–6.
38 Gupta PJ. Radiosurgical fistulotomy; an alternative to conventional procedure in fistula in ano. Curr Surg. 2003;60(5):524–8.
39 Gupta PJ. Anal fistulotomy with radiofrequency: a better option to a conventional procedure. Rom J Gastroenterol. 2003;12(4): 287–91.
40 Ortiz H, Marzo J, Ciga MA, Oteiza F, Armendáriz P, de Miguel M. Randomized clinical trial of anal fistula plug versus endorectal advancement flap for the treatment of high cryptoglandular fistula in ano. Br J Surg. 2009; 96(6):608–12.
41 van Koperen PJ, Bemelman WA, Gerhards MF, Janssen LW, van Tets WF, van Dalsen AD, et al. The anal fistula plug treatment compared with the mucosal advancement flap for cryptoglandular high transsphincteric perianal fistula: a double-blinded multicenter randomized trial. Dis Colon Rectum. 2011;54(4):387–93.
42 Altomare DF, Greco VJ, Tricomi N, Arcanà F, Mancini S, Rinaldi M, et al. Seton or glue for trans-sphincteric anal fistulae: a prospective randomized crossover clinical trial. Colorectal Dis. 2011;13(1):82–6.
43 van der Hagen SJ, Baeten CG, Soeters PB, van Gemert WG. Staged mucosal advancement flap versus staged fibrin sealant in the treatment of complex perianal fistulas. Gastroenterol Res Pract. 2011;2011:186350.
44 Ellis CN, Clark S. Fibrin glue as an adjunct to flap repair of anal fistulas: a randomized, controlled study. Dis Colon Rectum. 2006;49(11): 1736–40.
45 A ba-bai-ke-re M-M-T-J, Wen H, Huang HG, Chu H, Lu M, Chang ZS, et al. Randomized controlled trial of minimally invasive surgery using acellular dermal matrix for complex anorectal fistula. World J Gastroenterol. 2010; 16(26):3279–86.
46 Herreros MD, Garcia-Arranz M, Guadalajara H, De-La-Quintana P, Garcia-Olmo D. Autologous expanded adipose-derived stem cells for the treatment of complex cryptoglandular perianal fistulas: a phase III randomized clinical trial (FATT 1: fistula advanced therapy trial 1) and long-term evaluation. Dis Colon Rectum. 2012;55(7):762–72.
47 Zirak-Schmidt S, Perdawood SK. Management of anal fistula by ligation of the intersphincteric fistula tract: a systematic review. Dan Med J. 2014;61(12):A4977.
48 Meinero P, Mori L. Video-assisted anal fistula treatment (VAAFT): a novel sphincter-saving procedure for treating complex anal fistulas. Tech Coloproctol. 2011;15(4):417–22.
49 Williams G, Williams A, Tozer P, Phillips R, Ahmad A, Jayne D, et al. The treatment of anal fistula: second ACPGBI Position Statement: 2018. Colorectal Dis. 2018 Jul;20(Suppl 3):5–31.