Systematic review

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Systematic review of surgical interventions for Crohn's anal fistula

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Background: **Anal fistula occurs in approximately one in three patients with Crohn's disease and is typically managed through a multimodal approach. The optimal surgical therapy is not yet clear. The aim of this systematic review was to identify and assess the literature on surgical treatments of Crohn's anal fistula.**

Methods: **A systematic review was conducted that analysed studies relating to surgical treatment of Crohn's anal fistula published on MEDLINE, Embase and Cochrane databases between January 1995 and March 2016. Studies reporting specific outcomes of patients treated for Crohn's anal fistula were included. The primary outcome was fistula healing rate. Bias was assessed using the Cochrane ROBINS-I and ROB tool as appropriate.**

Results: **A total of 1628 citations were reviewed. Sixty-three studies comprising 1584 patients were ultimately selected in the analyses. There was extensive reporting on the use of setons, advancement flaps and fistula plugs. Randomized trials were available only for stem cells and fistula plugs. There was inconsistency in outcome measures across studies, and a high degree of bias was noted.**

Conclusion: **Data describing surgical intervention for Crohn's anal fistula are heterogeneous with a high degree of bias. There is a clear need for standardization of outcomes and description of study cohorts for better understanding of treatment options.**

*Other ENiGMA Collaborators can be found under the heading Collaborators

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Introduction

Crohn's disease affects an estimated 145 per 100 000 people in the UK[1]. One in three of these patients will develop a perianal fistula[2], of whom just one in three achieve long-term healing of the fistula[3]. This is a condition that should be managed in concert between surgeon and physician[4]. Published guidelines advocate sepsis control and use of anti-tumour necrosis factor (TNF) α therapy[5,6]. Some patients improve or heal with this treatment, although many require further surgical intervention. The selected intervention may vary, depending on whether the treatment aim is cure or symptom relief.

Previous studies have shown that a range of surgical techniques are employed[7]. These include the use of a draining seton, anal fistula plug, fistulotomy, stoma creation and proctectomy. Newer techniques such as video-assisted anal fistula treatment (VAAFT; Karl Storz, Tuttlingen, Germany) and over-the-scope clip (OTSC®; Ovesco Endoscopy, Tübingen, Germany) have also been introduced. This variation in practice suggests either that a widely acceptable and reproducible procedure has not yet been identified, or that additional factors may influence choice.

There is no current systematic assessment of all potential surgical interventions for the treatment of Crohn's anal fistula. The aim of this review was to collate data on the outcomes, including complications, of surgical interventions for the treatment of fistulating Crohn's anal disease.

Methods

Search strategy

A systematic literature search for all publications that reported a Crohn's anal fistula-specific outcome, or surgical treatment outcomes of Crohn's anal fistula published between 1995 and March 2016 was performed. Since 1995, supporting medical therapy has changed significantly[8]. MEDLINE, Embase and Cochrane Library databases were searched using a predefined and registered (PROSPERO database, CRD42016050316) search protocol. Original studies were eligible for inclusion. Hand-searching was limited to bibliographies from identified systematic reviews following experiences in the pilot searches. Conference proceedings were included when related full text could be identified. Only papers in English were included. Manuscripts that reported outcomes of Crohn's anal fistula as part of all fistula types, those with fistula related to ileoanal pouch only, or outcomes of Crohn's rectovaginal fistula only, were excluded.

Terms used included 'Crohn Disease', 'Rectal fistula' or 'anal fistula', 'surgery', 'Ligation of inter-sphincteric fistula tract' (LIFT), 'seton', 'fistula plug', 'advancement flap', 'vaaft', 'OTSC' 'stoma' and 'proctectomy' (*Appendix S1*, supporting information).

VAAFT involves insertion of a fistuloscope through the external opening of the track. Secondary tracks are then identified and electrocautery is performed through the scope. The internal opening is identified and closed using a full-thickness advancement flap, with excision of the primary track where possible.

The OTSC® technique is performed in the lithotomy position. The track is prepared using a fistula brush. Anal mucosa is excised circumferentially around the internal fistula opening. Sutures are placed into the internal anal sphincter around the internal fistula opening and all tied loosely together in a knot with a few centimetres of length. The knot is then pulled through a clip applicator that guides a circular nitinol metal clip on to the internal fistula opening in order to close it.

Data extraction

Inclusion and exclusion criteria were applied to retrieved citations by two independent reviewers. Abstracts were reviewed to identify full-text papers. Two reviewers had to agree on inclusion of an abstract. The same process was repeated for full-text articles. At this stage, the reason for exclusion was recorded.

Two reviewers recorded extracted data independently into a data collection form. These were compared and any variation was discussed with a third reviewer. Where data were missing or unclear, the corresponding author was contacted by e-mail for clarification.

Data items collected included study descriptors, data on patient cohort, primary outcome used (including definition) and corresponding event rate. Study descriptors were year of publication, first author, study design, number of participants and number of participants with Crohn's disease, originating hospital and country of author. Patient descriptors included mean or median age of patient cohort, sex, duration of Crohn's disease, fistula anatomy (defined using either Parks' classification or the American Gastroenterological Association definition) and, where available, concurrent medical therapy. Intervention details focused on the primary surgical intervention, such as seton placement, LIFT procedure or fibrin glue. Primary outcome was taken as defined by each paper, as was the interval to assessment. Additional outcomes, including complications, were recorded as available together with rates of long-term recurrence.

Quality analysis

The study was conducted according to PRISMA guidelines[9]. Risk of bias was assessed using the ROBINS-I tool for non-randomized interventions[10], and the Cochrane tool for bias assessment in randomized trials[11]. Bias was assessed independently by two reviewers and then reconciled. Where there was disagreement, a third reviewer acted as an arbiter. The IDEAL (Idea, Development, Exploration, Assessment, Long-term study) framework provides a means of categorizing the development stage of an intervention[12]. This allows categorization according to how technically developed a technique is, how well the indications are defined, what the risks and benefits of the procedure are, and long-term follow-up data. Studies were assessed by two authors and allocated to an IDEAL stage.

Statistical analysis

Although meta-analyses of the data were originally intended, the paucity of RCTs and prevalence of small case series led to the decision to perform a qualitative synthesis only using descriptive statistics. No assessment of heterogeneity, publication bias or any other statistical assessment was planned. The primary outcome was fistula healing rate, defined as a reduction of 50 per cent or more from baseline in the number of draining fistulas observed at two or more consecutive study visits, as per the ACCENT-II study[8].

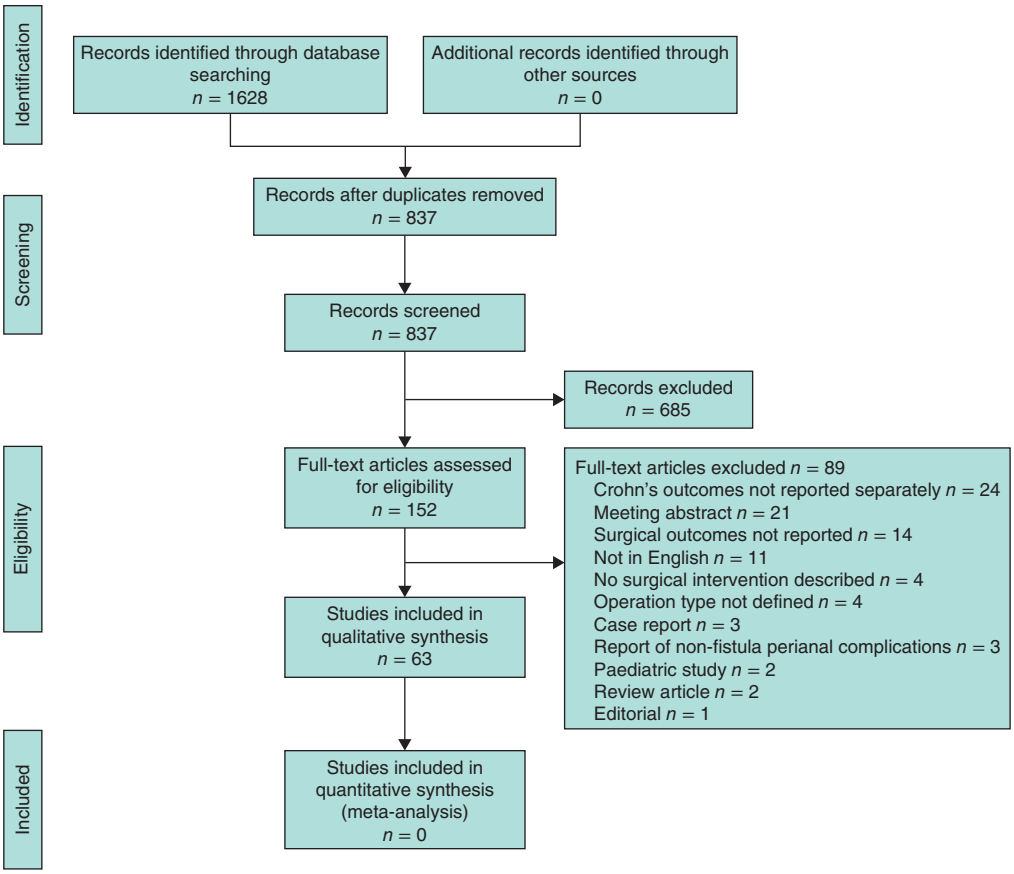

Fig. 1 PRISMA flow chart showing selection of studies for review

Results

Search results

Initial literature review identified 1628 citations, of which 791 were duplicates. Screened against the eligibility criteria, full-text manuscripts were retrieved and assessed. Of these 152 articles, 63 were included in the qualitative synthesis, reporting outcomes involving 1584 patients (*Fig. 1*). Study design was defined as retrospective cohort in 39 studies, as prospective cohort in 16, and as open-label or single-arm trial in five; there were three RCTs. The number of patients with Crohn's anal fistula ranged from two to 41 in prospective cohort studies, one to 119 in retrospective cohorts, and ten to 33 in open-label/single-arm trials. There were 141 patients in the randomized trials.

The surgical interventions described were draining seton, examination under anaesthesia (EUA) with local anti-TNFα therapy, fistulotomy, fistulectomy, fistula plug, fibrin glue, advancement flap, LIFT procedure, VAAFT, OTSC®, carbon dioxide laser therapy, diverting stoma and proctectomy. A summary of study characteristics is shown in *Table 1*[13–75].

Risk of bias within studies

Bias assessment for non-randomized and randomized studies is shown in *Tables S1* and *S2* (supporting information). Overall, bias in non-randomized studies tended to decrease as publication dates approached the present. Potential bias from confounders arose in studies with mixed populations (cryptoglandular and Crohn's fistula), with incomplete characterization of the cohort. This bias was reduced in cohorts limited to Crohn's fistula, where patient and disease factors were usually more clearly defined. Characterization was still suboptimal with regard to classification of fistulas, use of medical therapies, distribution of disease, smoking status and duration of perianal fistula.

Selection bias was an issue in retrospective studies that reported the outcomes of interventions in a single centre over a number of years. The criteria for offering interventions to patients were not clear: several studies stated

Table 1 Summary of included studies

Reference	Study design	Total no. of patients	No. of patients with Crohn's anal fistula	Intervention(s)
Buchanan *et al.*[13]	Retrospective cohort	24	6	Seton
Chung *et al.*[14]	Retrospective cohort	51	40	Seton, AFP
Gligorijević *et al.*[15]	Prospective cohort	24	24	Seton
Göttgens *et al.*[16]	Pilot trial	10	10	Seton
Kotze *et al.*[17]	Retrospective cohort	78	78	Seton
Sciaudone *et al.*[18]	Retrospective cohort	35	35	Seton
Sugita *et al.*[19]	Retrospective cohort	67	67	Seton
Tanaka *et al.*[20]	Retrospective cohort	14	14	Seton
Uchino *et al.*[21]	Retrospective cohort	62	62	Seton
Graf *et al.*[22]	Retrospective cohort	119	119	Seton, fistulotomy
Thornton and Solomon[23]	Retrospective cohort	28	28	Seton
Dursun *et al.*[24]	Retrospective cohort	81	81	Seton, fistulotomy
Alessandroni *et al.*[25]	Prospective cohort	12	12	Local anti-TNFα
Asteria *et al.*[26]	Prospective cohort	11	11	Local anti-TNFα
Faucheron *et al.*[27]	Retrospective cohort	41	41	Fistulotomy, seton
Halme and Sainio[28]	Retrospective cohort	35	35	Fistulotomy
Scott and Northover[29]	Retrospective cohort	59	59	Fistulotomy, seton
van Koperen *et al.*[30]	Retrospective cohort	61	61	Fistulotomy, MAF
de Parades *et al.*[31]	Retrospective cohort	30	11	Fibrin glue
Sentovich[32]	Retrospective cohort	48	6	Fibrin glue
Sentovich[33]	Retrospective cohort	40	4	Fibrin glue
Park *et al.*[34]	Prospective cohort	25	2	Fibrin glue
Loungnarath *et al.*[35]	Retrospective cohort	39	13	Fibrin glue
Zmora *et al.*[36]	Retrospective cohort	37	7	Fibrin glue, MAF
Mizrahi *et al.*[37]	Retrospective cohort	106	28	MAF
Hyman[38]	Prospective cohort	33	14	MAF
Jarrar and Church[39]	Retrospective cohort	98	19	MAF
Joo *et al.*[40]	Retrospective cohort	26	26	MAF
Makowiec *et al.*[41]	Prospective cohort	32	32	MAF
Ozuner *et al.*[42]	Retrospective cohort	101	47	MAF
Rieger *et al.*[43]	Retrospective cohort	35	6	MAF
Sonoda *et al.*[44]	Retrospective cohort	99	44	MAF
Marchesa *et al.*[45]	Retrospective cohort	13	13	MAF
Van der Hagen *et al.*[46]	Retrospective cohort	103	21	MAF, fistulotomy
Nelson *et al.*[47]	Retrospective cohort	65	17	Dermal advancement
Cintron *et al.*[48]	Prospective cohort, multicentre	73	8	AFP
El-Gazzaz *et al.*[49]	Retrospective cohort	33	13	AFP
Ky *et al.*[50]	Prospective cohort	45	14	AFP
O'Connor *et al.*[51]	Prospective cohort	20	20	AFP
Ommer *et al.*[52]	Retrospective cohort	40	4	AFP
Owen *et al.*[53]	Retrospective cohort	35	3	AFP
Schwandner and Fuerst[54]	Prospective cohort	16	10	AFP
Schwandner *et al.*[55]	Prospective cohort	19	7	AFP
Senéjoux *et al.*[56]	RCT	106	106	AFP, seton
Zubaidi and Al-Obeed[57]	Prospective cohort	22	2	AFP
Gingold *et al.*[58]	Prospective cohort	15	15	LIFT
Molendijk *et al.*[59]	Randomized phase II trial	21	21	MSC
Cho *et al.*[60]	Phase I trial	10	10	ASC
Cho *et al.*[61]	Prospective cohort	41	41	ASC
Ciccocioppo *et al.*[62]	Phase I trial	12	12	MSC
de la Portilla *et al.*[63]	Open-label trial	24	24	ASC
Garcia-Olmo *et al.*[64]	Prospective cohort	10	3	ASC
Garcia-Olmo *et al.*[65]	Randomized open-label trial	49	14	ASC, fibrin glue
Lee *et al.*[66]	Phase II trial	43	33	ASC
Schwandner[67]	Prospective cohort	13	11	VAAFT
Mennigen *et al.*[68]	Retrospective cohort	10	6	OTSC®
Regueiro and Mardini[69]	Retrospective cohort	32	32	EUA

Table 1 continued

Reference	Study design	Total no. of patients	No. of patients with Crohn's anal fistula	Intervention(s)
Schlegel *et al.*[70]	Retrospective cohort	11	11	IAR
Yamamoto *et al.*[71]	Retrospective cohort	31	31	Stoma
Schaden *et al.*[72]	Retrospective cohort	69	5	Myocutaneous flap
Ozturk[73]	Retrospective cohort	10	1	Free cartilage
Bodzin[74]	Retrospective cohort	7	7	Carbon dioxide laser
Moy and Bodzin[75]	Retrospective cohort	27	27	Carbon dioxide laser

AFP, anal fistula plug; TNF, tumour necrosis factor; MAF, mucosal advancement flap; LIFT, ligation of intersphincteric tract; MSC, mesenchyme-derived stem cells; ASC, adipose-derived stem cells; VAAFT, video-assisted anal fistula treatment; OTSC, over-the-scope clip; EUA, examination under anaesthesia; IAR, intersphincteric anal resection.

that patients offered a procedure 'typically' had certain characteristics. Studies from teaching hospitals reported outcomes of patients referred to their centre, likely to introduce further selection bias.

Bias associated with the classification of interventions tended to be low in studies reporting outcomes from one specific procedure. The details of the procedure and perioperative care were clear. In studies reporting the use of setons, some issues arose around the timing of removal, whether setons were removed or not, and the timing and nature of concurrent medical therapy[15,17].

Outcome measurement was highly variable. Many studies reported healing, without clear definition, as their primary outcome. Other commonly reported measures included absence of drainage from a fistula when compressed with a finger[56], or closure of the external and internal opening of a fistula track at variable time points. Occasional use of MRI to confirm fistula fibrosis was reported[25]. One study[29] reported a successful outcome as 'the patient and surgeon are both satisfied'. Only one study[56] had blinded assessors – a panel of three surgeons who reviewed perineal photographs to confirm fistula closure.

In the randomized trials, the main concerns involved allocation concealment and blinding of participants. One stem cell study[65] had patients allocated to receive liposuction to harvest cells only if they were in the intervention arm. Overall, these trials were of good quality.

Results of studies

A summary of the key outcomes by intervention is shown in *Table 2*.

Outcomes after seton insertion

Setons were used in a number of different ways. Use of a seton alone, with removal at various time points, was reported in six retrospective fistula cohort studies[13,14,18,19,21,22], and included a total of 329 Crohn's fistulas. In the four studies[14,18,19,22] assessing short-term healing, success rates ranged from 14 to 81 per cent. One study[21] looked at symptom improvement, defined as improvement by at least 1 point in all domains of the perianal disease activity index. This endpoint was achieved in 72 per cent of patients. Long-term recurrence was reported in 43 per cent[18] and 83 per cent[13] of patients. Further drainage of abscess was required in 42·8 per cent[19], and in one study[21] two patients developed a cancer related to the fistula.

Long-term setons were used for symptom control in one study[23] of 28 patients, of whom 26 noted symptomatic improvement. The two patients without improvement went on to have a proctectomy or defunctioning stoma.

Table 2 Summary of key outcomes by intervention, including classification of level of evidence[76]

Intervention	Highest level of evidence	Success rate (%)	Complication rate (%)
Seton	IIb	14–81	Abscess 7–8
Fistulotomy	IIIb	72–100	n.r.
Fibrin glue	IIIb	40–67	n.r.
Anal fistula plug	IIb	15–86	Abscess 4–54 Avulsion 10 Dehiscence 2
Advancement flap	IIIc	50–85	Haematoma 7 Flap retraction 7
LIFT procedure	IV	60	n.r.
Local stem cells	Ib	29–79	Pain 19 Anal inflammation 7 Abscess 17–19
VAAFT	IV	8	n.r.
OTSC®	IV	83	n.r.
Stoma	IIc	81	Death 5 Stoma complication 16

n.r., Not reported (used where no outcomes reported, or outcomes in patients with Crohn's disease not clear); LIFT, ligation of intersphincteric tract; VAAFT, video-assisted anal fistula treatment; OTSC, over-the-scope clip.

Seton therapy combined with anti-TNFα therapy was the focus of two retrospective cohort studies[17,20] and one prospective cohort study[15], accounting for a total of 116 patients. There was incomplete characterization of group demographics. The timing of anti-TNFα therapy in relation to sepsis drainage or seton insertion was not clear in these studies. Short-term success was defined as absence of drainage in two studies[15,17] (although the time point for measurement was unclear) and complete fistula healing in one[20]. These outcomes were achieved in 46 per cent[15], 53 per cent[17] and 79 per cent[20] of patients. Recurrence rates, where reported, were between 9 and 28 per cent[15,20]. Abscesses occurred in up to 8 per cent[15]. One study[20] reported no serious adverse effects related to systemic drug therapy. Seton with anti-TNFα therapy also formed the control arm of a randomized trial[56], which found short-term healing in 30·7 per cent of patients, with a recurrent abscess rate of 7·7 per cent.

Examination under anaesthesia with local or systemic anti-TNFα therapy

Two prospective studies[25,26] assessed responses to EUA and local injection of anti-TNFα drugs. In one study[26], 11 patients received between three and five injections, and eight patients achieved remission (cessation of fistula drainage) at the end of the treatment course. In the second study[25], 12 patients with Crohn's anal fistula underwent fistulectomy and local anti-TNFα injection. Definition of healing was based on clinical and MRI appearances at 1 year. With four patients lost to follow-up, healing was achieved in seven patients (88 (95 per cent c.i. 48 to 100) per cent). One patient developed a new perianal abscess and another developed pulmonary tuberculosis after treatment[25].

One retrospective study[69] assessed the use of EUA as an adjunct to systemic anti-TNFα therapy, and found no discharge from fistulas at 3 months, although subsequent recurrence occurred in 44 per cent.

Fistulotomy

Seven retrospective studies[22,24,27–30,46] reported on the outcomes of fistulotomy in 148 patients. Although baseline factors were poorly reported, these were typically for low fistulas – those involving a small part of sphincter where division would not alter function. Outcomes were defined as initial healing[22] or 3-month healing[24].

Short-term healing was successful in 72–100 per cent of patients[22,24,27,28]. Longer-term (6 months or more after treatment) fistula recurrence occurred in five of 28 patients[30] and three of nine patients[46] at 12 months. One study[29] found that 22 of 27 patients had a 'satisfactory' outcome, although the five patients in whom the outcome was unsuccessful developed significant incontinence. Higher rates of continence disturbance were seen in other studies[30].

Fibrin glue

Six studies (five retrospective[31–33,35,36] and one prospective[34]) included 219 patients, but only 43 of these had Crohn's disease. Short-term success rates for fibrin glue ranged from 40 to 67 per cent[31,33,34,36]. In one study[32] reporting long-term follow-up, three of four patients remained healed.

Fistula plug

Results of anal fistula plug were reported in 11 studies including 191 patients with Crohn's anal fistula. Study design included one RCT[56], six prospective cohort studies[48,50,51,54,55,57] and four retrospective cohort studies[14,49,52,53]. In the cohort studies, follow-up ranged from 0·75 to 29 months after the procedure. Definition of demographics was poor in these studies, and included 14 patients with a complex fistula in one study[50] (including 4 rectovaginal fistulas), and patients with a single transphincteric track and no proctitis in another[55]. In the RCT, the American Gastroenterological Association classification[77] was used, and included 18 patients with a complex fistula and 78 with a simple fistula. Ratios of men to women were 3 : 1 and 41 : 68 where reported, and age ranged from 26 to 43 years. Disease duration before the RCT was 3–13 years. One study[54] included the use of faecal diversion in addition to the anal fistula plug in some patients.

Success rates for the fistula plug technique ranged from 15 to 86 per cent. Where reported[49,50,52,56], postoperative abscess formation occurred in 4–54 per cent of patients. Additional complications included one wound dehiscence[52], five plug extrusions and two episodes of significant pain[56].

Advancement flaps

Eight retrospective[30,37,39,40,42–44,46] and two prospective observational[38,41] studies reported the outcome of mucosal advancement flaps in both Crohn's and cryptoglandular perianal fistulous disease. Of the 590 reported procedures, 204 were performed for Crohn's fistula. Where reported, treated fistulas were predominantly transphincteric, although studies included some rectovaginal fistulas.

Success in short-term healing was observed in 50–85 per cent of patients. Where reported[38,46], the recurrence rate at more than 1 year was 30–50 per cent. Complications were reported in only one study[40], with haemorrhage and flap retraction occurring in 7 per cent.

A retrospective study[45] reported on the use of a circumferential advancement flap for severe and multiple fistula tracks in 13 patients, combined with stoma formation in eight. This led to symptomatic improvement in eight patients, although all patients also had a stoma either before or as part of the procedure.

One retrospective study[47] reported on the use of dermal flaps to close the fistula opening, with 15 of 17 patients achieving short-term healing.

An augmented approach was used in a pilot trial[16]. This involved placement of a seton, followed by local treatment with platelet-rich plasma and mucosal advancement flap. Participants also received multiple concomitant medical therapies. At 1-year follow-up, seven of the ten patients had a dry fistula.

Ligation of intersphincteric fistula tract procedure

One study[58] reported the outcomes of patients undergoing the LIFT procedure. This was a retrospective study of 15 patients with transphincteric fistula, followed up for 1 year. At 2-month follow-up, nine (60 per cent) had healed, and eight of these remained healed at 1 year. Complications such as abscess were reported for this study; however, they were calculated as mean numbers for the cohort. The author was contacted, but data from this study were no longer available.

Stem cell therapy

Six studies reported the outcome of stem cell therapy; five open label/phase I or II trials[59,60,63,65,66], with longer-term follow-up[61] of the cohort initially reported by Cho *et al.*[60] in 2013. These studies assessed adipose-derived stem cells in 143 patients. One phase I trial[62] reported outcomes of mesenchymal stem cell treatment in 12 patients. Follow-up in these studies ranged from 8 weeks to 24 months. Cohorts were dominated by men and young patients, with a median age of about 32 years in several studies. Duration of Crohn's disease was approximately 4·5 years where reported. Most fistulas were transphincteric. Success rates for healing ranged from 29 to 79 per cent. Improvement in symptoms was noted in a large proportion of patients. This was assessed at 8 weeks[60], defined as a variable time point of 'no discharge for 6 weeks'[59], or at clinic appointments at 12 and 24 months[61].

Symptoms associated with disease flare, such as abdominal pain and diarrhoea, were reported in up to 60 per cent[66] and 7 per cent[61] respectively. Local complications included anal pain in 19 per cent[66], anal inflammation in 7 per cent[61], perianal swelling in 29 per cent[59] and perianal abscess in 17–19 per cent[59,66] of patients.

A single study[64] of recurrent anal fistula with a subgroup of three patients with Crohn's disease found that one patient healed and one improved when adipose-derived stem cells were injected into the fistula and the internal opening was closed.

Video-assisted anal fistula treatment

One prospective study[67] reported outcomes of patients treated with VAAFT. Thirteen patients were treated, of whom 11 had anal fistula related to Crohn's disease. Of these 11 fistulas, nine were transphincteric, one was suprasphincteric and one was rectovaginal. The mean age of patients was 34 years. This study[67] combined VAAFT with rectal advancement flap and faecal diversion. 'Short-term success' was achieved in nine patients. There was no reporting of complications.

Over-the-scope clip (OTSC®)

A single case series[68] reported the use of OTSC® in anal fistula. Of the ten patients treated, six had fistula associated with Crohn's disease. Four were women, and all had a transphincteric fistula. No information was available on mean duration of disease. Median follow-up was 230·5 (range 156–523) days. The study reported short-term healing in five of the six patients with Crohn's disease. It was not possible to extract complications specific to treated patients with Crohn's fistula.

Proctectomy and diversion

One retrospective study[70] reported the use of intersphincteric anal resection (IAR) for fistulating and fibrosing perianal Crohn's disease. In this series, 11 patients underwent IAR and five achieved closure of the fistula. Another retrospective study[72] assessed outcomes of proctectomy with one-stage myocutaneous reconstruction (gracilis) in five patients. Perianal fistula healed in four cases, and only two patients were free from complications at the end of follow-up (median 19·6 months).

Faecal diversion was reported as a sole intervention in a series of 31 patients[71]. In this cohort, 25 patients achieved early remission, although this was sustained in only eight (median follow-up 81 months). One patient died as a result of Fournier's gangrene and five developed stoma complications, of whom two required operative revision. No patient developed malignancy in the defunctioned rectum[71].

Other therapies

One retrospective study[75] reported outcomes of patients treated with carbon dioxide laser to the fistula track. This included 27 patients, with a mean duration of disease of 36 months. At 1-month follow-up, four patients had ceased fistula drainage. Another retrospective study[74] found that laser treatment healed or improved symptoms in five of six

Table 3 Interventions classified by the IDEAL framework

IDEAL stage	Intervention
1 (Idea)	Circumferential advancement flap
	VAAFT
	OTSC®
	Free cartilage
2a (Development)	Local anti-TNFα injection
	LIFT
	Carbon dioxide laser
2b (Exploration)	Local stem cell therapy
	Mucosal advancement flap
	Fibrin glue
3 (Assessment)	Anal fistula plug
4 (Long-term study)	Seton
	Fistulotomy
	Stoma/proctectomy

VAAFT, video-assisted anal fistula treatment; OTSC, over-the-scope clip; TNF, tumour necrosis factor; LIFT, ligation of intersphincteric tract.

patients. One other study[73] assessed the use of free cartilage as an interposition material in Crohn's fistula. This was unsuccessful.

Grading according to the IDEAL framework

Only seton, fistulotomy and faecal diversion/proctectomy are classified as IDEAL 4 interventions. The majority of interventions are classified as IDEAL 1–2b interventions (*Table 3*).

Discussion

Advances in the medical therapy of fistulating perianal Crohn's disease have been boosted by large RCTs[8,78,79]. The present study has highlighted a number of important features regarding surgical interventions. The level of evidence supporting these interventions was generally low. Studies often captured specific subsets of patients, and selection bias means that reported results are not always matched by real-world experience. The lack of a classification system with prognostic value means that a benefit produced in one (unknown and undefined) cohort may be masked by failure in another. Options for surgical management of Crohn's anal fistula, including seton insertion, advancement flap, anal fistula plug and stem cells, have been used in several studies, although success rates vary. Only three RCTs comparing therapies were retrieved. It should be noted that a number of feasibility studies were performed, particularly in relation to local stem cell therapy. Since searches for this review were performed, a randomized trial of stem cells has been reported[80]. A randomized trial of advancement flap *versus* seton drainage in the context of protocolled medical therapy is underway[81].

Meta-analyses were not appropriate for these data. The IDEAL classification was used to grade the interventions. Part of the categorization used in the IDEAL framework is the number and type of patients, with 'indication' being an important discriminator[12]. Although draining setons, fistulotomy and faecal diversion seem to have broadly agreed indications with long-term follow-up, this does not appear to be the case for other interventions. Classification of fistula anatomy varies between the Hughes–Cardiff classification[82], Parks classification[83] and American Gastroenterological Association definitions[77]. It is not always possible to consolidate these classifications. Some studies also specified whether or not patients had proctitis[55], as this is thought to be relevant to prognosis[5,6].

Current thinking suggests that optimal therapy involves a combined medical and surgical strategy. Smaller case series often described the current medical therapy of their patients, but larger retrospective studies typically failed to report this.

It was impossible to make meaningful comparisons of success rates between interventions, as selected outcomes and time points were heterogeneous. Pooled analysis was hampered by the bias inherent in the preponderance of retrospective studies, and the limited size of their cohorts. It was impossible to compare risk between the operative procedures, as reporting of complications was very poor, with the exception of clinical trials. Some studies[30,71] also reported 'long-term recurrence' at the end of their follow-up period as late as 6–8 years, but was this truly recurrence due to the surgical procedure or simply the natural history of the disease?

Only broad conclusions can be drawn from the present study. Setons provide palliation and can be used in the long term; advancement flap and stem cell therapy may emerge as effective therapies, but require well designed randomized trials. A number of other procedures including LIFT, VAAFT and OTSC® require further evaluation.

Fibrin glue has largely fallen out of favour, and fistula plugs are considered to have limitations, including failure and associated sepsis. Advancement flaps may not be technically possible with a 'woody' rectum, extensive fibrosis or active proctitis. The combination of recurrent Crohn's disease and loose stool means that any sphincter disruption or alteration in anocutaneous sensation may have an exaggerated impact on continence. Clinicians and patients may therefore understandably be keen to avoid procedures that pose additional risk to the sphincter, including fistulotomy. Given these technical considerations, fistula anatomy and the risk of recurrent episodes of anal perianal sepsis, including fistula in the long term, it is unsurprising that most

clinicians favour conservative interventions such as seton placement[7].

When considering these studies together, especially over longer-term follow-up, it may be inferred that Crohn's anal fistula is at best palliated by surgical intervention. Most studies report success in terms of short-term healing, and have not addressed the management or prevention of long-term recurrence. Although the idea of healing anal fistula is aspirational, work is required to understand how to control symptoms and limit recurrence with medical and surgical techniques. Patient-centred outcomes such as data on quality of life, impact on personal and social interactions, or lost work-days may be more helpful in decision-making. For example, faecal diversion has been shown to improve gastrointestine-specific domains of quality-of-life measures in this setting[84].

Work needs to be done to improve the quality of evidence for every type of surgical intervention. Transparent and thorough reporting on studies involving these patients is warranted. There needs to be international agreement on definitions to facilitate comparisons between institutions. Development and adoption of a core outcome set, including a validated, disease-specific quality-of-life score, would help. A classification system based on prognostic factors, and improved therapeutic options based on an understanding of the current mechanisms of treatment failure, are both crucial.

Collaborators

Other ENiGMA Collaborators are: A. Hart, A. J. Lobo, S. Sebastian (gastroenterology), P. Sagar, S. P. Bach, A. McNair (surgery), A. Verjee, S. Blackwell (patient representatives), P. F. C. Lung (radiology) and D. Hind (Sheffield Clinical Trials Research Unit).

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Graphical Abstract

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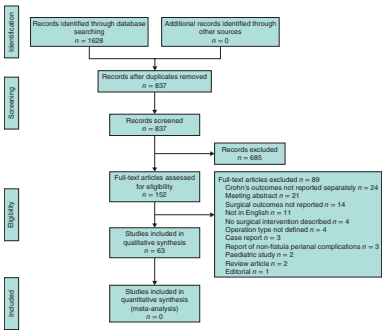

This study has systematically reviewed data on outcomes for surgery in Crohn's anal fistula. Studies have heterogenous outcomes precluding meta-analysis. This study highlights factors associated with poor generalizability of findings, which may be built upon by future researchers in this field.