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ORIGINAL ARTICLE

Permacol™ collagen paste for cryptoglandular and Crohn's anal fistula

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Abstract

Background Permacol™ collagen paste, an acellular crosslinked porcine dermal collagen matrix suspension, is a new treatment option for anal fistula. Data remain limited, however, and as yet only the results of one case of Crohn's fistula treated with Permacol™ paste has been reported. The aim of this study was to assess the use of Permacol™ collagen paste in patients with cryptoglandular and Crohn's perianal fistulae.

Methods A prospective study was conducted on patients with anal fistula, treated with Permacol™ paste. Patients were followed at 1 week, 6 and 12 months, and on demand thereafter. The main focus was on fistula healing and postoperative continence. The former was defined as the absence of signs of recurrence on clinical examination, proctoscopy and rigid rectoscopy. Fecal incontinence was assessed before surgery and at each follow-up.

Results Thirty patients (19 women, 11 men; mean age 46 years), 12 (40%) of whom had Crohn's disease were included. The average number of previous fistula operations was 6. All patients had ≥ 6 months of follow-up, and 24 patients (80%) had ≥ 12 months of follow-up. The healing rate in all patients was 57% (17 of 30 patients) at 6 months and 63% (15 of 24 patients) at 12 months. One patient reported a worsening of fecal incontinence at 12 months; 2 patients had adverse events (perianal pain: $n = 1$, fluid accumulation $n = 1$) requiring fistula drainage. Patient characteristics, healing, incontinence, and adverse events did not differ significantly between patients with and without Crohn's disease.

Conclusions Our data indicate that Permacol™ paste is a safe and moderately effective treatment for cryptoglandular and Crohn's fistulae.

Keywords Anal fistula · Collagen · Fistula treatment · Anal sphincter · Minimally invasive surgical procedures · Crohn's disease

Introduction

A variety of surgical methods are available for the treatment of anal fistulae, but surgery carries an inherent risk of postoperative fecal incontinence if the treatment involves division of the anal sphincter [1]. Therefore, several sphincter-preserving methods have been developed, including fistula laser closure (FiLaC), video-assisted anal fistula treatment (VAAFT), ligation of the intersphincteric fistula tract (LIFT), over-the-scope clip (OTSC) and the use of biological materials such as fibrin glue [2–8]. However, although the risk of postoperative fecal incontinence is low, the fistula recurrence rate appears to be high after sphincter-preserving interventions [2–8].

One of these novel sphincter-preserving methods is fistula closure with Permacol™, a sterile acellular crosslinked porcine dermal collagen matrix suspension, used as a supple paste that appears to conform well to the fistula tract. The collagen scaffold of Permacol™ paste may form a matrix that accelerates neovascularization and cell infiltration and promotes tissue remodeling and fistula closure.

As yet, data from the use of Permacol™ are scarce, and fistula closure with Permacol™ paste has been evaluated in only one prospective multicenter observational study and in three retrospective studies, in which only one patient with Crohn's disease is included [9–12]. In particular, Crohn's disease continues to present a challenge, because perianal

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fistulization is common, the recurrence rate is high and wound healing poor [13–18].

The aim of this clinical study was to assess the use of Permacol™ collagen paste in patients with cryptoglandular and Crohn's perianal fistulae.

Materials and methods

Patients

From October 2015 to May 2017, selected patients underwent anal fistula treatment with Permacol™ paste injection. The operations were performed either at the University Hospital Erlangen ($n=24$) or at the Clinic Hallerwiese Nürnberg ($n=6$). Data were prospectively collected on patient demographics including previous surgeries, factors potentially influencing the healing rate [sex, age over 50 years, active smoking, body mass index (BMI) above 25 kg/m^2, steroid medication, preoperative C-reactive protein above 5 mg/l preoperatively, prolonged hospital stay, type of fistula, presence of stoma], and postoperative outcome, with a focus on healing, complications, and fecal incontinence.

Inclusion criteria were as follows: patients with complex fistula (type II, III or IV according to Parks classification or rectovaginal fistulation) considered not suitable for fistulectomy or fistulotomy because of an increased postoperative risk of fecal incontinence were offered Permacol™ paste injection. Absence of acute inflammation at the time of operation was mandatory.

Surgical technique

All patients had fistula conditioning with seton drainage before definitive treatment. The surgical procedure is shown in Fig. 1. The internal and external fistula openings were identified. The seton was withdrawn and the fistula tract was de-epithelialized with a brush, removing all granulation tissue. Hemostasis was then achieved before placement of resorbable 3-0 Vicryl, without tying, at the internal fistula opening. An injection cannula was inserted into the external fistula tract and the paste was applied. When the paste emerged at the inner fistula opening, the entire tract was considered to be filled. The sutures at the internal fistula opening were then tied, and paste was again applied to ensure complete filling. Finally, the external fistula opening was closed using resorbable sutures (Vicryl 3-0).

Patients were instructed to keep the wound area dry for 2 days, with careful anal hygiene. Patients were hospitalized postoperatively for a median of 3 days (range 2–8 days) due to local arrangements or if requested by the patients.

Outcome assessments

Patients were seen at 1 week, 6 and 12 months, and on demand thereafter with special focus on healing rate and postoperative incontinence. Fistula healing was defined as the absence of recurrence at clinical examination, proctoscopy and rigid rectoscopy. Fecal incontinence was assessed with the St. Marks Score before surgery and at 12 months postoperatively.

Patient satisfaction was assessed at 12 months by the visual analog scale (VAS: 0, no satisfaction; 10, high satisfaction). In addition, patients were asked in a face-to-face interview at 12-month follow-up to compare their postoperative pain with that after their previous anal fistula operations and classify it as being the same, less or more. Patients in whom Permacol™ therapy failed were asked whether they would consider a second attempt.

Statistical analysis

Data were analyzed with SPSS software (version 21). Comparisons of metric and ordinal data were calculated with Student t test or Mann–Whitney U test. The Chi square test was used for categorical data. Statistical significance was set at $p<0.05$.

Results

Patient demographics and fistula characteristics

There were 30 patients [median age 46 years (range 17–78 years); 63% women ($n=19$)] included in the study. Twelve (40%) had Crohn's disease, of whom 10 (83%) were on systemic medical therapy. No patients had clinical signs of active local infection at operation.

Table 1 shows the demographics of all patients with a comparison of those with and without Crohn's disease. Only preoperative C-reactive protein (CRP) was found to differ significantly [10.2 mg/l in the Crohn's group vs. 2.1 mg/l in those without ($p=0.027$)].

Transsphincteric fistulas were seen in 24/30 (80%), with 6/30 (20%) having rectovaginal fistulae (Table 2). The median number of operations the patients had already undergone was 6 (range 1–25 operations). The median time between the first fistula operation and Permacol™ treatment was 35 months (range 4–136 months). There were no significant differences in fistula characteristics between patients with and without Crohn's disease.

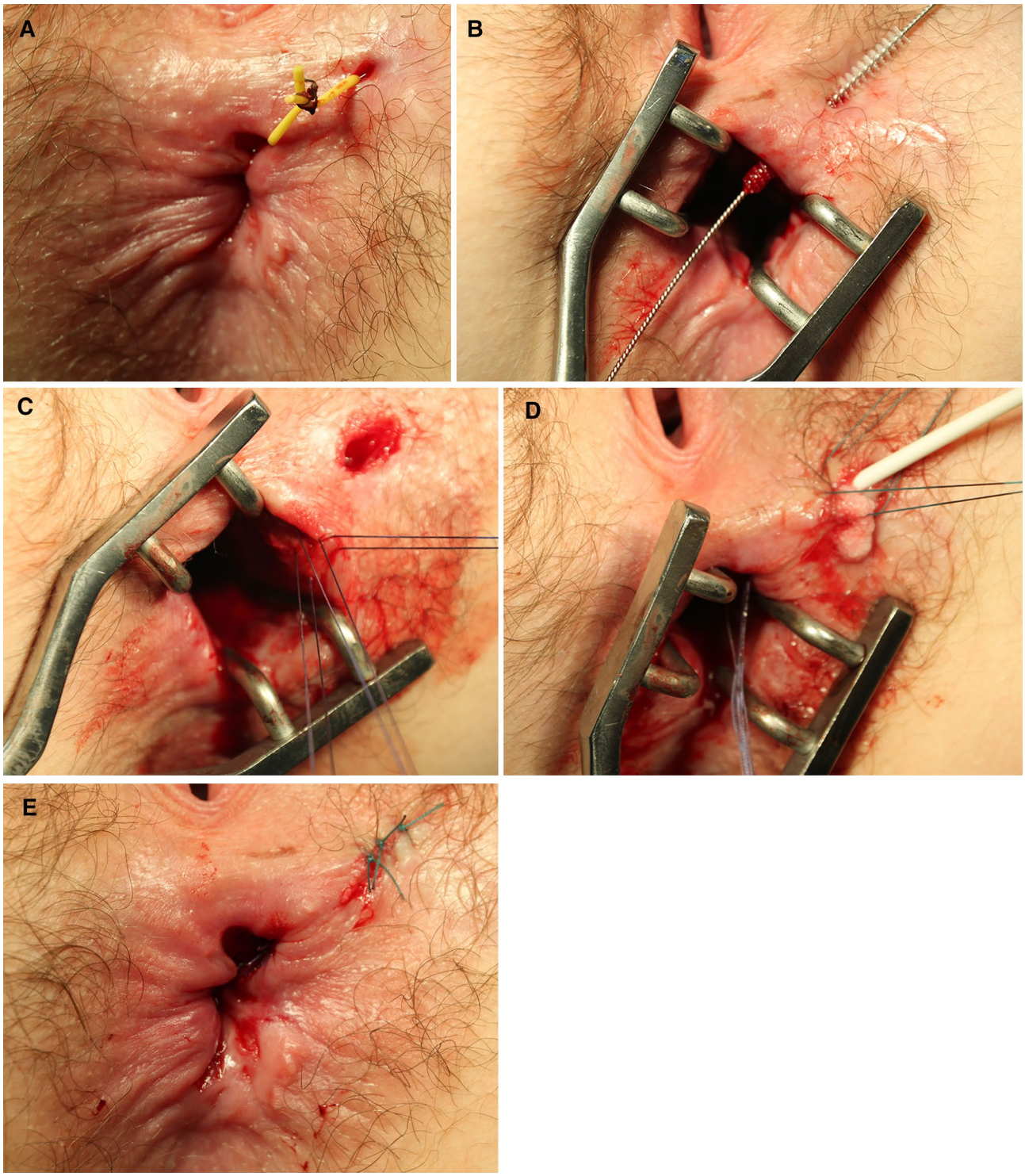

Fig. 1 Fistula closure with Permacol™ collagen paste; **a** loop-conditioned fistula; **b** de-epithelialization of the fistula tract; **c** closure of the inner fistula opening; **d** injection of the Permacol™ collagen paste; **e** closure of the outer fistula opening

Follow-up and outcome parameters

All 30 patients had a follow-up of ≥ 6 months, and 24 (80%) had a follow-up of ≥ 12 months. Table 3 presents the postoperative and outcome parameters. Median length of hospital stay was 3 days (range 2–8 days). Healing was seen in 17/30 (57%) at 6 months and 15/24 (63%) at 12 months, with no significant difference between Crohn`s patients and

Table 1 Patient demographics

	All patients	Crohn's patients	Other patients	*p* value
Number	30	12	18	
Sex (female/male)	19/11	9/3	10/8	0.442
Age (years) [range]	45 [17–78]	33 [17–78]	50 [27–78]	0.078
BMI (kg/m$^{2)}$ [range]	24.9 [19.4–37.4]	25.0 [20.2–37.4]	24.9 [19.4–33.0]	0.676
ASA (I/II/III/unknown)	5/13/3/9	1/7/1/3	4/6/2/6	0.562
Active smoker	12/30 (40%)	4/12 (33%)	9/18 (50%)	0.713
Steroid medication	2/30 (7%)	2/12 (17%)	0/18 (0%)	0.152
Stoma	2/30 (7%)	2/12 (17%)	0/18 (0%)	0.152
Preoperative leukocytes (/µl) [range]	8000 [4600–12,500]	8700 [4600–12,500]	7800 [5100–11,400]	0.568
Preoperative CRP (mg/l) [range]	2.5 [0.2–43.2]	3.5 [1.5–43.2]	1.7 [0.2–5.2]	**0.027**

Bold—*p* value < 0.05 (significant difference)

Data presented as median (range)

BMI body mass index, *ASA* American Society of Anesthesiologists, *CRP* C-reactive protein

Table 2 Fistula characteristics

	All patients ($n=30$)	Crohn's patients ($n=12$)	Other patients ($n=18$)	*p* value
Fistula type				1.000
Transsphincteric	24/30 (80%)	10/12 (83%)	14/18 (78%)	
Rectovaginal	6/30 (20%)	2/12 (17%)	4/18 (22%)	
Number of prior fistula operations [range]	4 [1–25]	3 [1–17]	5 [1–25]	0.278
Time between first surgical intervention and Permacol™ application (months) [range]	19 [4–136]	23 [4–136]	19 [5–101]	0.835

Data presented as median (range)

those with a cryptoglandular aetiology at either time point ($p=0.465$ and $p=1.000$, respectively). There was no statistical difference in the healing rate between transsphincteric (15/24 (63%) at 6 months and 13/19 (68%) at 12 months) and rectovaginal fistulas (2/6 (33%) at 6 months and 2/5 (40%) at 12 months) ($p=0.326$ and $p=0.360$, respectively). Fifty-nine percent of fistulas (10/17) healed primarily, 41% (7/17) healed only secondarily after a phase of secretion, but without typical signs of infection such as pain, swelling and reddening. Primary and secondary healing pattern did not differ significantly between groups ($p=0.630$). The median healing time was 7 weeks (range 2–20 weeks). Patients with Crohn`s disease had significantly higher St. Marks score than non-Crohn's patients (preoperative: 5.4 vs. 1.9, $p=0.009$ and at 12 months: 5.4 vs. 3.3, $p=0.049$). One patient (3%) (in the non-Crohn's disease group) reported a worsening of preexisting fecal incontinence symptoms; continence was not affected by surgery in the other patients. Median patient satisfaction was 7 (range 0–10) on VAS. Forty-eight percent of patients (12/25) described the postoperative pain level as comparable to that after their previous fistula operations; in 32% (8/25) it was less and in 20% (5/25) more. In the 9 patients in whom Permacol™ treatment failed, 7 (78%) agreed that they would consider a second attempt.

Adverse events

Two patients (7%) experienced an adverse event (perianal pain $n=1$, fluid accumulation $n=1$), which required seton drainage of the fistula. Although both events occurred in patients without Crohn's disease, the rate of adverse events was not significantly different between groups ($p=0.503$).

Discussion

Fistula closure with Permacol™ collagen paste represents a new method for treating anal fistulas. As yet, only four studies have been published [9–12], none of which included patients with Crohn's disease [9, 10].

Our results indicate a healing rate of about 60% after 12 months, similar to that previously reported (53.5% and 47.6%) [9, 10]. Although Crohn's fistulae are a particular challenge, our data showed that Permacol™ paste was as

Table 3 Intra-, postoperative and outcome parameters

	All patients ($n=30$)	Crohn's patients ($n=12$)	Other patients ($n=18$)	p value
Duration of operation (min) [range]	21 [10–65]	21 [10–34]	22 [10–65]	0.650
Hospital length of stay (days) [range]	3 [2–8]	3 [2–8]	3 [2–3]	0.226
Healing rate at 6 months	17/30 (57%)	8/12 (67%)	9/18 (50%)	0.465
Transsphincteric	15/24 (63%)	7/10 (70%)	8/14 (57%)	0.678
Rectovaginal	2/6 (33%)	1/2 (50%)	1/4 (25%)	1.000
Healing rate at 12 months	15/24 (63%)	6/9 (67%)	9/15 (60%)	1.000
Transsphincteric	13/19 (68%)	5/7 (71%)	8/12 (67%)	1.000
Rectovaginal	2/5 (40%)	1/2 (50%)	1/3 (33%)	1.000
Duration for healing (weeks) [range]	6 [2–20]	7 [3–20]	6 [2–9]	0.391
Primary/secondary healing[a]	10/7	4/4	6/3	0.630
Vaizey score				
Preoperative	0.0 [0–22]	5,0 [0–12]	0.0 [0–22]	**0.009**
At 12 months	1.0 [0–22]	5,0 [0–12]	0.0 [0–22]	**0.049**
Patient satisfaction (VAS)	8 [0–10]	8 [0–10]	6 [0–10]	0.922
Postoperative pain[b]				**0.035**
Same	12/25 (48%)	2/10 (20%)	10/15 (67%)	
Less	8/25 (32%)	6/10 (60%)	2/15 (13%)	
More	5/25 (20%)	2/10 (20%)	3/15 (20%)	
Open to a second attempt with Permacol™ paste[b]				1.000
Yes	7/9 (78%)	3/4 (75%)	4/5 (80%)	
No	2/9 (22%)	1/4 (25%)	1/5 (20%)	

Bold—p value < 0.05 (significant difference)

Data presented as median (range)

VAS visual analog scale

[a]Of the 17 patients with healing at 6 months

[b]Data of 25 of 30 patients available

[c]Data of 9 of 13 patients in whom Permacol™ failed available

effective in Crohn's patients as in those with cryptoglandular fistulae.

In 7/9 treatment failures, fistulas persisted without healing being achieved at any time (Fig. 2). In the other two cases of failure at 1 year, the fistulas initially healed but a recurrent fistula was diagnosed 4 months later.

One patient reported a significant worsening of preexisting fecal incontinence 12 months postoperatively.

In our series, Permacol™ paste injection was only applied in complex perianal fistula, because "simple" fistulas were considered suitable for fistulectomy or fistulotomy, associated with low recurrence and complication rates. Based on our experience, Permacol™ paste can be used in both recurrent and primary fistulas. In all our cases, Permacol™ paste was only applied after prior seton insertion, as we believe conditioning of the anal fistula helps to ensure absence of inflammation, which is considered essential at the time of surgery. A combination of collagen matrix injection with flap repair also seems to be feasible and effective [13]. We consider Permacol™ paste application an alternative to other sphincter-sparing fistula procedures, such as OTSC, FiLaC or VAFFT. Its role in the treatment algorithm needs to be determined. Conceptually, it should be positioned before surgical procedures with a higher risk of sphincter damage.

Positive aspects of anal fistula treatment with Permacol™ are a low complication rate, comparable postoperative pain to patient's experience with other methods, and high patient satisfaction.

Limitations of this observational study are the small number of patients included, making prediction of risk factors for recurrence and comparison of outcomes between groups less reliable.

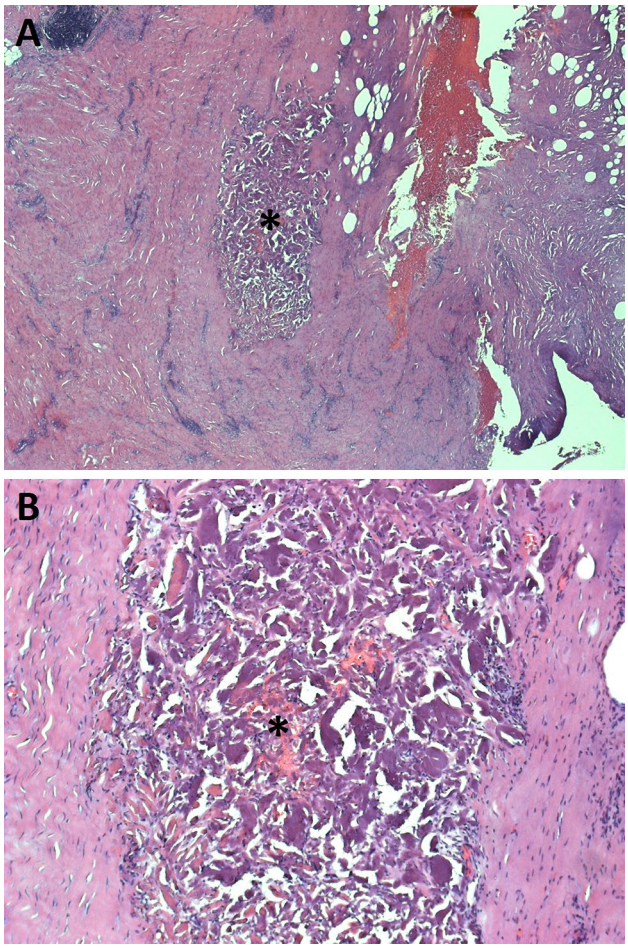

Fig. 2 Histopathological findings of an excised fistula sample in a patient after Permacol™ treatment failure: slightly chronic and sometimes mildly active inflammation; **a** ×2.5 magnification; **b** ×10 magnification; *Permacol™ paste

Conclusions

Our results suggest that Permacol™ collagen paste may be equally effective in patients with and without Crohn's disease. Although the rate of healing is moderate (50–60%), Permacol™ may be a good alternative for complex perianal fistulas because of sphincter-preserving effects, a low complication rate, and high patient satisfaction.

Compliance with ethical standards

Conflict of interest K.E. Matzel is medical adviser to Medtronic. M. Brunner has received an honorarium for lecturing at a Medtronic workshop.

Ethical approval This report contains no animal studies.

Informed consent For this type of study, formal consent is not required, as this report contains no identifying patient information.

References

1. Van Tets WF, Kuijpers HC (1994) Continence disorders after anal fistulotomy. Dis Colon Rectum 37:1194–1197
2. Giamundo P, Esercizio L, Geraci M, Tibaldi L, Valente M (2015) Fistula-tract laser closure (FiLaC™): long-term results and new operative strategies. Tech Coloproctol 19(8):449–453
3. Giamundo P, Geraci M, Tibaldi L, Valente M (2014) Closure of fistula-in-ano with laser–FiLaC™: an effective novel sphincter-saving procedure for complex disease. Colorectal Dis 16(2):110–115
4. Meinero P, Mori L (2011) Video-assisted anal fistula treatment (VAAFT): a novel sphincter-saving procedure for treating complex anal fistulas. Tech Coloproctol 15(4):417–422
5. Emile SH, Elfeki H, Shalaby M, Sakr A (2017) A systematic review and meta-analysis of the efficacy and safety of video-assisted anal fistula treatment (VAAFT). Surg Endosc. https://doi.org/10.1007/s00464-017-5905-2
6. Sileri P, Giarratano G, Franceschilli L, Limura E, Perrone F, Stazi A, Toscana C, Gaspari AL (2014) Ligation of the intersphincteric fistula tract (LIFT): a minimally invasive procedure for complex anal fistula: two-year results of a prospective multicentric study. Surg Innov 21(5):476–480
7. Prosst RL, Joos AK (2016) Short-term outcomes of a novel endoscopic clipping device for closure of the internal opening in 100 anorectal fistulas. Tech Coloproctol 20(11):753–758
8. Haim N, Neufeld D, Ziv Y, Tulchinsky H, Koller M, Khaikin M, Zmora O (2011) Long-term results of fibrin glue treatment for cryptogenic perianal fistulas: a multicenter study. Dis Colon Rectum 54(10):1279–1283
9. Giordano P, Sileri P, Buntzen S, Stuto A, Nunoo-Mensah J, Lenisa L, Singh B, Thorlacius-Ussing O, Griffiths B, Ziyaie D (2017) Final results of a European, multi-centre, prospective, observational Study of Permacol™ collagen paste injection for the treatment of anal fistula. Colorectal Dis. https://doi.org/10.1111/codi.13715
10. Fabiani B, Menconi C, Martellucci J, Giani I, Toniolo G, Naldini G (2017) Permacol™ collagen paste injection for the treatment of complex anal fistula: 1-year follow-up. Tech Coloproctol 21(3):211–215
11. Bayrak M, Altıntas Y (2018) Permacol™ collagen paste injection in anal fistula treatment: a retrospective study with one-year follow-up. Adv Ther 35(8):1232–1238
12. Schiano di Visconte M, Braini A, Moras L, Brusciano L, Docimo L, Bellio G (2018) Permacol collagen paste injection for treatment of complex cryptoglandular anal fistulas: an observational cohort study with a 2-year follow-up. Surg Innov. https://doi.org/10.1177/1553350618808120
13. Taxonera C, Schwartz DA, Garcia-Olmo D (2009) Emerging treatments for complex perianal fistula in Crohn's disease. World J Gastroenterol 15:4263–4272
14. Gold SL, Cohen-Mekelburg S, Schneider Y, Steinlauf A (2018) Perianal fistulas in patients With Crohn's disease, Part 2: surgical, endoscopic, and future therapies. Gastroenterol Hepatol (NY) 14(9):521–528
15. Safar B, Sands D (2007) Perianal Crohn's disease. Clin Colon Rectal Surg 20(4):282–293
16. Kotze PG, Shen B, Lightner A, Yamamoto T, Spinelli A, Ghosh S, Panaccione R (2018) Modern management of perianal fistulas in Crohn's disease: future directions. Gut 67(6):1181–1194

17. Sica GS, Di Carlo S, Tema G, Montagnese F, Del Vecchio Blanco G, Fiaschetti V, Maggi G, Biancone L (2014) Treatment of perianal fistula in Crohn's disease. World J Gastroenterol 20(37):13205–13210
18. Marzo M, Felice C, Pugliese D, Andrisani G, Mocci G, Armuzzi A, Guidi L (2015) Management of perianal fistulas in Crohn's disease: an up-to-date review. World J Gastroenterol 21(5):1394–1403
19. Sileri P, Boehm G, Franceschilli L, Giorgi F, Perrone F, Stolfi C, Monteleone G, Gaspari AL (2012) Collagen matrix injection combined with flap repair for complex anal fistula. Colorectal Dis 3:24–28