Perianal Surgery in Crohn's Disease

18

Gaspare Solina, Sara Renna, and Ambrogio Orlando

18.1 Anatomy and Clinical Definitions

The perineum is a diamond-shaped anatomic region bounded anteriorly by the pubis, posteriorly by the end of last coccygeal vertebra and laterally by the ischial tuberosities. The perineum contains anteriorly the penis and the scrotum in males and the vulva in women and posteriorly the anus. Lesions of the anus and perianal region are localized by convention and independently by position of the patient (genucubital, gynecological, etc.) dividing the area into four quadrants and localizing the injury as if there was a clock with 12 o'clock (anterior perineum) corresponding to the scrotum in males or the vulva in females and 6 o'clock corresponding to the coccyx. Hence, all anal and perianal lesions on the left are between 12 o'clock, 3 o'clock and 6 o'clock, while the ones on the right are identified as being between 12 o'clock, 9 o'clock and 6 o'clock.

The anus is the external opening of the digestive system and continues proximally with the rectum through the anal canal.

The anal canal is lined by transition mucosa. More in the submucosa there is the hemorrhoidal

G. Solina (🖂)

S. Renna • A. Orlando

© Springer International Publishing Switzerland 2016

venous plexus. More deeply there is the sphincter apparatus deputy to fecal continence. This sphincter apparatus consists of two concentric sphincter muscle layers, which are structurally different: the internal sphincter muscle, which is a muscle thickening in continuity with smooth muscle fibers of the rectum and the voluntary external sphincter muscle which is a continuation of the levator ani muscles.

The mucosal transit from the anal canal to rectum is lined by the pectinate line, a wavy line where the crypts of Morgagni lie. At the base of these crypts of Morgagni, in the antigravity position, there are the glands of Hermann and Desfosses that often involve also the fibers of the internal sphincter muscle.

The outside of the rectum is covered with adipose tissue that fills the ischiorectal space. It is bounded superiorly by the pelvic diaphragm that separates it from the pelvis-rectal space; this latter represents the pelvic preperitoneal part of the pouch of Douglas.

Therefore, a penetrating lesion of the anal canal may involve these perirectal spaces.

18.2 Types of Perianal Lesions

Perianal involvement in Crohn's disease may present with a variety of perianal lesions [1].

This variety is related to the different stages of the progression of the disease itself. Whether the origin is from the crypts of Morgagni (cryptogenic origin) or from Crohn's ulcer of the anal

UOC General Surgery, "V. Cervello" Hospital, Azienda Ospedaliera "Ospedali Riuniti Villa Sofia-Cervello", Palermo, Italy e-mail: g.solina@villasofia.it

UOC Internal Medicine, "V. Cervello" Hospital, Azienda Ospedaliera "Ospedali Riuniti Villa Sofia-Cervello", Palermo, Italy

G. Lo Re, M. Midiri (eds.), Crohn's Disease: Radiological Features and Clinical-Surgical Correlations, DOI 10.1007/978-3-319-23066-5_18

canal, these lesions evolve penetrating in the submucosal layer, thus becoming septic and giving rise to an abscess. The natural evolution of the abscess is a fistula with the skin.

According to the fistula path, we can distinguish different types of perianal fistulae, including the rectovaginal fistula.

If the inflammatory process is extended and long-lasting, chronic inflammation may be responsible for anal stenosis and/or fecal incontinence and may lead to dysplasia or neoplasia.

The short-term goals in the treatment of perineal Crohn's disease are abscess drainage and reduction of symptoms.

The long-term goals are resolving fistula discharge, improvement in quality of life, fistula healing, preserving continence, and avoiding proctectomy with stoma.

18.2.1 Anal Ulcer and Fissure

Anal canal ulcer denotes an involvement of this region by Crohn's disease and is often associated with perianal fistula, being often its origin: in these cases, it is possible to find the entrance of the fistulous track on its undermined edge.

Anal ulcer is often confused with an anal fissure, but it may be placed either eccentrically around the anal canal in contrast to idiopathic fissure in ano which tends to lie in the midline and is not associated with the so-called sentinel skin tag.

Considering that this lesion has to be accounted as a Crohn's disease localization, surgical treatment is not indicated, while systemic and local drugs are required.

The anal ulcer and fissure are usually painless and spontaneously heal in more than 80 % of patients [2].

Operative intervention in unselected patients does not improve the outcome and should generally be avoided.

However, patients who have pain and who do not have macroscopic evidence of rectal inflammation or local sepsis, lateral sphincterotomy may achieve healing without subsequent incontinence in most patients. Fissurectomy is contraindicated [3].

18.2.2 Skin Tag

There are two types of skin tags:

- Large, edematous, hard, cyanotic skin tag and often tender or painful. Typically arising from a healed anal fissure or ulcer. Excision contraindicated due to problems with a high rate of postoperative complications, including poor wound healing
- "Elephant ear" tag is flat, broad, long (up to 2 cm) and narrow polypoid lesions (fibroepi-thelial polypoid tags), soft, painless. May cause perianal hygiene problems and can be safely excised (however, excision of these innocuous tags is rarely required) [2, 3]

18.2.3 Perianal Abscess

Potential anorectal spaces may become infected with an abscess, including intersphincteric, ischiorectal and supralevator or pelvic-rectal spaces. If fistula is present, the abscess is resultant of obstruction of a perianal fistula tract.

The symptoms are perianal pain, tenderness, swelling, and fever.

Perianal abscesses must be drained surgically. Superficial perianal abscesses may be associated with a low perianal fistula and can be treated with incision and drainage. Deep perianal abscesses may be associated with a complex perianal fistula and should be treated with incision and drainage and placement of a noncutting seton if the fistula can be identified or placement of a mushroom catheter if an associated fistula cannot be identified. The placement of setons, while allowing prolonged drainage of the abscess, in essence perpetuates a perianal fistula [2, 3].

18.2.4 Perianal Fistula

A fistula is a tract of pus and/or granulation tissue between two epithelial surfaces lined with a fibrous wall. Primary tracts are connections between the internal and external openings, while secondary tracts are blind extensions [2]. Surgical treatment of perianal fistulas differs depending upon the anatomic classification and the overall treatment; both medical and surgical depend upon the stage of anal and rectal disease.

The most commonly used anatomic classification is the St. Mark's Hospital [4] one, which distinguishes simple and complex fistulas; this classification is adopted by the ECCO guidelines [5] and accepted by the American Gastroenterological Association Clinical Practice Committee [2].

The presence of proctitis, defined as any ulceration and/or stricture in the rectum, or inflammation and/or stricture of the anal canal, is an important component for fistula assessment (Statement 4 IOIBD and European Society of Coloproctology Guidelines) [6].

Patients without macroscopic evidence of proctitis who have *simple fistulas* may be treated by laying open the fistula tract (fistulotomy) or by a complete fistula excision (fistulectomy). The use of a noncutting seton rather than fistulotomy in patients with low fistulas and proctitis is preferred.

A noncutting seton is a suture or drain that is threaded into the cutaneous orifice of a perianal fistula, through the fistula tract, and across the mucosal orifice of the fistula into the rectum and then out the anal canal. A noncutting seton maintains drainage of the fistula, thereby reducing the risk of perianal abscess formation.

In general, there is a trend toward greater healing rates following fistulotomy for simple fistulas in patients without macroscopic evidence of inflammation of the rectum when compared with patients with active proctocolitis [3].

Complex fistulas require a more conservative surgical approach. Indeed, we cure the fistula problem at the price of leaving the patient with fecal incontinence. The main objective is to reduce the risk of incontinence or proctectomy. The secondary objective is the healing and/or the elimination of recurrent disease.

In the complex fistulas, there are many steps of treatment.

In patients with complex fistula, the treatment is aimed at a cone-like excision of all the tissue in

the ischiorectal fossa that contains the extrasphincteric part of the fistula with its eventual branches. The base of the cone is the perianal skin with one or more external fistulous tracks and the apex in the external side of the external sphincter muscle. This excision may be performed at one time or at multiple times if the extension of the removal would be too excessive and consequently too uncomfortable for patient's life and relationship. The residual cavity, in fact, heals by secondary intention and the healing time is proportional to the amount of removed tissue. If repeated removals are needed, the remaining fistulous branches are stabilized with extrasphincteric loose setons. When the removed parts heal, these residual fistulous branches are removed. Then a seton is put in the trans-sphinteric part of the fistula.

As in a tree, whose trunk is the trans-sphinteric part of the fistula and whose branches are the extrasphincteric parts, surgery consists in removing, at one or more times, all the branches, so that only the trunk, that corresponds as said to the trans-sphinteric part of the fistula, will remain (see Figs. 18.1 and 18.2).

Perianal disease is considered an exacerbation of CD or a resistance to the current treatment; hence, after reduction of the sepsis and downgrading of the disease, a biological therapy is needed (IG-IBD Statement 5D) [7].

The seton is left in place until at least the induction of the anti-TNF treatment period has

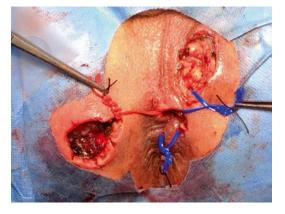


Fig. 18.1 Extra-sphinteric fistulectomy and setons placement



Fig. 18.2 Seton positioned only in the trans-sphinteric tract



Fig. 18.3 Courettage to remove the seton

been completed. Then, the seton is removed (clearing the fistulous track) (see Fig. 18.3) and the fistula healed by the drug.

To date, this multidisciplinary approach represents the best management of complex perianal disease.

Indeed, the results of combined treatment lead to closure rate of the fistula of 78.5 % (11 out of 14) of patients who completed the surgical program after a mean follow-up of 18.8 months [8]. But in another study, the fistula closure rate was significantly lower (29 %, 14 out of 48) after a mean follow-up of 20 months [9]. In the only published abstract by Rizzello et al. [10], 100 patients were treated with adalimumab after a deep surgical perineum sanitization. A complete fistula closure was observed in 77 % of treated patients at 156 weeks. In the only published controlled trial (ADAFI) planned on patients with perianal disease treated with biologics (\pm ciprofloxacin), the fistula closure rate at 24 weeks was 33 % (12 out of 36) in those treated with adalimumab and 53 % (18 out of 34) in those treated with adalimumab plus ciprofloxacin, but this difference was not significant (p=0.098). Nevertheless in this trial, the number of patients with complex perianal disease was not specified; only about 20 % of patients were treated with seton placement presuming that the number of patients with complex perianal disease was low [11].

Finally, data from the retrospective study by El-Gazzaz et al., including more than 100 patients, the fistula closure rate, in those who completed the surgical program and started biologics, was 36.6 % (37 out of 101) after a mean follow-up of 3.2 years [12]. In the ADAFI trial and in the study by El-Gazzaz et al., the recurrence rate was not reported.

The large published series on perianal fistulizing CD treated with infliximab showed a long-term cumulative probability of recurrence of 16.6 %, 31.3 %, and 40 % at 1, 2, and 5 years, respectively. When considering only the subgroup of patients treated with maintenance infliximab treatment, the cumulative probability of recurrence was 12 % and 36.6 % at 1 and 5 years, respectively [13].

In the prebiological era, the cutting seton was used. An analysis in the St. Mark's Hospital of London showed that complex fistulas are treated obteining healing in 55 out 79 fistulas (70 %). But this result has been obtained just using in 26 out 79 (33 %) fistulas the local conventional surgery (the study does not mention the incontinence rate) and in 21 out of 79 (38 %) treated with major surgery (defunctioning stoma, proctectomy)! [4].

The recurrence rate for "complex" fistulas managed with a cutting seton is reported to be 0-8 % with minor incontinence in 34–63 % and major incontinence reported in 2–26 % of patients [14, 15].

Cutting setons are also associated with significant morbidity related to discomfort from the seton [16].

In patients not responding or intolerant to biological therapy, a local biological therapy has been proposed. Evidences suggest that local injection of anti-TNF- α into the fistula tract may be beneficial. Two Italian groups described in pilot trials show local injections of both infliximab and adalimumab could improve fistula healing avoiding their systemic actions, but controlled and randomized trials are required to prove the value of this technique [17–20].

18.2.5 Rectovaginal Fistula

It is a particular type of fistula in ano, whose external opening is not on perianal skin but in the vagina. Rectovaginal fistula may be classified according to its track according to Parks classification in superficial, intersphincteric, trans-sphincteric, suprasphincteric and extrasphincteric fistulas.

This kind of fistula arises from penetrating ulceration of the anal canal or rectum into the vagina.

Surgical treatment of rectovaginal fistulas in patients with perianal Crohn's disease should only be attempted in the absence of active inflammation of the rectosigmoid colon.

Fistulotomy should rarely be used to treat low rectovaginal fistulas due to sphincter injury risk.

Placement of noncutting setons in this setting tends to enlarge the opening, making the fistula more symptomatic. An exception is when there is a rectovaginal septal abscess or inflammatory mass in addition to the fistulas.

Patients with rectovaginal fistulas may be treated by a number of other approaches, including primary closure, transanal advancement flap, sleeve advancement flap, and transvaginal advancement flap.

All the above-described techniques for fistulas have been used for this particular case but results were worse, while encouraging data were those using interposition of gracilis muscle [3].

18.2.6 Anorectal Stricture and Incontinence

Anorectal stricture may be short annular diaphragm-like strictures <2 cm in length or longer tubular strictures.

Anal or rectal strictures may arise as complications of ulceration of the anal canal or rectum, perianal abscesses, and complex perianal fistulas. They are often associated with ongoing proctitis.

Symptoms are typically those of urgency, incontinence, tenesmus, frequency, and difficulty with defecation. Some patients are asymptomatic.

The treatment is dilation: endoscopic and intraoperative during intervention for other associated lesions (gentle finger dilation to preserve sphincter function) and/or with specific devices like finger or bougie or Hegar's dilators at home. Repeat dilations are often required.

Some patients will require proctectomy [2, 3].

18.2.7 Anal Cancer

Cancer occurs rarely with an incidence rate of 0.2 per 1000 patient-years [21].

A systematic review of 34 case series and reports published in English language between 1950 and 2008 reports 61 cases of cancer, mainly in females (61 %). Females were significantly younger than males at the time of diagnosis of cancer (47 vs. 53 years, P < 0.032).

Females were noted to have the fistula for significantly shorter duration prior to cancer transformation when compared to males (8.3 vs. 16 years, P=0.0035). The average duration of CD was 18 years for female versus 24 years for male (p 0.005).

Cancer was detected at the first visit and diagnosed with biopsy in only small number of patients (20 %). In 59 % of patients, the cancer was detected anywhere between 1 month and 2 years after the initial presentation. The average delay in diagnosis of carcinoma in fistula tract was 5.8 months (median 3 months).

Adenocarcinoma was the most common histology (59 %), followed by squamous cell carcinoma (31 %).

The most common presenting complaints were pain (39 %) and persistent fistula (25 %). An abscess was reported at the time of examination in 41 % of patients [22].

The treatment *is* the one reported by oncologic guidelines and the prognosis for these patients is poor [23].

18.3 Adjunctive techniques to fistula closure

The not entirely encouraging results of combined treatment pushed the research toward finding new therapies hoping in better results.

The presence of proctitis is a bad prognostic index due to the rate of not healing and/or relapse. Hence, in patients with proctitis, relapse or absence of healing with biological therapy, surgical sphincter-saving surgery can be associated to strengthen the biological drug.

These techniques have been borrowed from the treatment of cryptogenic fistulas and data for Crohn's fistulas are not enough.

Some of these techniques then are aimed at closing the internal orifice, others at closing the fistula although branched (liquids) and others at finding the best application in simple tracks. The various options can be combined. The best prerequisite for optimal results is the absence of sepsis and the presence of a single fistula track.

18.3.1 Surgical Techniques for the Closure of Internal Orifice

An *Mucosal Advancement Flap (MAF)* can be used as an alternative to noncutting setons or after stabilization of the fistula through the noncutting seton and the removal of sepsis, in patients with complex fistulas who *do not* have macroscopic evidence of rectal inflammation.

The concept of endorectal advancement flaps is to preserve the sphincter by closing off the primary opening by means of a mobilized flap.

An advancement flap consists of incising a flap of tissue (mucosa, submucosa, circular muscle) around the internal opening of a fistula, excising the internal opening of the fistula tract and pulling the flap down to cover the primary fistula opening. Thereby we close the high pressure end of the fistula tract but we untouch the sphincter complex. The excluded fistula segment is expected to dry out over time. It is more difficult to use this technique for anteriorly positioned internal orifices.

The guidelines provided by the American Society of Colon and Rectal Surgeons [24] in 2005 have established that an endorectal advancement flap should be the best option to treat a recurrent complex fistula.

In a systematic review of 35 studies with an average follow-up of 28.9 months, the success rate of MAF for Crohn's fistulas was 64 % (range 33.3–92.9 %). The incontinence rate was 9.4 % with a wide interstudy variability (range 0–28.6 %). Re-interventions were needed in almost 50 % of patients [25]. Data from Cleveland, after a mean follow-up of 7 years, report a healing rate of 68 %, but report also the opportunity, in case of failure, to repeat a second, and, if necessary a third flap. Hence, the healing rate in Crohn's diseases rises from 68 % to 89 % [26].

Ligation of the intersphincteric fistula tract (*LIFT*) is a surgical option in the management of trans-sphinteric fistulas when the tract has matured into a fibrotic tube with granulation tissue enabling ligation and transection.

The surgical approach consists of ligation of intersphincteric tract close to the internal opening and removal of intersphincteric tract, scraping out all granulation tissue in the rest of the fistulous tract and suturing of the defect at the external sphincter muscle [27, 28].

In a prospective study of 15 consecutive cases of *CD patients* with trans-sphinteric fistulas, none of them developed fecal incontinence, and LIFT site healing was seen in 67 % of patients with a follow-up of 12 months [29].

In a review of 18 studies, 592 patients were considered with trans-sphinteric fistula reported in 73.3 % of cases. The mean healing rate was 74.6 %. The mean healing time was 5.5 weeks, and the mean follow-up period was 42.3 weeks. No de novo incontinence developed secondary to the LIFT procedure [30].

18.3.2 Surgical Technique for Closure of the Fistulous Track

The aim is to facilitate the closure of the fistula tract using materials that serve as solid or semisolid matrix to incorporate fibroblasts and tissue regeneration. Critic points: these materials are absorbed before scar tissue has formed, especially if there is sepsis. The semisolid material would have the advantage of filling also any associated ramifications or sinus.

18.3.2.1 Liquid or Semisolid Materials

Fibrin glue consists of fibrinogen and thrombin. Upon mixing, a fibrin clot is formed, which is thought to stimulate wound healing by inducing angiogenesis and fibroblast growth.

Initial studies of fibrin sealant for the management of anal fistulas were promising [31, 32]. Tyler et al. [33] reported also a prospective series of 89 patients with "complex" anal fistulas managed by obliteration of the fistula tract by fibrin glue. With at least 1 year of follow-up, 70.7 % of fistulas were healed. In contrast, a prospective series of 42 patients by Loungnarath et al. [34] reported that 31 % of fistulas were healed by use of fibrin sealant.

In a study of Johnson EK et al. [35], the success rate of plug vs. the fibrin glue was 87 % vs. 40 %. A meta-analysis found no significant difference between fibrin glue and conventional surgery with regard to recurrence and fecal incontinence rates [36] mainly between flap +/– fibrin glue showing worse outcomes after the combination of the two compared to flap repair alone [37]; thus, this material has not been used anymore.

As an alternative, it has been proposed the use of an injectable mixture consisting of *acellular porcine dermal matrix cross-linked* (Permacol[®]). The technique is the same as the glue one. Hammond TM et al. reported results of complex fistulas not related to IBD at 29 months: in 12 of 15 patients they healed [38].

It has been proposed the association of the flap with the mixture of Permacol[®] with a reported success after follow-up of only 6 months of 10 healings/11 patients including six IBD patients. The recurrence occurred in an IBD fistula [39].

18.3.2.2 Solid Materials

Bioprosthetic anal fistula plugs are more resistant to depolymerization, but they imply disadvantages in case of not previously detected secondary fistulous tracks (relapse).

Plugs, made of collagen, or *lyophilized porcine intestinal submucosa* (Surgisis[®] acellular biomaterial created from the endothelium of the porcine small bowel) or Gore-Tex[®], are inserted via the internal fistula opening to fill the fistula tract and leave the sphincter apparatus untouched.

Plugs are put under general anesthesia. All fistula tracts and primary openings are identified using conventional fistula probe and/or hydrogen peroxide instillation. All tracts are irrigated with hydrogen peroxide; however, the tracts are not curetted to avoid enlarging or damaging the fistula tract. The plug is pulled tip-first into the internal opening until resistance is encountered. The excess plug material is trimmed flush with the mucosa, and the plug is buried into the primary opening using a figure-of-eight 2–0 vicryl, which is inserted deep to the internal sphincter muscle. The plug is trimmed at skin level at the secondary opening. Care is taken not to occlude the secondary opening to allow drainage of material and to avoid a closed system. At the end of the procedure, the plug is completely buried within the fistula tract. In the case of multiple separate fistulas, this is repeated for each fistula tract. In the event of an excessively large-diameter fistula, the tract is "matured" using setons and 10 % topical metronidazole, for a period of 6–8 weeks, before anal fistula plug insertion. This narrows the diameter of the fistula tracts to dimensions that are amenable to "plugging."

Success rates in retrospective cohorts and one open-label study with a median follow-up of 6–15 months varied between 24 % and 88 %. Patients with multiple fistula tracts had a significantly higher failure rate [6].

In a prospective study with porcine intestinal submucosa anal fistula plug on complex Crohn's anorectal fistula, 80 % of patients were healed [40], but in later studies, data were opposite with low healing rate (33 %) [41].

One of the studies reported that failure was caused by dislodgement of the plug in 22 % of the cases [42].

It is commercially available a type of Surgisis[®] modified with a "button" that should be fixed in the internal opening at the plane of the internal sphincter (Biodesign[®] Anal Fistula Plug with biologic button) [43].

The Gore Bio-A Fistula Plug[®] is made from a *synthetic bioabsorbable polyglycolidetrimethylene carbonate copolymer* and comprises a *disk* attached to six tubes. The Bio-A[®] Fistula Plug is designed to prevent unexpected migration or extrusion. Its round disk has been designed to cover the internal opening sufficiently to prevent passage of the plug down the track. It virtually prevents plug dislodgement. Furthermore, the disk and the submucosal covering should offer a double barrier to the passage of feces through the track.

The tracks are curetted and then irrigated with hydrogen peroxide. A small submucosal pocket is created around the internal opening to allow the disk of the device to be accommodated. The submucosal pocket is then closed with 3–0 absorbable stitch. The disk is included in the suture to prevent plug migration, and the protruding tubes were trimmed 2–3 mm beyond the surface of the perianal skin.

In a prospective study on 11 cryptoglandular fistulae, the success was reported in 72.7 % (8/11) of patients, but the follow-up was short and healing evaluation not performed through MR [44].

These data are better than the ones published by Portilla et al. [45]: in their study, the successful closure was observed in 3 of 19 patients (15.8 %), but in only 3 patients, setons had been previously placed and the treatment of sepsis may be responsible of the different healing rates.

Lastly, the study by Buchberg B et al. is also interesting, in which Cook $Plug^{\otimes}$ is retrospectively compared to Gore $Plug^{\otimes}$. The overall procedural success rate in the Gore group was 6 of 11 (54.5%) versus 2 of 16 (12.5%) in the Cook group. A total of 19/27 (70%) procedures failed to resolve the fistulas. The reasons for failure were plug dislodgement in two attempts (10.5 %) and persistent drainage in 17 attempts (89.5 %) [46].

Data show varying success rates for fistula closure, which may be due to the heterogeneity of the studies regarding fistula origin (Crohn's vs. cryptoglandular) and follow-up.

In general, plugs may offer a valid first-line option for surgical treatment; measures to prevent dislodgement and perioperative antibiotics may increase success and safety, although costs can be a major concern [7].

In conclusion, there are very few randomized controlled trials comparing the various modalities of surgery for fistula in ano. Newer operations like the anal fistula plug and the LIFT procedure need to be evaluated by randomized clinical trials [55].

18.3.3 Other Techniques for Local Therapy

Mesenchymal stem cells seem to have promising applications in perianal CD. They are non-hematopoietic precursors of connective tissue cells with anti-inflammatory and tissueregenerative properties, extracted from subdermal adipose tissue obtained through liposuction. They may be injected into the rectal mucosa around fistula opening and into fistula tract with fibrin glue [47, 48].

García-Olmo et al. [48] reported a phase II study in which adipose-derived stem cells in fibrin glue vs. fibrin glue alone were administered in 49 patients (14 affected by CD): fistula healing was observed in 16 % of the patients who received only fibrin glue vs. 71 % of the patients who received stem cells plus fibrin glue (p < 0.001). In another phase II study [49], complete fistula healing was observed in 27/33 patients (82 %) by 8 weeks after ASC injection.

An Italian study, employing autologous bone marrow-derived mesenchymal stromal cells, confirmed that this novel approach represents a feasible, safe, and beneficial therapy in refractory CD [50]. A recent multicenter open-label, single-arm clinical trial was conducted at six Spanish hospitals. Twenty-four CD patients with complex fistulas were treated intralesionally with 20–40 millions of expanded allogenic adipose-derived stem cells: 69 % of patients showed a reduction in the number of draining fistulas at week 24, while 56 % achieved complete closure of the treated fistula, and only 6/24 patients (30%) obtained complete closure of all existing fistula tracts [51].

However, double-blind randomized placebocontrolled trials are needed to draw any conclusions on this therapeutic modality [6, 52].

In those patients with extensive and severe sepsis, mainly in the case of early relapse and conspicuous leakage of pus, it may be necessary to have a *diverting temporary stoma*. The rationale for fecal diversion is to reduce fecal flow across the fistula tract by reducing flow through the rectum, allowing the rectal mucosa to heal and the fistula to close. These procedures are now only rarely performed after a number of studies showed that most patients who undergo placement of a temporary diverting ileostomy or colostomy for perianal Crohn's disease never have intestinal continuity restored [4].

Complex fistulas associated with uncontrollable and recurrent sepsis and/or anal stenosis and/or incontinence are candidate, as last option, to perform *proctectomy* with a permanent stoma [52].

This proctectomy rates for patients with perianal Crohn's disease managed conservatively range from 10 % to 18 % [3].

Proctectomy does not always eradicate problems, as up to 40 % of patients experience delayed healing of a perineal wound and/or a persistent perineal sinus [53]. In these cases, it is possible to do a gracilis muscle transposition associated to proctectomy or to treat the residual sinus after previous proctectomy. In a single retrospective study including 18 CD patients, gracilis transposition was successful for complex fistulas in 64 % and for persistent nonhealing perineal sinuses in 50 % of the cases with maintained efficacy (90 % upon 10 months median follow-up) [54].

Bibliography

- Hughes LE. Clinical classification of perianal Crohn's disease. Dis Colon Rectum. 1992;35:928–32.
- Sandborn JW, Fazio WV, Feagan GB, Hanauer BC, American Gastroenterological Association Clinical Practice Committee. AGA technical review on perianal Crohn's disease. Gastroenterology. 2003;125: 1508–30.
- American Gastroenterological Association Clinical Practice Committee. American gastroenterological association medical position statement: perianal Crohn's disease. Gastroenterology. 2003;125:1503–7.
- Bell SJ, Williams AB, Wiesel P, Wilkinson K, Cohen RC, Kamm MA. The clinical course of fistulating Crohn's disease. Aliment Pharmacol Ther. 2003;17: 1145–51.
- Caprilli R, Gassull MA, Escher JC, Moser G, Munkholm P, Forbes A, Hommes DW, Lochs H, Angelucci E, Cocco A, Vucelic B, Hildebrand H, Kolacek S, Riis L, Lukas M, de Franchis R, Hamilton M, Jantschek G, Michetti P, O'Morain C, Anwar MM, Freitas JL, Mouzas IA, Baert F, Mitchell R, Hawkey CJ, European Crohn's and Colitis Organisation (ECCO). European evidence based consensus on the diagnosis and management of Crohn's disease: special situations. Gut. 2006;55(Supplement 1): i36–58.
- 6. Gecse KB, Bemelman W, Kamm MA, Stoker J, Khanna R, Ng SC, Panés J, van Assche G, Liu Z, Hart A, Levesque BG, D'Haens G, World Gastroenterology Organization, International Organisation for Inflammatory Bowel Diseases IOIBD, European Society of Coloproctology and Robarts Clinical Trials. A global consensus on the classification, diagnosis and multidisciplinary treatment of perianal fistulising Crohn's disease. Gut. 2014;63:1381–92.
- Orlando A, Armuzzi A, Papi C, Annese V, Ardizzone S, Biancone L, Bortoli A, Castiglione F, D'Incà R, Gionchetti P, Kohn A, Poggioli G, Rizzello F, Vecchi M, Cottone M. The Italian Society of Gastroenterology (SIGE) and the Italian Group for the study of Inflammatory Bowel Disease(IG-IBD) Clinical Practice Guidelines: the use of tumor necrosis factoralpha antagonist therapy in inflammatory bowel disease. Dig Liver Dis. 2011;43(1):1–20.
- Sciaudone G, Di Stazio C, Limongelli P, Guadagni I, Pellino G, Riegler G, Coscione P, Selvaggi F. Treatment of complex perianal fistulas in Crohn disease: infliximab, surgery or combined approach. Can J Surg. 2010;53(5):299–304.
- Antakia R, Shorthouse AJ, Robinson K, Lobo AJ. Combined modality treatment for complex fistulating perianal Crohn's disease. Colorectal Dis. 2013;15(2): 210–6.
- Rizzello F, Calabrese C, Calafiore A, Laureti S, Poggioli G, Campieri M, Gionchetti P. Adalimumab in the treatment of perianal Crohn's disease: short and

long term results in a Single Tertiary Center AGA Abstract Sa. 2014;S-358.

- 11. Dewint P, Hansen BE, Verhey E, Oldenburg B, Hommes DW, Pierik M, Ponsioen CI, van Dullemen HM, Russel M, van Bodegraven AA, van der Woude CJ. Adalimumab combined with ciprofloxacin is superior to adalimumab monotherapy in perianal fistula closure in Crohn's disease: a randomised, double-blind, placebo controlled trial (ADAFI). Gut. 2014;63(2):292–9.
- El-Gazzaz G, Hull T, Church JM. Biological immunomodulators improve the healing rate in surgically treated perianal Crohn's fistulas. Colorectal Dis. 2012;14(10):1217–23.
- Bouguen G, Siproudhis L, Gizard E, Wallenhorst T, Billioud V, Bretagne JF, Bigard MA, Peyrin-Biroulet L. Long-term outcome of perianal fistulizing Crohn's disease treated with infliximab. Clin Gastroenterol Hepatol. 2013;11(8):975–81.
- Garcia-Aguilar J, Belmonte C, Wong WD, Goldberg SM, Madoff RD. Cutting seton vs. two-stage seton fistulotomy in the surgical management of high anal fistula. Br J Surg. 1998;85:243–5.
- Hamalainen KP, Sainio AP. Cutting seton for anal fistulas: high risk of minor control defects. Dis Colon Rectum. 1997;40:1443–6.
- Ellis NC, Rostas JW, Greiner FG. Outcomes with bioprosthetic plugs for management of anal fistulas. Dis Colon Rectum. 2010;53:798–802.
- Poggioli G, Laureti S, Pierangeli F, Rizzello F, Ugolini F, Gionchetti P, Campieri M. Local injection of Infliximab for the treatment of perianal Crohn's disease. Dis Colon Rectum. 2005;48:768–74.
- Poggioli G, Laureti S, Pierangeli F, Bazzi P, Coscia M, Gentilini L, Gionchetti P, Rizzello F. Local injection of adalimumab for perianal Crohn's disease: better than infliximab? Inflamm Bowel Dis. 2010;16: 1631.
- Tonelli F, Giudici F, Asteria CR. Effectiveness and safety of local adalimumab injection in patients with fistulizing perianal Cohn's disease: a pilot study. Dis Colon Rectum. 2012;55:870–5.
- 20. Asteria CR, Ficari F, Bagnoli S, Milla M, Tonelli F. Treatment of perianal fistulas in Crohn's disease by local injection of antibody to TNF-alpha accounts for a favourable clinical response in selected cases: a pilot study. Scand J Gastroenterol. 2006;41: 1064–72.
- Laukoetter MG, Mennigen R, Hannig CM, Osada N, Rijcken E, Vowinkel T, Krieglstein CF, Senninger N, Anthoni C, Bruewer M. Intestinal cancer risk in Cohn's disease: a meta-analysis. J Gastrointest Surg. 2011;15:576–83.
- Thomas M, Bienkowski R, Vandermeer TJ, Trostle D, Cagir B. Malignant transformation in perianal fistulas of Cohn's disease: a systematic review of literature. J Gastrointest Surg. 2010;14:66–73.
- Beaugerie L, Itzkowitz SH. Cancers complicating inflammatory bowel disease. N Engl J Med. 2015; 372(15):1441–52.

- 24. Whiteford MH, Kilkenny III M, Hyman N, Buie WD, Cohen J, Orsay C, Dunn G, Perry WB, Ellis CN, Rakinic J, Gregorcyk S, Shellito P, Nelson R, Tjandra JJ, Newstead G. Practice parameters for the treatment of perianal abscess and fistula-in-ano. Dis Colon Rectum. 2005;48:1337–42.
- Soltani A, Kaiser AM. Endorectal advancement flap for cryptoglandular or Cohn's fistula-in-ano. Dis Colon Rectum. 2010;53:486–95.
- Jarrar A, Church J. Advancement flap repair: a good option for complex anorectal fistulas. Dis Colon Rectum. 2011;54(12):1537–41.
- 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.
- Rojanasakul A. LIFT procedure: a simplified technique for fistula-in- ano. Tech Coloproctol. 2009;13: 237–40.
- 29. Gingold DS, Murrell ZA, Fleshner PR. A prospective evaluation of the ligation of the intersphincteric tract procedure for complex anal fistula in patients with Crohn's disease. Ann Surg. 2014;260:1057–61.
- Vergara-Fernandez O, Espino-Urbina LA. Ligation of intersphincteric fistula tract: what is the evidence in a review? World J Gastroenterol. 2013;19(40): 6805–13.
- Cintron JR, Park JJ, Orsay CP, Pearl RK, Nelson RL, Sone JH, Song R, Abcarian H. Repair of fistulas-inano using fibrin adhesive: long-term follow-up. Dis Colon Rectum. 2000;43(7):944–9.
- Sentovich SM. Fibrin glue for all anal fistulas. J Gastrointest Surg. 2001;5:158–61.
- Tyler KM, Aarons CB, Sentovich SM. Successful sphincter-sparing surgery for all anal fistulas. Dis Colon Rectum. 2007;50:1535–9.
- 34. Loungnarath R, Dietz DW, Mutch MG, Birnbaum EH, Kodner IJ, Fleshman JW. Fibrin glue treatment of complex anal fistulas has a low success rate. Dis Colon Rectum. 2004;47:432–6.
- Johnson EK, Gaw JU, Armstrong DN. Efficacy of anal fistula plug vs. fibrin glue in closure of anorectal fistulas. Dis Colon Rectum. 2006;49(3):371–6.
- 36. Cirocchi R, Santoro A, Trastulli S, Farinella E, Di Rocco G, Vendettuali D, Giannotti D, Redler A, Coccetta M, Gullà N, Boselli C, Avenia N, Sciannameo F, Basoli A. Meta-analysis of fibrin glue versus surgery for treatment of fistula-in-ano. Ann Ital Chir. 2010;81:349–56.
- 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.
- Hammond TM, Porrett TR, Scott SM, Williams NS, Lunniss PJ. Management of idiopathic anal fistula using cross-linked collagen: a prospective phase 1 study. Colorectal Dis. 2011;13(1):94–104.
- 39. Sileri P, Franceschilli L, Del Vecchio Blanco G, Stolfi VM, Angelucci GP, Gaspari AL. Porcine dermal collagen matrix injection may enhance flap repair

surgery for complex anal fistula. Int J Colorectal Dis. 2011;26(3):345–9.

- O'Connor L, Champagne BJ, Ferguson MA, Orangio GR, Schertzer ME, Armstrong DN. Efficacy of anal fistula plug in closure of Crohn's anorectal fistulas. Dis Colon Rectum. 2006;49:1569–73.
- Owen G, Keshava A, Stewart P, Patterson J, Chapuis P, Bokey E, Rickard M. Plugs unplugged. Anal fistula plug: the Concord experience. ANZ J Surg. 2010;80:341–3.
- 42. Thekkinkattil DK, Botterill I, Ambrose NS, Lundby L, Sagar PM, Buntzen S, Finan PJ. Efficacy of the anal fistula plug in complex anorectal fistulae. Colorectal Dis. 2009;11:584–7.
- 43. Köckerling F, von Rosen T, Jacob D. Modified plug repair with limited sphincter sparing fistulectomy in the treatment of complex anal fistulas. Front Surg. 2014;1:17. www.frontiersin.org.
- 44. Ratto C, Litta F, Parello A, Donisi L, Zaccone G, De Simone V. Gore Bio-A Fistula Plug: a new sphinctersparing procedure for complex anal fistula. Colorectal Dis. 2012;14:e264–9.
- 45. de la Portilla F, Rada R, Jiménez-Rodríguez R, Díaz-Pavón JM, Sánchez-Gil JM. Evaluation of a new synthetic plug in the treatment of anal fistulas: results of a pilot study. Dis Colon Rectum. 2011;54(11):1419–22.
- 46. Buchberg B, Masoomi H, Choi J, Bergman H, Mills S, Stamos MJ. A tale of two (anal fistula) plug: is there a difference in short-term outcomes? Ann Surg. 2010;76:1150–3.
- 47. García-Olmo D, García-Arranz M, Herreros D, Pascual I, Peiro C, Rodríguez-Montes JA. A phase I clinical trial of the treatment of Crohn's fistula by adipose mesenchymal stem cell transplantation. Dis Colon Rectum. 2005;48:1416–23.
- Garcia-Olmo D, Herreros D, Pascual I, Pascual JA, Del-Valle E, Zorrilla J, De-La-Quintana P, Garcia-

Arranz M, Pascual M. Expanded adipose-derived stem cells for the treatment of complex perianal fistula: a phase II clinical trial. Dis Colon Rectum. 2009;52:79–86.

- 49. Lee WY, Park KJ, Cho YB, Yoon SN, Song KH, Kim DS, Jung SH, Kim M, Yoo HW, Kim I, Ha H, Yu CS. Autologous adipose tissue-derived stem cells treatment demonstrated favorable and sustainable therapeutic effect for Cohn's fistula. Stem Cells. 2013;31:2575–81.
- 50. Ciccocioppo R, Bernardo ME, Sgarella A, Maccario R, Avanzini MA, Ubezio C, Minelli A, Alvisi C, Vanoli A, Calliada F, Dionigi P, Perotti C, Locatelli F, Corazza GR. Autologous bone marrow-derived mesenchymal stromal cells in the treatment of fistulising Crohn's disease. Gut. 2011;60:788–98.
- 51. de la Portilla F, Alba F, García-Olmo D, Herrerías JM, González FX, Galindo A. Expanded allogeneic adipose-derived stem cells (eASCs) for the treatment of complex perianal fistula in Crohn's disease: results from a multicenter phase I/IIa clinical trial. Int J Colorectal Dis. 2013;28:313–23.
- Marzo M, Felice C, Pugliese D, Andrisani G, Mocci G, Armuzzi A, Guidi L. Management of perianal fistulas in Crohn's disease: an up-to-date review. World J Gastroenterol. 2015;21(5):1394–403.
- Yamamoto T, Bain IM, Allan RN, Keighley MR. Persistent perineal sinus after proctocolectomy for Crohn's disease. Dis Colon Rectum. 1999;42: 96–101.
- 54. Maeda Y, Heyckendorff-Diebold T, Tei TM, Lundby L, Buntzen S. Gracilis muscle transposition for complex fistula and persistent nonhealing sinus in perianal Crohn's disease. Inflamm Bowel Dis. 2011;17: 583–9.
- Jacob TJ, Perakath B, Keighley MR. Surgical intervention for anorectal fistula. Cochrane Database Syst Rev. 2010;(5):CD006319.