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REVIEW ARTICLE

Imaging techniques and combined medical and surgical treatment of perianal Crohn's disease

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Abstract Crohn's disease is a chronic inflammatory disease which may involve any segment of the gastrointestinal tract, most frequently the terminal ileum, the large intestine, and the perianal region. The symptoms of perianal Crohn's disease include skin disorders, hemorrhoids, anal ulcers, anorectal stenosis, perianal abscesses and fistulas, rectovaginal fistulas and carcinoma of the perianal region. The perianal manifestations of Crohn's disease cause great discomfort to the patient and are among the most difficult aspects to treat. Management of perianal disease requires a combination of different imaging modalities and a close cooperation between gastroenterologists and dedicated surgeons.

Keywords Crohn's disease · Perianal Crohn's disease · Diagnostic imaging in Crohn's disease

Riassunto La malattia di Crohn è una malattia infiammatoria cronica che può coinvolgere qualsiasi segmento del tratto gastroenterico, più frequentemente l'ileo terminale, il grosso intestino e la regione perianale. Le manifestazioni della malattia di Crohn perianale comprendono: alterazioni cutanee, emorroidi, ulcere anali, stenosi ano-rettali, ascessi e fistole perianali, fistole retto-vaginali e cancro della regione perianale. Le manifestazioni perianali della malattia sono una delle principali fonti di disagio per il paziente ed uno degli aspetti della malattia di Crohn più difficili da trattare. La gestione della malattia perianale richiede un'integrazione fra differenti metodiche di imaging e una stretta collaborazione fra gastroenterologi e chirurghi dedicati.

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Introduction

The prevalence of perianal fistulas in Crohn's disease reported in studies performed in tertiary referral centers varies from 17 to 43 % [1–3], while population studies show a cumulative incidence of perianal fistulas of 23–26 % occurring 20 years after the onset of the disease [4, 5]. Perianal fistulas precede the onset of intestinal disease in 10 % of patients [4]. The presence of perianal fistulas is in different ways associated with the location of the disease: in one study, the incidence of perianal fistulas was higher in patients with Crohn's disease confined to the colon, with the highest incidence found when the rectum was involved [4]; another study reported that perianal fistulas were associated with ileocolonic disease [5].

There are few studies in the literature describing the clinical course of perianal fistulizing disease; however, this disorder is characterized by periods of remission alternating with periods of exacerbation. In a study carried out in a tertiary referral center [6], the authors estimated active

inflammation to recur in 48 % of patients 1 year after induction of remission and in 59 % after 2 years. Persistent perianal disease activity was observed in a small percentage of patients. This course of the disease is confirmed in several studies which have evaluated medical and/or surgical treatment of perianal Crohn's disease, revealing that sustained remission of perianal fistulas is obtained only in a proportion of patients. As an example, numerous trials have evaluated the clinical response to treatment using anti-TNF-α monoclonal antibodies (infliximab) in patients with perianal fistulas: 36 % of patients maintained remission after 54 weeks of therapy, while the remainder showed only partial or no clinical response [7].

Classification of perianal fistulizing Crohn's disease

A correct diagnosis and classification is essential for an effective treatment of perianal disease. Definition of the type of fistula, extension, relationship with the perineal structures and the presence of abscesses are elements which are important for planning the most appropriate medical and/or surgical treatment. Anatomical classification of a fistula is still done according to Parks et al. [8] classification, which identifies the relationship of the fistula with the anal sphincter complex and particularly with the external anal sphincter. According to this classification, a fistula can be defined as intersphincteric, transsphincteric, suprasphincteric, extrasphincteric or superficial.

However, a more operative classification divides fistulas into simple and complex fistulas. A fistula is referred to as simple if it is low (superficial, low intersphincteric, low transsphincteric), has only one external orifice, shows no sign of abscess formation, has no communication with the rectum or the vagina and there is no anorectal stenosis. A fistula is referred to as complex when it is high (high intersphincteric, high transsphincteric, suprasphincteric or extrasphincteric), has multiple external orifices, shows signs of abscess formation, presents communication with the rectum or the vagina, anorectal stenosis or active rectal disease [1].

Diagnosis: the role of imaging techniques

In addition to clinical and surgical assessment, diagnosis of a perianal fistula cannot be made accurately without the use of imaging techniques which allow correct anatomical classification of the disease, demonstrate the relationship with the anal sphincter complex and evaluate disease activity. Fistulography (direct radiological assessment after injection of contrast medium through the external orifice of the fistula) and computed tomography (CT) used to be performed in the past. However, in view of the poor diagnostic performance of these techniques, they have been abandoned.

The techniques currently used in clinical practice are pelvic magnetic resonance imaging (MRI) and endoanal ultrasonography (EUS). Pelvic MRI is usually performed using dedicated surface coils and acquiring T1- and T2-weighted sequences with and without fat suppression on the coronal and axial planes. Intravenous administration of gadolinium-based contrast medium allows differentiation of the contents of the fistula (liquid collection, inflammatory or fibrotic tissue).

EUS is performed using a dedicated 7.5–16 MHz rotating transducer probe. The examination is fast, inexpensive and well tolerated by the patient, and has the advantage that it can be performed also during surgery. The limitations of this technique are the inability to accurately assess possible rectovaginal involvement and cranial extension to the levator ani plane, and that it cannot be performed in case of severe anorectal stenosis.

Another proposed technique is transperineal ultrasonography (US), which is not widely available, and its effectiveness still has to be extensively assessed. However, in small series, it has demonstrated the same diagnostic accuracy as EUS and MRI [9].

Role of imaging in anatomical classification of perianal fistulizing Crohn's disease

Examination under anesthesia (EUA), i.e. surgical evaluation using malleable blunt probes, is considered the reference standard in the assessment of perianal fistulas with a sensitivity of 90 %. In this context, MRI and EUS have been compared to EUA, and sensitivity of both methods was similar to that of EUA.

A recent meta-analysis [10], which evaluated the diagnostic performances of EUS and MRI in the identification and classification of perianal fistulas in patients with Crohn's disease, confirmed a high sensitivity (87 %) of both techniques. In contrast, the specificity of both methods was low with MRI being slightly higher (69 %) than EUS (43 %).

Diagnostic accuracy in defining the anatomical features of a perianal fistula can be increased up to 100 % by combining two of the three above-described techniques, as demonstrated in the study published by Schwartz et al. [11]. For this reason, this combination is considered to be the optimal diagnostic approach to the assessment of perianal fistulizing Crohn's disease.

Role of imaging in assessing disease activity in perianal fistulizing Crohn's disease

Another important step in the treatment planning of perianal fistulizing Crohn's disease is assessment of disease

activity. Active fistulas require medical therapy (antibiotics, immunosuppressant drugs, anti-TNF-α monoclonal antibodies) and possibly surgery (fistulotomy, seton placement, fistulectomy, mucosal advancement flap). If an abscess is detected, surgical drainage and seton placement are required, whereas administration of immunosuppressant drugs is contraindicated or should be postponed [12].

The degree of disease activity can be assessed by both clinical indices and imaging techniques.

Among clinical indices, the most widely used are the Perianal Disease Activity Index (PDAI) [13] and the Fistula Drainage Assessment (FDA) [14]. PDAI was developed to provide a comprehensive clinical measure of the morbidity caused by the disease. It includes five functional parameters (discharge, pain/restriction of activities, restriction of sexual activity, type of perianal disease, and degree of induration), each of which is assigned a value from 0 to 4 and provides a total score ranging from 0 to 20 [13].

FDA is the most frequently used index in therapeutic trials. It is based on evaluation of drainage from the external orifice of the fistula upon gentle compression [1, 14]. FDA is widely used in clinical trials assessing response to medical treatment, but numerous studies have demonstrated that cessation of drainage is not necessarily associated with complete regression of the track on imaging studies, and may also conversely be a sign of abscess formation [15–18]. Diagnostic imaging is therefore now considered to be an essential complementary tool to clinical assessment in the evaluation of perianal disease activity.

At MRI, active fistulas appear as hyperintense tracks on T2-weighted images due to a predominantly liquid content, and they are enhanced on T1-weighted sequences after intravenous injection of contrast agent [19–24] (Figs. 1, 2).

Similarly, at EUS, a fistula is considered active if it appears strongly hypoechoic, possibly with hyperechoic internal echoes as a result of a predominantly liquid content and the presence of gas bubbles deriving from suppurative inflammation [25–28] (Figs. 3, 4, 5).

In the assessment of perianal disease activity, MRI has proved to be more accurate than EUS [28]. However, the accuracy of EUS can be increased by computerized evaluation of US images as demonstrated by Caprioli et al. who reported an increased diagnostic accuracy of EUS by using computerized image analysis, thereby achieving results which were similar to those of pelvic MRI.

A recent study showed that the combined use of a clinical activity index (FDA or PDAI) and an imaging technique such as EUS can improve diagnostic accuracy in

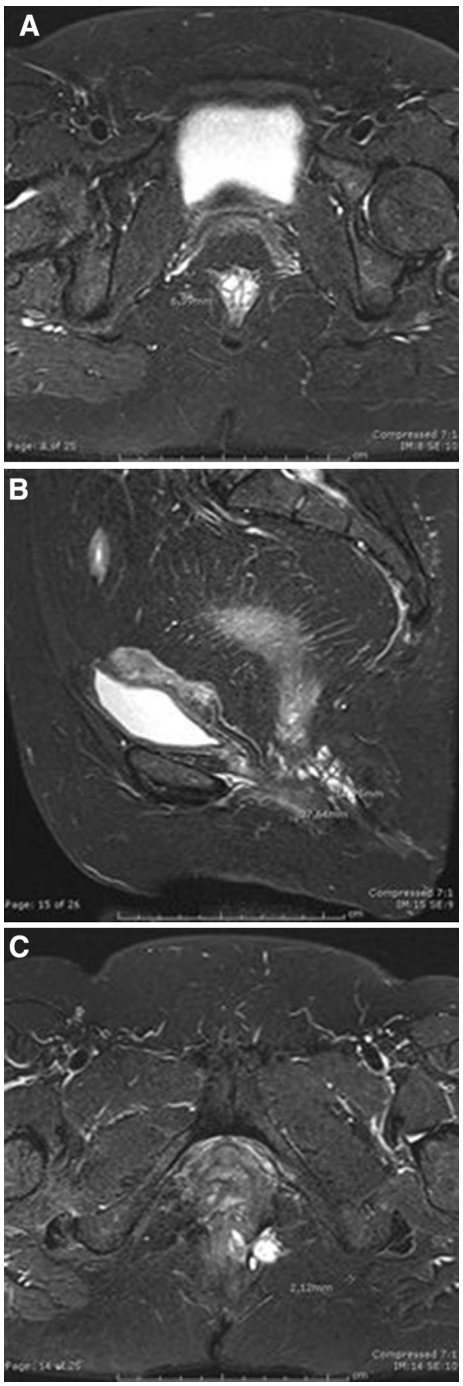

Fig. 1 MRI images of a complex transsphincteric fistula; fat-saturated T2-weighted STIR sequences. A horseshoe collection is visible in the internal sphincter, thickness about 6 mm (**a**); it is situated anteriorly in the 9 to 4 o'clock position; from it an irregular, transsphincteric tortuous fistula tract arises with small communicating inter- and extrasphincteric fluid collections in an area ~3.7 cm long and 1.5 cm thick (**b**, sagittal projection); the tract is extended to the adipose tissue of the left ischiorectal fossa traversing the fibers of the external sphincter to the left (**c**)

Fig. 2 MRI images of a high transsphincteric fistula with posterior horseshoe extension. **a** A hyperintense horseshoe-shaped collection is visible on the T2-weighted (STIR) image; it is situated in the intersphincteric space from 3 to 10 o'clock, thickness 1.9 cm; on the right, it traverses the external sphincter extending cranially along the levator ani muscle without crossing it, being confined within the ischiorectal fossa (**b**); inferiorly, it extends into the ischioanal fossa and the right buttock; vertical extension about 7 cm, anteroposterior diameter about 5.7 cm and max. transverse diameter 6.1 cm; transsphincteric fistula tract at 7 o'clock at the rectum, which is probably the origin of the horseshoe tract (**c**)

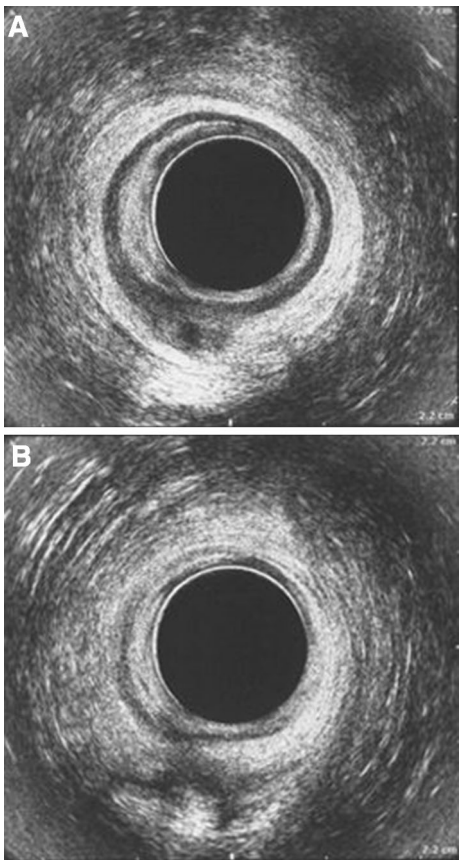

Fig. 3 EUS image of a low transsphincteric posterior fistula. **a** A tiny hypoechoic area is visible, starting from the subepithelial layer (hyperechoic *inner ring*), which is the US appearance of the internal orifice of the fistula; it traverses the internal anal sphincter (hypoechoic ring) extending toward the external anal sphincter (hyperechoic *outer ring*). **b** The caudal course of the fistula is evidenced; it appears as a hypoechoic tract with short ramifications within the external anal sphincter

assessing disease activity [29]; this demonstrates that the two approaches can complement each other.

Impact of diagnostic imaging on therapeutic outcome

The advantage of using imaging techniques in the evaluation of perianal fistulizing disease is the possibility to adequately plan the treatment. Either medical or surgical therapy only, or possibly combinated medical and surgical therapy, is required according to the degree of complexity [30].

Before initiation of immunosuppressive therapy (particularly anti-TNF-α monoclonal antibodies), it is essential to exclude the presence of undrained sepsis.

If surgical treatment is required, detection of possible secondary ramifications of complex fistulas is essential, as misrecognition has been identified as a risk factor for

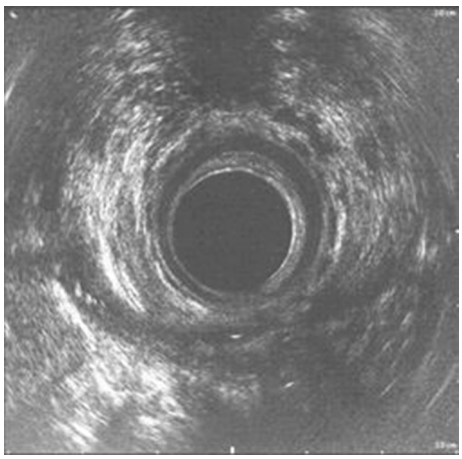

Fig. 4 EUS image of a transsphincteric posterior horseshoe fistula. The fistula appears as a hypoechoic area extending deeply into the sphincter complex posteriorly subverting its anatomical appearance; the area traverses the midline posteriorly and this is what is usually referred to as a posterior horseshoe fistula. Within the hypoechoic area, internal hyperechoic spots are visible, thus suggesting the presence of gas caused by suppurative inflammation

recurrence requiring reoperation [31, 32]. It has also been demonstrated that diagnostic imaging before surgery can influence surgical planning and thereby improve the outcome of the operation.

Spencer et al. [33] conducted a study in patients with cryptoglandular fistulas and demonstrated that MRI was able to predict the risk of recurrence better than EUA. Beets-Tan et al. [34] furthermore showed that preoperative MRI modified the surgeon's operative management at EUA in 40 % of patients with perianal fistulas in Crohn's disease. Finally, Buchanan et al. [35] reported that MRI before surgery provided an adequate depiction of the anatomy of the fistula identifying possible abscesses that could be treated during surgery; in this way, recurrence rate in patients with complex fistula was significantly reduced.

Also EUS has been evaluated for the ability of this method to reduce the risk of recurrence after medical and surgical treatment. In 2008, Spradlin et al. [36] reported on a pilot study involving a small number of patients in which the support of EUS imaging reduced the need for reoperation and improved the outcome of therapy.

Medical therapy

Medical treatment of perianal fistulizing disease is based on the use of antibiotics, immunosuppressant drugs, and anti-TNF-α monoclonal antibodies. Medical therapy is the therapy of choice and first-line treatment in patients with simple fistulas [1].

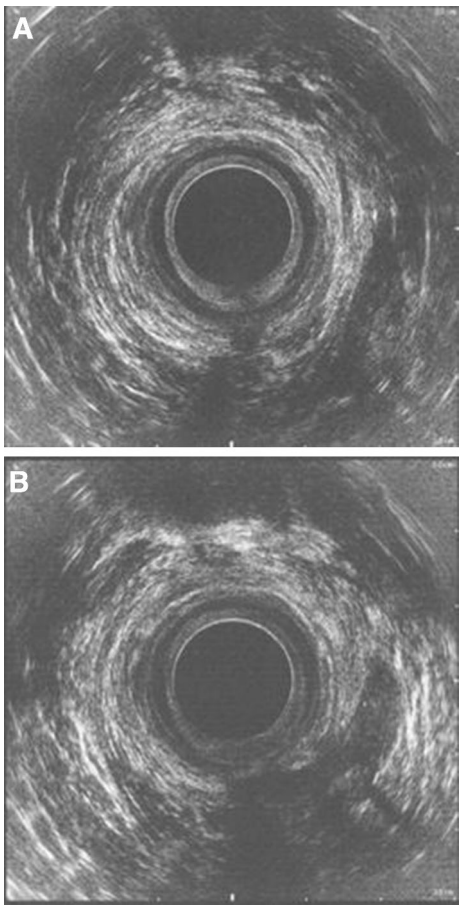

Fig. 5 EUS image of a posterior transsphincteric fistula with fluid collection within the external anal sphincter. **a** A hypoechoic area, i.e. the fistula tract, starting from the submucosal layer at 6 o'clock, then traversing the sphincter complex extending posteriorly and laterally to the left. **b** The area of inflammation appears posteriorly as a small fluid collection within the external anal sphincter, extending toward the left ischiorectal fossa

Antibiotics

Administration of ciprofloxacin 500–1,000 mg/day and metronidazole 750–1,500 mg/day (10–20 mg/kg/day) is a widespread practice in the treatment of perianal fistulizing disease, although there are no controlled data to support it. For both types of antibiotics, response to therapy is slow and incomplete. Early relapse is common when the therapy is discontinued, and there are significant side effects (metronidazole: mainly nausea, metallic taste, and peripheral neuropathy; ciprofloxacin: nausea, diarrhea, rash, headache, and tendinopathy) [37–42]. Despite the side effects, these drugs maintain a role as first-line treatment and therapy of choice in the presence of perineal abscess.

Immunomodulators

The existing data supporting the use of thiopurine drugs (azathioprine and 6-mercaptopurine) were obtained in uncontrolled case series and in randomized controlled trials which evaluated response of perianal disease to these drugs as a secondary outcome. Meta-analysis of the available data shows that clinical response is obtained in 54 % of patients treated with thiopurine drugs compared to 21 % of patients treated with placebo [43–45]. The main limitations of thiopurine therapy are that onset of action is slow, effectiveness is limited and recurrence rate is high. There are other immunosuppressant drugs, such as cyclosporine, tacrolimus, mycophenolate mofetil, thalidomide, and methotrexate, but in the literature few data are reported on their efficacy.

Anti-TNF-α monoclonal antibodies

The introduction of anti-TNF-α monoclonal antibodies has revolutionized treatment of perianal disease by achieving clinical remission and response rates which had never been obtained before with other medical therapies.

In 1999, a randomized controlled trial in patients with fistulizing Crohn's disease, mainly perianal, who received induction therapy with infliximab, demonstrated a clinical response rate of 68 % (vs 26 % in patients receiving placebo, $P = 0.002$) and a clinical remission rate (complete closure of fistulas) of 55 % (vs 13 % in patients receiving placebo, $P = 0.001$) [14]. Infliximab has thus proven effective in inducing clinical remission in patients with perianal fistulizing Crohn's disease, but the high recurrence rate after discontinuation of therapy implies that induction treatment has to be followed by maintenance therapy. The ACCENT II trial showed that maintenance therapy provided maintenance of clinical remission in 39 % of infliximab-treated patients vs 19 % in the placebo group ($P = 0.009$) after 1 year [7, 46].

Adalimumab is another monoclonal antibody directed against TNF-α, more recently introduced in the treatment of Crohn's disease. Unlike infliximab, adalimumab is fully humanized and administered as a subcutaneous injection. The data regarding its efficacy in fistulizing disease are similar to those reported for infliximab. However, the evidence level is lower, as no study has been specifically designed to evaluate the efficacy of adalimumab in perianal disease as the primary endpoint [47]. Recent open-label studies have shown clinical remission rate (complete closure of fistulas) in 23–39 % of patients with fistulizing disease in whom previous therapy with infliximab had failed [48, 49].

Surgical treatment

Surgical treatment of perianal disease may be performed as urgent surgery (due to abscess) or elective surgery. Onset of perianal disease may precede visceral disease by months or even years. The patient's clinical history can therefore often help to confirm diagnosis of Crohn's disease, particularly if it is positive for nonspecific perianal disorders, such as skin tags, hemorrhoids, fissures or ulcerations. These conditions rarely require surgical treatment. In the presence of anal stenosis, gradual dilatation using Hegar dilators or balloon dilators may be required; however, in this case, coexistence of visceral disease and particularly rectal disease means that the patient should be considered at risk of developing more complex forms of perianal disease [50–52].

Perianal abscess

Urgent surgery may be required in patients with perianal abscess in rapid progression and resistant to antibiotic therapy [53], as this condition requires evacuation of purulent material (which should always be submitted to laboratory examination including bacterial culture and antibiogram) to prevent systemic sepsis [54–58].

A superficial abscess develops through superficial fistula tracts (intersphincteric with no cranial extension or simple transsphincteric), and inflammatory involvement is limited to the subcutaneous tissues. Surgical treatment involves skin incision and abscess drainage, and in some cases also fistulotomy may be performed as described below to treat the associated fistula. However, in case of associated fistulotomy, problems related to failure of wound healing in a region affected by acute inflammation should not be underestimated.

Deep abscesses develop far from the perianal skin. They may involve the ischiorectal fossa or the space lying above the levator ani muscle and may be caused by cranial extension of intersphincteric abscesses or complex transsphincteric, suprasphincteric or extrasphincteric fistula tracts as well as local fistulization in areas with active inflammatory rectal disease. In these cases, it may be necessary to identify and open possible abscess concamerations, sometimes leaving a drainage tube in a residual cavity for a few days to ensure complete drainage. In both superficial and deep lesions, the fistula tract may be stabilized by seton placement using loosely tied elastic seton, i.e. non-cutting seton (as described below); this procedure can be carried out when the internal orifice is easily identified [59] (Fig. 6). However, it is not always required at this stage, also to avoid creating false tracts. In this

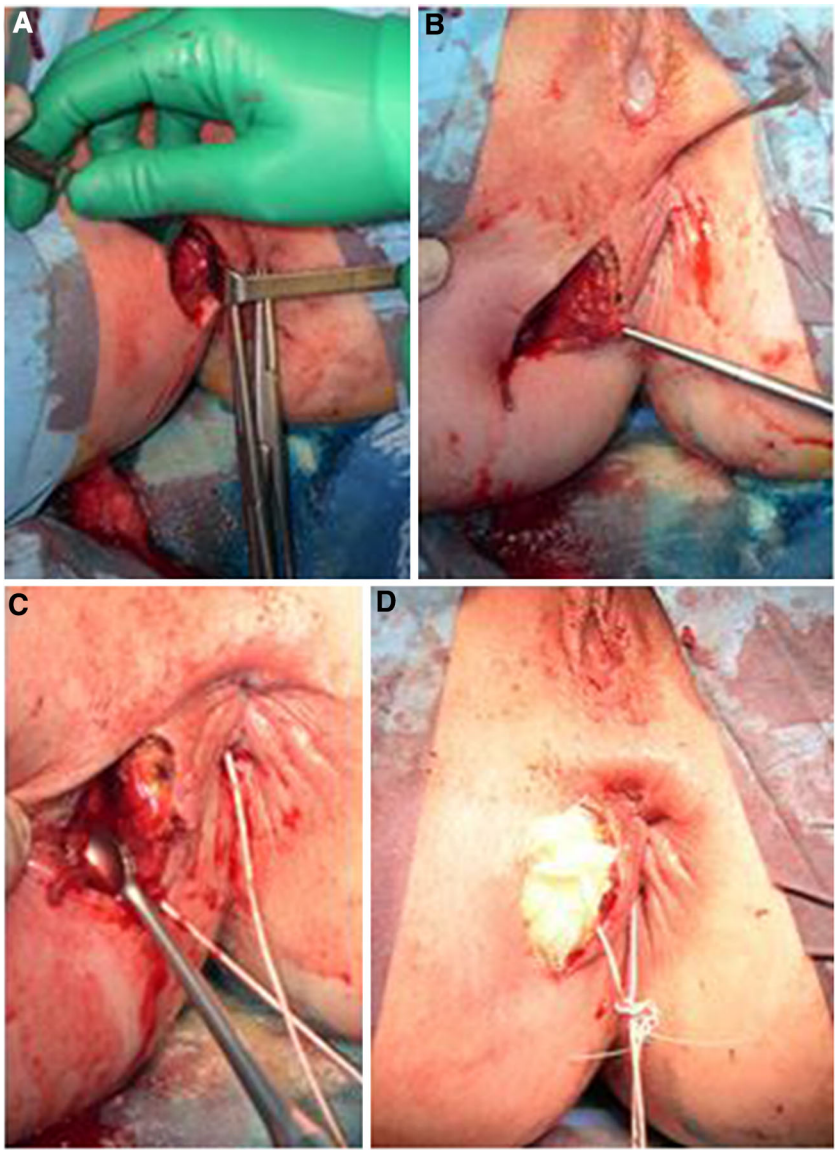

Fig. 6 Incision of perianal abscess (**a**), positioning of the malleable blunt probe in the fistula tract (**b**), curettage of the residual cavity after seton placement guided by the probe (**c**); at the end of the procedure, the seton is loosely tied and the residual cavity is closed using a gauze package and left to heal by second intention (**d**)

connection, it should be underlined that fistulas associated with Crohn's disease tend to have an anterior orifice, but they do not follow Goodsall's [60] rule regarding the correspondence between internal and external orifice in anterior fistulas. The reason is that the origin is different from that of cryptoglandular fistulas. Moreover, in patients with Crohn's disease anterior horseshoe fistulas are more common and they tend to present a secondary orifice in the vagina (horseshoe means that the tract traverses the midline) (Figs. 1, 2, 4) [61–65].

When the acute phase is over and an external communication has been produced creating a fistula, other diagnostic techniques can be used to obtain detailed information about the origin, course, and ramifications of the fistula to consider further medical therapy and/or surgical procedures [1].

Perianal fistulas

External opening of the abscess usually develops spontaneously in patients already diagnosed with Crohn's disease and perianal involvement. In some cases, the fistula may present a straight tract, which is readily identifiable and explorable throughout its course using malleable blunt probes at physical examination. If the patient does not feel pain and if the physician can identify the internal orifice of the fistula, it may be possible already in the outpatient setting to place a loosely tied seton, which stabilizes the fistula using the technique described below. It must be borne in mind that the internal orifice does not always correspond to the dentate line as it is the case with idiopathic perianal fistulas. If the patient has a coexisting rectal disease, a mucosal ulcer may penetrate the perirectal tissue

leading to the formation of a perirectal abscess which opens outside the perianal region. In these cases, identification of the internal orifice may be possible only using accurate imaging or EUA, although the latter may cause problems of organization and involve considerable costs.

EUA allows the physician to examine the fistula and identify its course using malleable blunt probes, possibly using hydrogen peroxide or vital dyes, and at the same time provide the most suitable surgical solution (fistulotomy, seton placement, fistulectomy, straightening of complex fistulas). However, diagnostic accuracy of EUA is 100 % only if combined with an imaging technique, such as MRI or EUS [11]. It should furthermore be kept in mind that preoperative imaging provides the information required to properly inform the patient about the surgical options, which is obviously impossible if EUA is performed without previous imaging.

If surgery is indicated, the strategy can change considerably from patient to patient according to the complexity of the clinical picture and possible rectal involvement. In 2003, the American Gastroenterological Association (AGA) proposed a classification of perianal fistulas associated with Crohn's disease dividing them into simple and complex fistulas, providing a treatment algorithm for each of the two categories [1].

In simple fistulas with a linear tract (superficial, low intersphincteric, and low transsphincteric), the surgeon may longitudinally incise and lay open the tract with the guidance of a probe introduced into the tract itself (fistulotomy) [2]. Fistulotomy exposes the patient to a mild to moderate risk of fecal incontinence except in superficial fistulas which do not involve the sphincter complex [66–68]. For this reason, many authors recommend loosely tied seton placement also in simple fistulas with sphincter involvement, especially in the presence of active rectal disease. This choice is also determined by the risk of recurrence, resulting in increasingly complex surgery and a growing risk of sphincter injury.

Seton is generally made of an elastic, non-allergenic material; it is placed in the fistula guided by a malleable blunt probe positioned along the course of the tract. Usually the probe is introduced through the external orifice and directed to exit from the internal orifice, with the latter being identified by digital exploration (possibly preceded by an injection of hydrogen peroxide or dye through the external orifice) and with the aid of preoperative imaging. In this process, particular care should be taken to avoid creating false tracts. Subsequently, the two ends of the seton are loosely tied to keep it in place, but without exerting traction on the sphincter (i.e. non-cutting seton) (Fig. 6). The technique involving the use of cutting seton to produce a slow and progressive dissection of the sphincter allowing an equally progressive repair has been completely abandoned. The purpose of seton placement is thus to stabilize the fistula tract and to avoid recurrent abscess formation caused by premature closure of the external orifice.

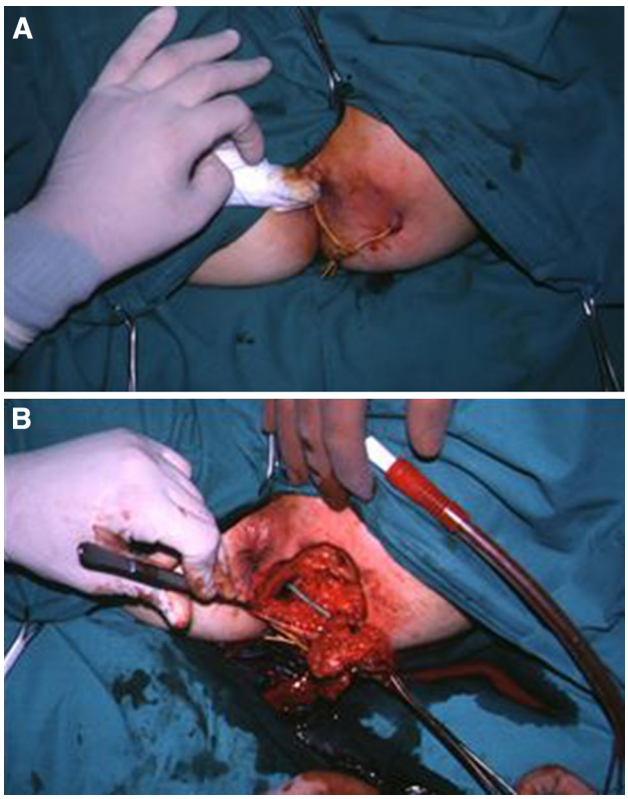

Fig. 7 Fistulectomy: removal of inflamed tissue surrounding the fistula using the cone-like technique; the procedure is guided by the loosely tied seton placed in the fistula tract some weeks before to drain the abscess

Seton placement may be combined with fistulectomy, i.e. removal of the fistula tract and the inflamed tissue surrounding it until the point where it traverses the sphincter (or the muscle layers of the rectum in fistulas arising from deep ulcers in the rectal mucosa). In this case, the seton is left to drain only the residual tract, i.e. the tract where the fistula traverses the anal muscle, from which the inflamed tissue is removed by meticulous curetting (Fig. 7). This seems to be the best treatment in the presence of complex fistulas (high intersphincteric, high transsphincteric, suprasphincteric and extrasphincteric, which often present multiple secondary tracts) in which fistulotomy (or "lay-open") would inevitably cause sphincter injury leading to fecal incontinence.

Fistulectomy is performed using the cone-like technique with removal of the inflamed tissue surrounding the fistula by making a sufficiently large skin excision around the external orifice and extending it up to the point where the tract traverses the sphincter or the rectal wall (Fig. 8). All possible secondary tracts must be removed or meticulously

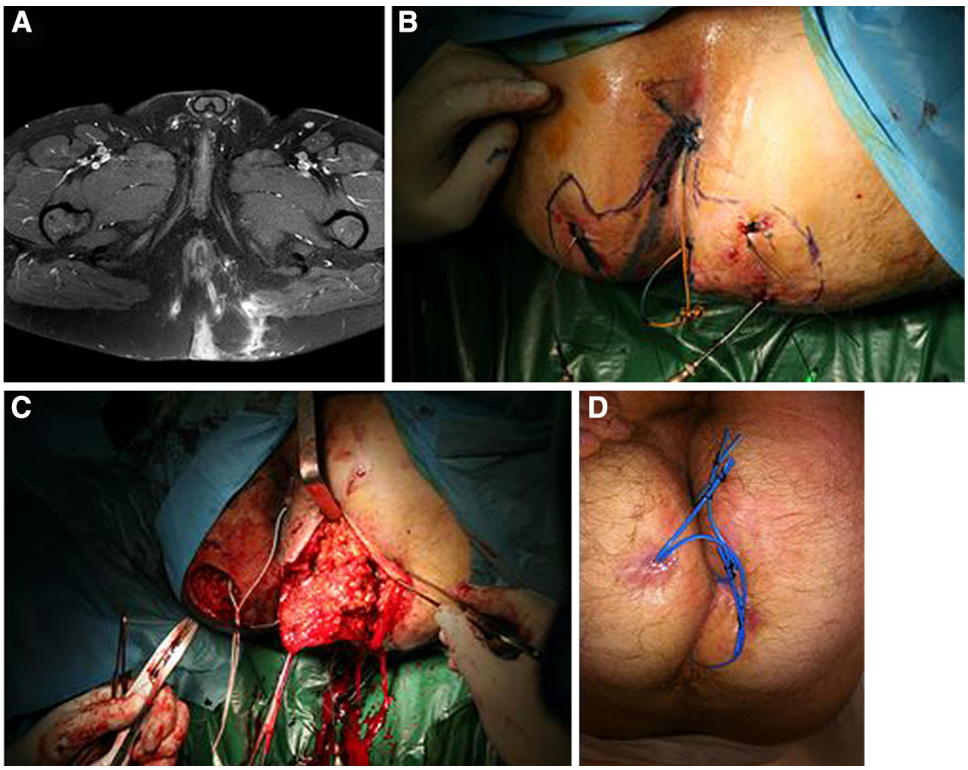

Fig. 8 Very complex recurrent fistula previously treated with seton placement without fistulectomy. MRI (T1) image shows small presacral collections and multiple fistula tracts originating from an internal orifice situated at 5 o'clock; the fistula tracts are directed toward both buttocks and the sacrococcygeal region which are affected by widespread surrounding inflammation (**a**). Surgery: preliminary inspection reveals seton placed during previous surgery; primary fistula tract is situated at 5 o'clock and secondary track at 7 o'clock; small fistula tracts have invaded the left buttock and presacral skin; both main tracts are undermined by inflammatory infiltrate on whose margins cutaneous excision is performed (marked with a pencil) (**b**). Surgery using the cone-like technique: removal of the two main fistula tracts and inflamed tissue (hemostasis using radiofrequency energy); loosely tied seton is already placed on the right. Other loosely tied setons will be placed, one on the left in the main transsphincteric fistula tract and two externally to the sphincter complex (**c**). Clinical picture after 6 months of anti-TNF-α monoclonal antibodies therapy: the former abscess cavities are healed, the two transsphincteric setons and the two external to the sphincter complex (one connecting the two main residual cavities and the other connecting the right residual cavity to the main tract in the presacral region) have been replaced with other softer setons which are left in place to stabilize the tracts **d**

scraped out with a curette. Also horseshoe extensions must be identified, as they may require a separate distant incision with possible loosely tied seton placement also outside the sphincter complex to create communication with residual abscess cavities without cutting too much of the skin, which may result in deforming scars (Fig. 9). The residual cavities are then left to heal by second intention [54–59, 69–71]. Removal of the main tract and possible secondary tracts or curetting is done to remove all inflamed tissue, which may hinder pus drainage and thus lead to delayed or incomplete healing of the fistula, particularly when the rectum is involved. In such cases, the patient should be warned of the possibility that the seton may be left indefinitely in place to prevent the formation of abscesses by keeping the exterior orifice open [72–75].

The aim at avoiding scarring and reducing possible risks of sphincter injury may lead to the choice of more conservative surgical strategies in the treatment of complex fistulas. In that case, surgery is limited to stabilization of the tracts (which are left almost entirely in situ) using loosely tied setons acting as drains without performing fistulectomy, i.e. removal of inflamed tissue. In these cases, there will be persistent discharge of mucopurulent material due to persistent inflammation, but it will be reduced, and the patient's quality of life will be improved if compared to a situation of recurrent abscesses. The patient is furthermore not exposed to the risk of fecal incontinence caused by cone-like fistulectomy, particularly if the procedure is repeated [76, 77]. On the other hand, if fistulectomy is not performed, this increases the possibility of missing secondary tracts, which, as already mentioned, are considered a risk factor for recurrence and reoperation [31, 32]. Moreover, particularly diseases of long duration present the risk of malignant transformation of the fistula [78, 79]. For these reasons, the best surgical solution seems to be removal of fistula tracts and the surrounding inflamed

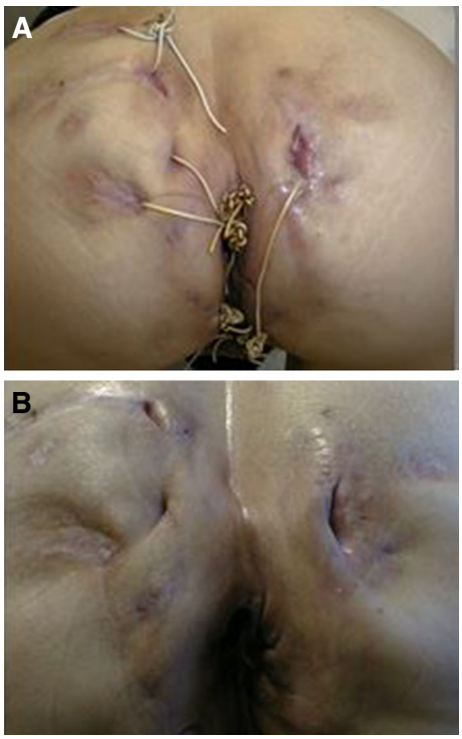

Fig. 9 The patient in the prone position in an outpatient setting: multiple perianal fistulas treated with fistulectomy, seton placement (also outside the anal canal, e.g. at 5 o'clock in the gynecological position) and closure of residual cavities by second intention. **a** Before and **b** after infliximab therapy (and removal of setons)

tissue to submit the specimen to histological evaluation. However, stabilization of the fistula through seton placement and possible fistulectomy is not proposed as a definitive solution, as this treatment must be combined with medical therapy (mainly biological anti-TNF-α monoclonal antibody drugs), particularly when not all the inflamed tissue is removed.

As already mentioned, it may sometimes be necessary to leave the non-cutting seton in situ also over a longer period. In order to avoid this, mucosal advancement flap procedure was introduced in the treatment of recurrent transsphincteric and suprasphincteric cryptogenic perianal fistulas. Although no authors reported success rates exceeding ~70 % [80, 81], the outcome of this procedure was considered satisfactory until 2011 when Jarrar and Church [82] reported a success rate of 98 % in the treatment of cryptogenic fistulae, performing in some cases two or three mucosal advancement flap operations.

This technique can be used in patients with Crohn's disease and simple fistulas as an alternative to fistulotomy and in complex fistulas to avoid seton placement, but only if there are no signs of active rectal inflammation [63, 83–86]. According to the American Gastroenterological Association statement of 2003, mucosal advancement flap repair involves incision of a tissue flap comprising the mucosa, submucosa, and circular muscle around the internal orifice of the fistula; the internal orifice is then removed and the tissue flap is slid forward to cover the residual orifice in the muscle layer [1, 87].

A more complex technique is advancement sleeve flap procedure. This surgical procedure may be performed when the anal canal is ulcerated or shows signs of recent inflammatory involvement, but again only if the rectum appears macroscopically normal. In these cases, tissue excision is circumferential, and the anal mucosa is lifted from the dentate line while a full-thickness rectal flap is circumferentially mobilized (similarly to Altemeier's procedure performed in rectal prolapse) and subsequently anastomosed to the dentate line. This procedure is technically very complex and therefore performed only in a few selected patients. In most cases, the anastomosis is excluded from the fecal stream by performing diverting ileostomy or colostomy. This precaution is often advisable also in mucosal advancement flap repair of fistulas associated with Crohn's disease [88]. In order to simplify the technique and reduce the risk of sphincter injury, mucosal flaps are generally preferred. However, also in this case, the outcome is not particularly satisfactory. In 2002, Mizrahi et al. [89] thus identified Crohn's disease as the main factor predicting failure of mucosal advancement flap repair performed in complex perianal fistulas. Despite the much higher success rates reported by Jarrar in 2011, success rates of mucosal advancement flap procedures performed in patients with Crohn's disease are generally reported to be ~50 % [80, 82, 90].

Recto- or anovaginal fistulas present a particular problem. Traditional fistulotomy has been performed in simple anovaginal fistulas, but this technique is considered to carry a high risk of sphincter injury [91]. On the other hand, seton placement may be associated with impaired quality of life in these patients, as this treatment may result in increased discharge of air and fecal material from the tract into the vagina [73]. The most commonly performed procedure in anovaginal fistula is therefore closure of the tract, both from the vaginal and the rectal side, by primary closure or using advancement flap or sleeve flap procedure. It should be kept in mind that the advancement flap procedure can be performed also inside the vagina [92–96].

Local therapies, fibrin glue, and fistula plugs

In recent years, numerous treatment procedures have been introduced to provide local treatment aimed at facilitating or accelerating the healing of external fistulas to avoid fistulectomy. These treatments may or may not be associated with treatment of the internal orifice as described above. Various materials are used to close the external orifice: fibrin or collagen glues and plugs, also with the

addition of fibroblasts and stem cells of various origins and possibly combined with different surgical techniques (fistulotomy, partial fistulectomy, advancement flap procedure) [97–105].

All authors have reported remarkable therapeutic success, and the risk related to this type of treatment is virtually absent. However, the risk of malignant transformation should not be underestimated in cases of long-standing chronic inflammation. Moreover, none of these procedures (which are sometimes very costly) have provided clinical outcomes which have resulted in their inclusion in official guidelines, also because of the lack of randomized controlled trials with long-term follow-up and radiological proof of fistula healing. The data are furthermore often influenced by the fact that both patients with fistulas associated with Crohn's disease and patients with idiopathic anal fistulas were enrolled in the studies [90].

This also applies to intralesional injections of anti-TNF-α monoclonal antibody. Uncontrolled, observational pilot studies have been carried out using infliximab [106–108] and adalimumab [109, 110], and the results are reported as promising. However, the characteristics of these studies do not justify the use of this method in everyday clinical practice. In Italy, the use of these drugs for this purpose is therefore still off-label. Injection of anti-TNF-α monoclonal antibody into the fistula tract furthermore requires particular care in the treatment of long-standing chronic fistulas due to the difficulty linked to the diagnosis of possible malignant transformation. However, the possibility that more satisfactory results may be achieved using this method compared to the traditional surgical techniques will probably lead to more research and randomized controlled trials in the treatment of rectovaginal fistulas.

Combination medical and surgical therapy

Combination treatment is recommended in complex fistulas using both medical therapy (antibiotics, immunomodulators, and/or biological agents) and surgical treatment (EUA with seton placement and/or other surgical procedures) [1]. Studies evaluating the effectiveness of surgical treatment report a favorable outcome only in ~50 % of patients [53] with a higher recurrence rate in complex than in simple fistulas [111]. On the other hand, medical therapy (particularly administration of anti-TNF-α monoclonal antibody biological agents) is estimated to achieve remission in 50–60 % of cases and maintenance of remission in 30–40 % of cases. On the basis of these results, combination treatment is recommended in complex fistulas with the objective to combine the benefits of both approaches, i.e. surgical treatment to stabilize the fistula tract and prevent occurrence or recurrence of abscesses combined with the ability of anti-TNF-α monoclonal antibodies to induce complete closure of the tract (Fig. 9).

However, reports have only recently appeared in the literature publishing data obtained in controlled studies evaluating the efficacy of combination therapy compared to medical therapy or surgical treatment alone. The two types of therapy are combined in different ways: infliximab before surgery, surgery before infliximab or maintenance using infliximab and revision surgery at regular intervals.

In a retrospective study published by Regueiro et al. [112], 32 patients were treated with infliximab. One group underwent EUA with seton placement before initiation of infliximab therapy and presented a better initial response than the other group who received infliximab only (100 vs 83 %, $P = 0.014$). Moreover, EUA with seton placement combined with infliximab yielded a lower recurrence rate (44 vs 79 %, $P = 0.001$). Another retrospective study of 62 patients evaluated the benefit of adding infliximab to surgical treatment demonstrating a trend toward a better clinical response, yet not statistically significant, and no benefit in terms of long-term risk of recurrence [113]. A similar, recently published paper [114] reports the results of a retrospective study of 218 patients submitted to surgery for perianal disease with a mean follow-up of 3.2 ± 3 years; 117 patients underwent surgery only, while 101 underwent combination therapy (surgery plus infliximab). Even though complete clinical remission rates were similar, a significantly greater proportion of patients receiving combination therapy achieved clinical improvement (71 vs 36 %, $P = 0.001$).

It should be kept in mind that comparison of data obtained in retrospective series may be largely affected by the risk that the two patient groups were not homogeneous, especially with regard to the severity and complexity of the disease. Particularly in older series, it is plausible to assume that patients who received combination therapy had a more severe or more complex disease. It is therefore reasonable to believe that the above data tend to underestimate the effectiveness of combination therapy.

In a recent small prospective study, Sciaudone et al. [115] evaluated the outcome in patients who underwent EUA with seton placement plus infliximab therapy, and compared it to the outcome in patients who underwent monotherapy, i.e. surgery only or infliximab therapy only. The authors did not find statistically significant differences between the three groups in terms of overall clinical response, but mean time to recurrence was longer in the patients who underwent combination therapy (10.1 ± 2.4 vs 2.6 ± 0.7 months in the group treated with infliximab monotherapy, vs 3.6 ± 0.5 months in the group undergoing surgery only; $P < 0.05$ in both cases).

Moreover, various uncontrolled series are reported in the literature, which evaluate the effectiveness of combination

therapy [71, 116–119]. In two prospective, larger studies with a median follow-up of 20 months, complete clinical remission was reported in 29–47 % of patients and a partial response in 42–53 % of patients [120, 121].

Role of imaging techniques in the monitoring and planning of therapy

Recently, studies have been carried out to identify the role of imaging in monitoring response to treatment and thereby in guiding management decisions. A basic fact has emerged from numerous studies reported in the literature, particularly in the early years following the introduction of biological therapy, namely that clinical response to therapy is often not in agreement with radiological or ultrasound outcome. Even if fistula drainage is improved or the orifice is closed, MRI and EUS frequently show persistent fistula tracts with a varying degree of activity [15–18, 122] (Fig. 10). In this context, some authors have proposed scores to assess perianal disease activity [17, 122]. Particularly Van Assche et al. [17] proposed a radiological index to be applied to MRI findings. It considers hyperintensity on T2-weighted images as well as number, location and ramification of the fistulas, the presence of abscesses and involvement of the rectal wall. The authors demonstrated that the score changed during infliximab therapy although the fistula tract persisted.

After these observations, it was suggested that imaging methods could be used to monitor the response to therapy and guide the choice and/or timing of medical and surgical therapies [123–127]. In 2008, Ng et al. [126] enrolled 34 patients with Crohn's disease who were treated with infliximab, adalimumab or thalidomide for perianal fistulizing disease. The authors confirmed that radiological healing demonstrated at MRI lagged behind clinical remission. However, once radiological remission was achieved, the risk of relapse was reduced also after discontinuation of therapy. In this way, the authors managed to identify a subgroup of patients who could discontinue biological therapy as a result of a reduced risk of recurrence.

Similar results were obtained in a subsequent study [127] which enrolled 41 patients with perianal fistulizing Crohn's disease. The patients were administered biological therapy associated with thiopurine. The authors concluded that patients, whose clinical response was reflected by radiological evidence of improvement, were more likely to maintain remission during infliximab therapy. However, in this study only 43 % of patients who discontinued treatment maintained clinical remission.

Also EUS outcome has been used to guide the choice of medical and surgical therapy in patients with perianal Crohn's disease. In 2005, Schwartz et al. [128] published a preliminary, retrospective study in which they reported that clinical response achieved after treatment with antibiotics, conventional immunosuppressant drugs and infliximab was not associated with ultrasonographic improvement in a significant proportion of patients. They identified a subgroup of patients who presented long-lasting remission of fistula activity evidenced at EUS and maintained remission also after discontinuation of biological and antibiotic therapy. Later, the same research group (Nashville, Tennessee) [36] published the first prospective randomized trial which evaluated the role of EUS in guiding medical and surgical therapy of perianal fistulas in Crohn's disease. Only ten patients were enrolled in this trial; all underwent EUS and EUA with possible drainage and/or seton placement whenever indicated, and they subsequently started thiopurine, antibiotic and infliximab therapy. The patients were randomly divided into two groups: one group was managed by a surgeon, who was blinded to baseline EUS outcome. He had no access to further EUS scans and based

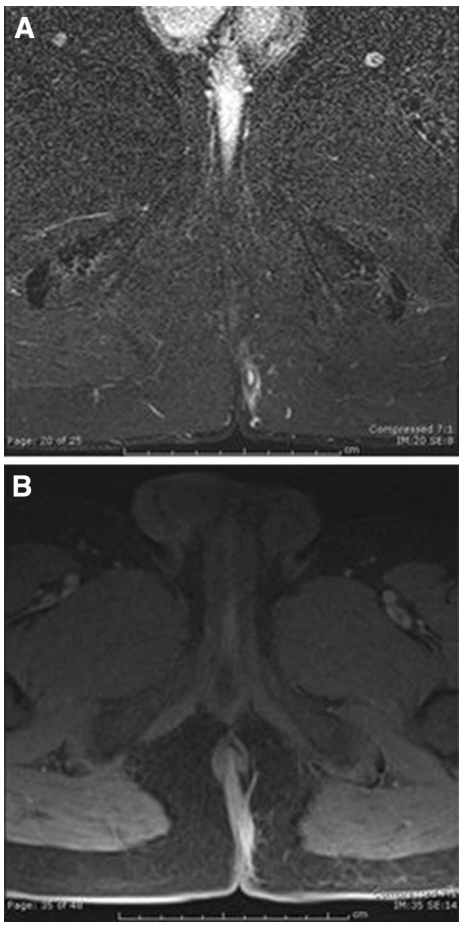

Fig. 10 MRI image (STIR T2-weighted and T1 sequences) of a fistula tract after removal of seton and during treatment with anti-TNF-α monoclonal antibody. The tract appears partly fibrotic, but the most caudal portion at the intergluteal sulcus is enhanced, compatible with granulation tissue

management on clinical judgment. In the second group, the surgeon took the outcome of baseline EUS and two EUS scans performed during follow-up into account when deciding for or against possible further surgical treatment. At the end of the follow-up (54 weeks), the EUS monitored group presented a higher rate of complete cessation of drainage and a lower rate of recurrence.

These publications have thus identified a new therapeutic goal in the management of patients with perianal fistulizing disease, including not only clinical but also radiological remission of disease. A body of evidence is accumulating and seems to indicate that pursuance of this composite goal of treatment improves long-term remission rates. However, further prospective studies of larger patient populations are needed to define adequate timing and use of imaging techniques in guiding medical and surgical therapy.

Diversion and demolition techniques, indications and the risk of malignant transformation

Diversion of fecal stream and proctectomy

In a case series study carried out in 2007, removal of the rectum was required in about 10 % of patients with complex fistulas due to persistent disease despite medical and surgical therapies in various combinations [129].

In order to avoid proctectomy, diversion of the fecal stream, i.e. temporary colostomy or ileostomy, can be attempted. This solution is often used to protect sutures at risk, e.g. in advancement flap procedures, but colostomy/ileostomy performed to improve the therapeutic effect of combination medical and surgical treatment rarely proves effective. Numerous studies have shown that, only in a reduced number of cases (10–30 % in different series), treatment of complex fistulas achieves such favorable therapeutic results that stoma reversal is actually performed. Reversal rate is also low because colostomy/ileostomy often determines such an improvement in the patient's quality of life that he/she refuses stoma reversal operation [130, 131].

Protective stoma can be performed with pure laparoscopic or laparoscopic-assisted techniques, particularly if the disease is not associated with visceral involvement that required laparotomic procedures in the past. In view of the fact that protective stoma often becomes definitive, it is strongly recommended that the location on the abdominal wall is carefully chosen (with the assistance of a stomal therapy nurse) in order that the patient achieves the best management of his/her stoma.

The same careful approach should be adopted when failure of therapies indicates proctectomy, or proctocolectomy in case of concomitant involvement of the colon. This type of surgery is often feared because of the potential risk of injury to the pelvic nerves, a risk which is actually slightly increased in the presence of severe distortion of the pelvic anatomy due to inflammation. However, in cases where the disease is strictly perianal or limited to the perineal region, proctectomy is performed in the mesorectal plane, and the risk of nerve injury is therefore limited. The most serious complication in these patients is failure of the perineal wound to heal, which may occur in more than 10 % of cases 6 months after surgery or more. In these patients, repeated surgery is sometimes required involving curettage of the inflamed tissue or myocutaneous flap repair [90].

Conservative treatment of the mesorectal fascia cannot be performed if preoperative investigation detects malignancy. Malignant transformation in perianal Crohn's disease is rare (adenocarcinoma is more common than squamous cell carcinoma) [79, 132], but diagnosis is often delayed because of the very low sensitivity of MRI, EUS, and CT in identifying neoplastic transformation in an environment of severe chronic inflammation [78, 133, 134].

The existence of this diagnostic problem has been confirmed by several authors. Thomas et al. [79] reviewed 61 cases of malignant transformation published in the literature of which only 20 % had received a correct preoperative diagnosis. In 2013, Ogawa et al. [133] reported on four cases of adenocarcinoma developing in perianal fistulas in Crohn's disease. The authors strongly recommend surgical biopsy also when the surgeon decides to leave fistulous and perifistulous tissue in situ. It is interesting to note that in two of the four reported cases of malignancy, the outcome of perianal surgical biopsy was negative, and the correct diagnosis was achieved only later when intractability of the disease led to proctectomy. Moreover, Ogawa et al. put particular emphasis on the fact that all four cases were associated with administration of biological therapy. However, these patients were all affected by the long-lasting disease which required advanced treatment strategies. At present, there are no other reports of potentially increased local cancer risk in patients receiving biological agents. On the other hand, exclusion of the fecal stream and particularly Hartmann's procedure (terminal colostomy or ileostomy and closure of the rectal stump) seem to be a risk factor [135].

In the absence of diagnostic techniques capable of signaling neoplastic transformation, the recommendations issued by the AGA in 2003 are still valid. The possibility of malignant transformation should always be kept in mind in the presence of a persistent fistula, and cytological and histological evaluation of the fistula tracts should be carried out regularly, particularly if associated with increased risk

factors such as long duration of the disease or changes in the symptomatology, especially in case of worsening pain. In case of malignant transformation, surgical resection following oncological procedures is always indicated. This involves abdominoperineal resection of the rectum with total mesorectal excision and radical lymphadenectomy, possibly including excision of inguinal lymph nodes. Often, diagnostic delay has already permitted the perineal neoplasia to infiltrate the surrounding tissues thereby requiring removal of large portions of tissue, sometimes extended to the vagina. In this situation, wound healing becomes very difficult, and the prognosis is generally dismal [1, 78].

Conflict of interest Fiorenzo Botti, Alessandra Losco, Chiara Viganò, Barbara Oreggia, Matteo Prati and Ettore Contessini Avesani declare that they have no conflict of interest related to this article.

Informed consent No patient information was included in this study. However, the authors have the patients' consent to the publication of images that could potentially lead to their identification.

Human and animal studies In connection with this study, the authors did not carry out any procedures involving humans or animals.

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