Crohn's Disease

James Fleshman and Rachel Tay

Background

Perianal and anovaginal fistulas represent a very challenging problem in 20–30 % of patients with Crohn's disease. Of these patients, 80 % will also have or develop intestinal disease. Perianal fistulas are more likely to develop in patients with Crohn's disease involving the colon or rectum as opposed to those with isolated ileocolic disease. Men, those who develop Crohn's at a younger age, and non-Caucasians are also at an increased risk of developing perianal disease. The development of perianal fistulas is oftentimes a poor prognostic indicator and portends a worse course of disease in patients who are afflicted. The priority for physicians treating patients with Crohn's fistulas of the anus should be preservation of the anal sphincter and avoidance of a permanent ostomy.

Types of Fistulas

The classification of fistulas of common (cryptoglandular) anal fistulas was described by Parks and Gordon in 1976. There are four types of fistulas within this classification (Fig. 19.1). Intersphincteric fistulas are the most common, and comprise approximately 45 % of all fistulas. These fistulas only traverse the internal anal sphincter and connect to the perianal skin. Transsphincteric fistulas comprise 30 % of fistulas and involve both the external and internal anal sphincters. A small portion of the external anal sphincter is usually involved. Suprasphincteric fistulas comprise 20 % of anal fistulas and cross the internal anal sphincter, then pass upwards and around the majority of the external anal sphincter

back to the skin. Extrasphincteric fistulas encompass the entire sphincter complex and open internally into the bowel above the anus. They are the least common type and represent only 2–5 % of all fistulas. The most common cause is iatrogenic injury to the levator plate when draining a large suprasphincteric abscess. They are very often related to an intra-abdominal intestinal source in patients with Crohn's disease, which will respond only to bowel resection.

Fistula classification and location can be very important with regard to selecting the appropriate treatment options in both cryptoglandular and Crohn's disease patients. Fistulas rarely follow these rules of classification in patients with Crohn's disease. Even so, males with a low, intersphincteric, posterior Crohn's fistula may be treated successfully with primary fistulotomy with good success and minimal risk of incontinence. In contrast, women with anterior fistulas have a high risk of incontinence even when treated with superficial fistulotomy and will often require an alternative form of surgical therapy such as a sliding flap repair. Regardless of the position of the fistula around the circumference of the anal canal, high fistulas are less likely to heal, more likely to result in incontinence after treatment, and may require diversion.

Cryptoglandular Fistulas Versus Crohn's Disease

It may be difficult at times to distinguish between cryptoglandular and Crohn's fistulas even though the pathogenesis and natural history are very different. This distinction is important to make, as the treatment of these diseases is very different. Fistulas which develop in an atypical location or do not heal regardless of multiple attempts with medical and surgical treatment point to a diagnosis of Crohn's fistula. Cryptoglandular fistulas are thought to arise from the blockage and infection of one of the anal glands at the dentate line. The gland normally empties into the anal crypt. Abscess formation results in the development of an anal fistula in up

J. Fleshman, M.D., F.A.C.S., F.A.S.C.R.S. (✉) • R. Tay, M.D.
Department of Surgery, Baylor University Medical Center,
3500 Gashan Ave, Dallas, TX 75204, USA
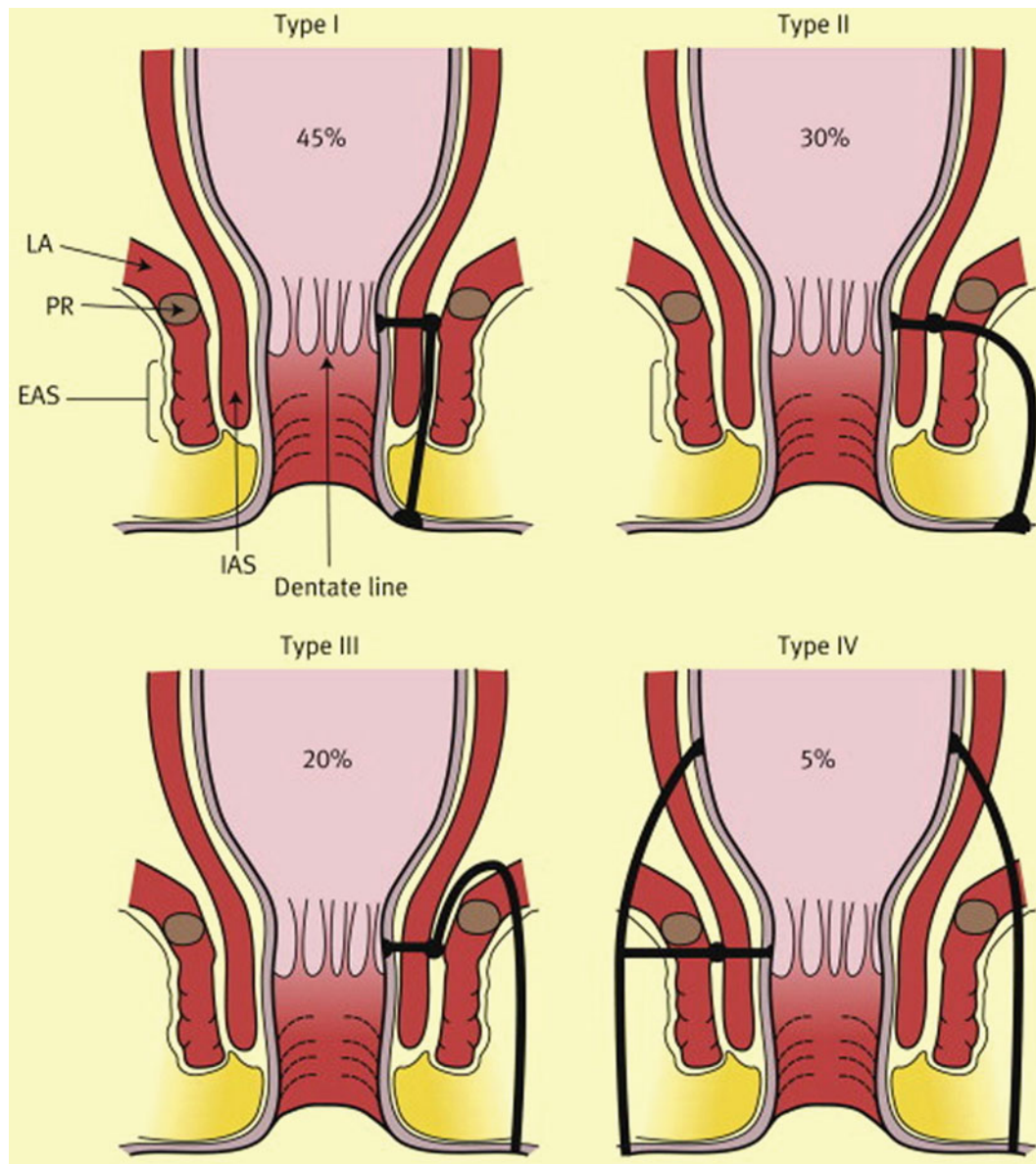e-mail: fleshman@wudosis.wustl.edu

Fig. 19.1 Parks' classification of fistula-in-ano. Type I, intersphincteric; Type II, transsphincteric; Type III, suprasphincteric; Type IV, extrasphincteric. The terms trans-, supra-, and extra- refer to the external sphincter mass. *EAS* external anal sphincter, *IAS* internal anal sphincter, *LA* levator ani, *PR* puborectalis. (With permission from: Tiernan JP, Brown Sr. Benign anal conditions: haemorrhoids, fissures, perianal abscess, fistula-in-ano, and pilonidal sinus. Surgery (Oxford) 2011;29(8):382–386)

to 1/3 of patients. The pathogenesis of Crohn's fistulas remains poorly understood but is thought to be different than that of the cryptoglandular form. One theory is that a deep anorectal ulcer forms, which subsequently becomes invaded by fecal material and bacteria. The tract is then created by the pressure from the anorectum. Crohn's fistulas are generally more complex with branching and multiple tracts, which do not follow the typical pattern of cryptoglandular fistulas or Goodsall's Rule. Unlike patients with cryptoglandular fistulas, Crohn's fistulas usually do not respond to operative therapy alone. A different algorithm of treatment must be followed with a stronger emphasis on optimal medical management to control rectal disease and reduce the autoimmune inflammatory component of the fistulization.

The possibility that fistulas are due to Crohn's disease should trigger a search for active disease in the colon or small bowel. Even if intestinal disease is not present, it is possible to distinguish Crohn's from cryptoglandular fistulas by identifying granulomas in the curettings from the fistula tract or areas of undermined skin. Perianal skin tags may also yield pathognomonic non-caseating granulomas. Zawadzki and colleagues in Sweden reported a unique imaging characteristic

on 3D endoanal ultrasound (EUS) for Crohn's fistulas. This was defined as a hypoechogenic fistula track surrounded by a hyperechogenic area extending into the perianal tissue with a thin, regular hypoechogenic edge. They noted that 20 of 29 (69 %) patients with Crohn's had a positive Crohn ultrasound fistula sign (CUFS) while 125 out of 128 (98 %) patients with cryptoglandular fistulas did not [1]. This may be a useful, noninvasive method which helps to distinguish Crohn's fistulas from other forms of perianal disease.

Differential Diagnosis

It is not uncommon (≈20 %) for patients to present with perianal Crohn's disease as their first symptom. As already mentioned, it can be difficult to distinguish between this and other etiologies of perianal disease. Hidradenitis is a common diagnosis which may be confused with Crohn's fistulas and may also occur in association with severe perianal Crohn's disease. Clues to a diagnosis of hidradenitis include additional tracts or abscesses within the groin or armpit, multiple tracts in the perianal skin without connection to the anal canal, and severe disease at onset rather than a gradual worsening in severity over time. Other diagnoses within the differential include cryptoglandular fistula, pilonidal cysts, sexually transmitted diseases, anal fissure, Kaposi's sarcoma, and anal squamous cell cancer. Knowledge of each of these and heightened suspicion are necessary as one evaluates a patient with unusual findings or presentations.

Clinical Manifestations and Diagnosis

Undiagnosed patients may present with constant anal pain, pain with defecation, a painless draining perianal skin opening, a painful persistent abscess in the perineum, or unexplained fever. Proper evaluation of the patient includes taking a thorough history with regard to any prior episodes in the past as well as other symptoms of Crohn's disease including abdominal pain, diarrhea (with or without blood), tenesmus, fevers, or weight loss. A perianal and rectal exam should be performed in the prone jackknife position, looking for fistula tracts, fluctuance, erythema, strictures, or skin tags. An exam under anesthesia (EUA) is necessary if the patient does not tolerate the in-office exam and an anal probe would be used to identify and define the tract and location of the internal opening. If there is difficulty delineating the tract, dilute hydrogen peroxide or betadine may be injected through the external opening in order to aid in locating the internal opening. EUA has long been recognized as the gold standard for identifying tracts and delineating the extent of disease in fistula disease. A lighted Buie Hirschman anoscope is essential

to provide good vision in the office while the half circle Hill Ferguson retractor usually gives adequate exposure and vision with reflected light in the operating room. Lighted Hill Ferguson retractors are also available.

A complete evaluation of the rectum should also be performed using either flexible sigmoidoscopy or rigid proctoscopy. Documentation of rectal mucosa involvement is essential to planning treatment. Eventually, colonoscopy should be performed to evaluate the rest of the colon.

Imaging

EUS, MRI, CT, fistulography, and endoscopy have been used in diagnosing and evaluating Crohn's fistulas. Fistulography is an older imaging modality which involves the injection of contrast into the visible external opening, with subsequent radiography. This technique has fallen out of favor for use in perianal disease as it has been shown to have a low accuracy rate. A retrospective study showed that it was accurate in only four of 25 patients in delineating fistulas compared to operative findings. Fistulography may be helpful in the circumstance of extrasphincteric disease or when used with other modalities. CT has been used for fistula imaging; however, it is limited by lower resolution, artifact, image blurring, streaking due to fistula contents, and an inconsistency identifying the levator ani. CT has not been useful to classify fistulas or guide appropriate treatment [2, 3].

MRI is a proven technique for detecting and delineating fistula tracts. The internal and external anal sphincters are well characterized, and therefore the relationship of the fistula tract to these structures can be determined. Endoanal coils may be used to enhance the resolution of the MRI, though this technique may be limited by patient discomfort. For patients suspected to have complex disease extending into the pelvis, such as in suprasphincteric fistulas, 1 mL of glucagon may be administered intramuscularly to help decrease bowel motion [4]. Fibrotic fistulous tracts will appear hypo-intense on T1- and T2-weighted images and enhance with administration of gadolinium (Fig. 19.2). Fluid and granulation tissue will both appear hyper-intense but only granulation tissue will enhance with gadolinium (Figs. 19.3 and 19.4). Buchanan found that disease recurrence after surgery in patients with fistula-in-ano was decreased by 75 % in those who underwent preoperative MRI [5].

EUS of the anal canal was introduced in the 1980s [6, 7], and multiple studies have shown this technique to be accurate in defining fistula anatomy with greater ease and lower cost than MRI. Injection of peroxide into the fistula tract has been found to help accurately (95 %) delineate fistula tracts [8]. The tract will become hyper-echoic on ultrasound with this technique. Accuracy may be improved further by using
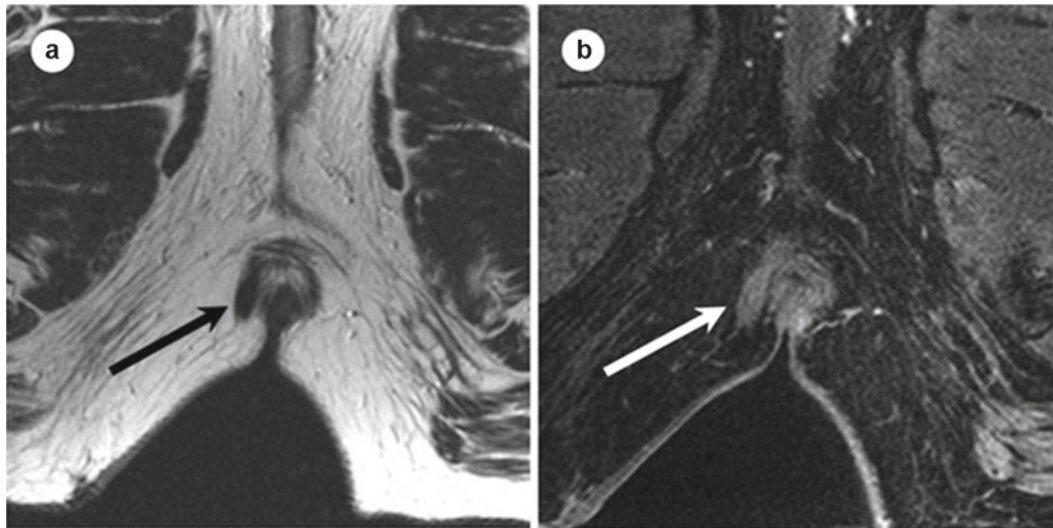
Fig. 19.2 Appearance of fibrotic fistula track at MR. Sixty-three-year-old male with right lateral fibrotic intersphincteric fistula track. Axial T2 FSE (**a**) and axial T1W SPGR postgadolinium images with fat saturation (**b**) obtained at 1.5 T below the level of the anal sphincters. Fibrotic tracks at MR appear as bands of homogenous low signal intensity at T2W1 (*black arrow* in **a**). After the administration of gadolium, enhancement is homogenous throughout the fibrotic track (*white arrow* on **b**). *FSE* fat spin echo, *SPGR* spoiled gradient recalled echo. (Adapted from Sun MR, Smith MP, Kane RA. Current techniques in imaging of fistula in ano: 3D endoanal ultrasound and magnetic resonance imaging. Semin Ultrasound CT MRI 2008;29:454–471, with permission)
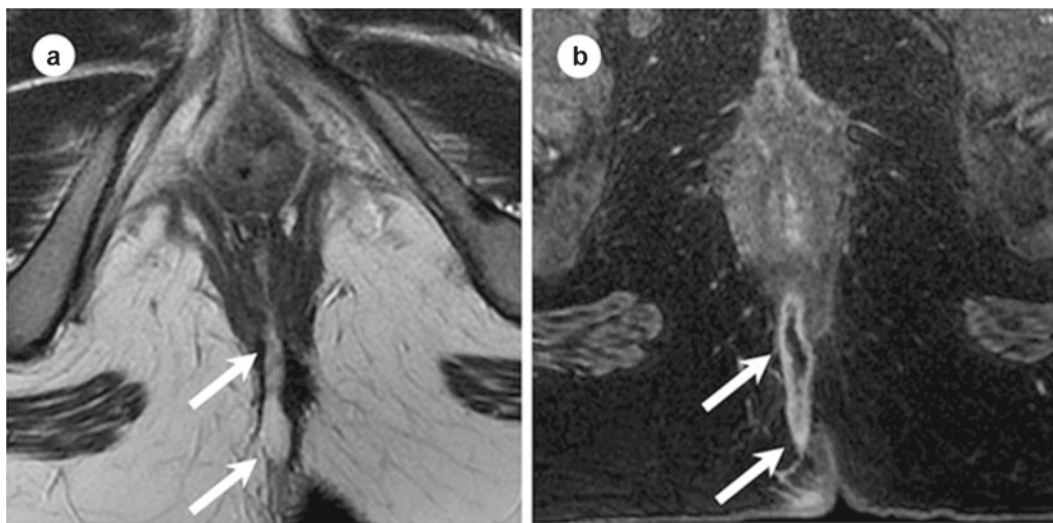

Fig. 19.3 Appearance of fluid-containing track at MR. Twenty-five-year-old female with posterior transsphincteric fistula. Axial T2 FSE (**a**) and postgadolinium T1W SPRG (**b**) images obtained at 1.5 T. Fluid-containing tracks show peripheral low signal intensity and linear central high signal intensity on T2WI (*arrows* in **a**). After the administration of intravenous gadolinium the track enhances peripherally but the fluid within the track lumen does not enhance (*arrow* in **b**). *FSE* fat spin echo, *SPGR* spoiled gradient recalled echo. (Adapted from Sun MR, Smith MP, Kane RA. Current techniques in imaging of fistula in ano: 3D endoanal ultrasound and magnetic resonance imaging. Semin Ultrasound CT MRI 2008;29:454–471, with permission)

the 3D EUS (Fig. 19.5). EUS is less accurate in detecting disease extending into the pelvis or ischiorectal fossa [9]. Crohn's patients especially are less likely to tolerate the endoanal probe due to pain or the presence of stricture and this may limit the usefulness of EUS. The accuracy rate of EUS remains, in part, operator-dependent [10]. Multiple studies comparing EUS with MRI provide no clear consensus regarding superiority. Schwartz prospectively demonstrated equivalent accuracy between MRI, EUS, and EUA (87 %, 91 %, and 91 %, respectively) for determining fistula anatomy in Crohn's disease patients. Combining MRI and EUS was noted to have a near 100 % accuracy rate for the detection and delineation of fistula tracts [11]. Sahni et al. found MRI to be superior to EUS with regard to specificity and sensitivity
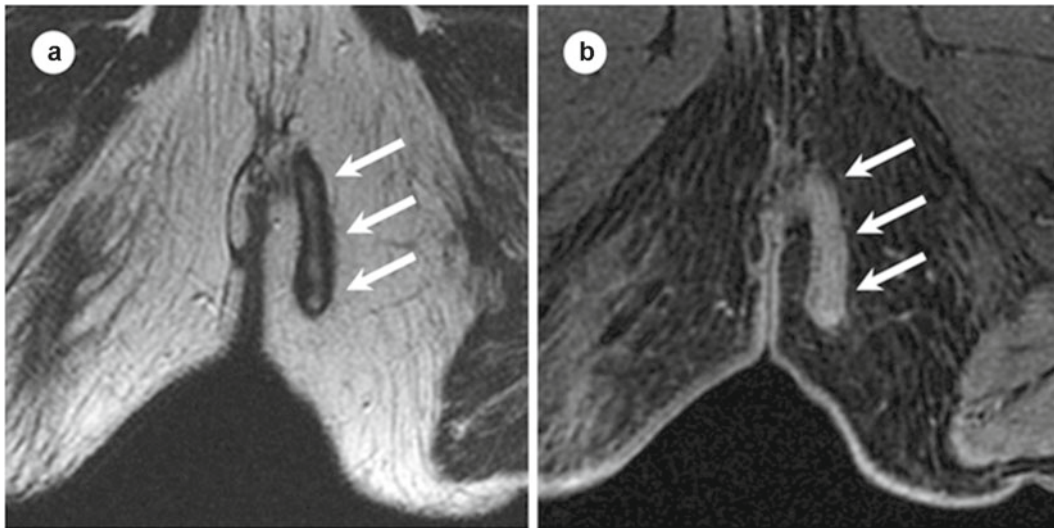
Fig. 19.4 Fistula track containing granulation tissue at MR. Seventy-seven-year-old male with transsphincteric fistula track containing granulation tissue. Axial T2 FSE (**a**) and axial T1W SPGR postgadolinium (**b**) images, obtained at 1.5 T. Granulation tissue within a fistula track appears similar to fluid within a track on T2WI, visible as a linear area of hyperintensity at T2WI (*arrows* in **a**). However, after the administration of intravenous gadolinium, granulation tissue enhances (*arrows* in **b**), while fluid within a track does not. *FSE* fast spin echo, *SPGR* spoiled gradient recalled echo. (Adapted from Sun MR, Smith MP, Kane RA. Current techniques in imaging of fistula in ano: 3D endoanal ultrasound and magnetic resonance imaging. Semin Ultrasound CT MRI 2008;29:454–471, with permission)

(97 % and 96 % vs. 92 % and 85 %, respectively) [12]. Selective use of MRI and EUS in conjunction with EUA is probably the best approach.

Medical Therapy

Once a diagnosis of Crohn's fistula is made, it is important to have a treatment strategy planned. Crohn's fistulas are often very complex, and the initial treatment modality should always be with medical therapy combined with drainage if necessary. Medical therapy may include appropriate antibiotics, immunosuppressive agents, or biologic agents. There is no role for corticosteroids in the treatment of perianal Crohn's disease.

Ciprofloxacin and Metronidazole

Ciprofloxacin and metronidazole have a role in the treatment of Crohn's perianal fistulas. West prospectively compared ciprofloxacin in conjunction with infliximab vs. infliximab alone, and found that the response rate (50 % reduction in the number of draining fistulas) was 8 of 11 (73 %) in the combination therapy group vs. 5 of 13 (39 %) with infliximab alone [13]. However, this difference was not significant due to the small number of patients in the groups. Bernstein found that, in a series of 21 patients treated with metronidazole 20 mg/kg/day for 6–8 weeks, all patients noticed less discomfort, and 56 % had complete healing. However, the fistulas recurred in 75 % of patients on stopping the drug [14] and severe side effects included nausea and peripheral neuropathy. A small randomized, double blinded, placebo-controlled pilot trial at the Mayo clinic showed that remission and response occurred more frequently (but not significantly) in patients treated with ciprofloxacin [15]. The use of ciprofloxacin and metronidazole remains widespread for the treatment of this disease, despite the lack of conclusive evidence of their benefit.

Immunosuppressants

6-Mercaptopurine (6-MP) and Azathioprine (AZT) have been used in the treatment of intestinal Crohn's disease for many years. However, there have been no randomized controlled trials testing their efficacy in the treatment of perianal fistulas as a primary endpoint. Several reports have shown improvement or complete healing in up to 70 % of patients [16–19]. Ochsenkühn et al. combined azathioprine, 6-MP, and infliximab in patients with Crohn's fistulas refractory to conventional management [20]. The 14 patients with perianal fistulas received 3–4 infusions of infliximab followed by long-term therapy with 6-MP and azathioprine. Complete closure of the fistula occurred in 13 patients for more than 6 months. They concluded that 6-MP and azathioprine may prolong the fistula closure achieved with infliximab.
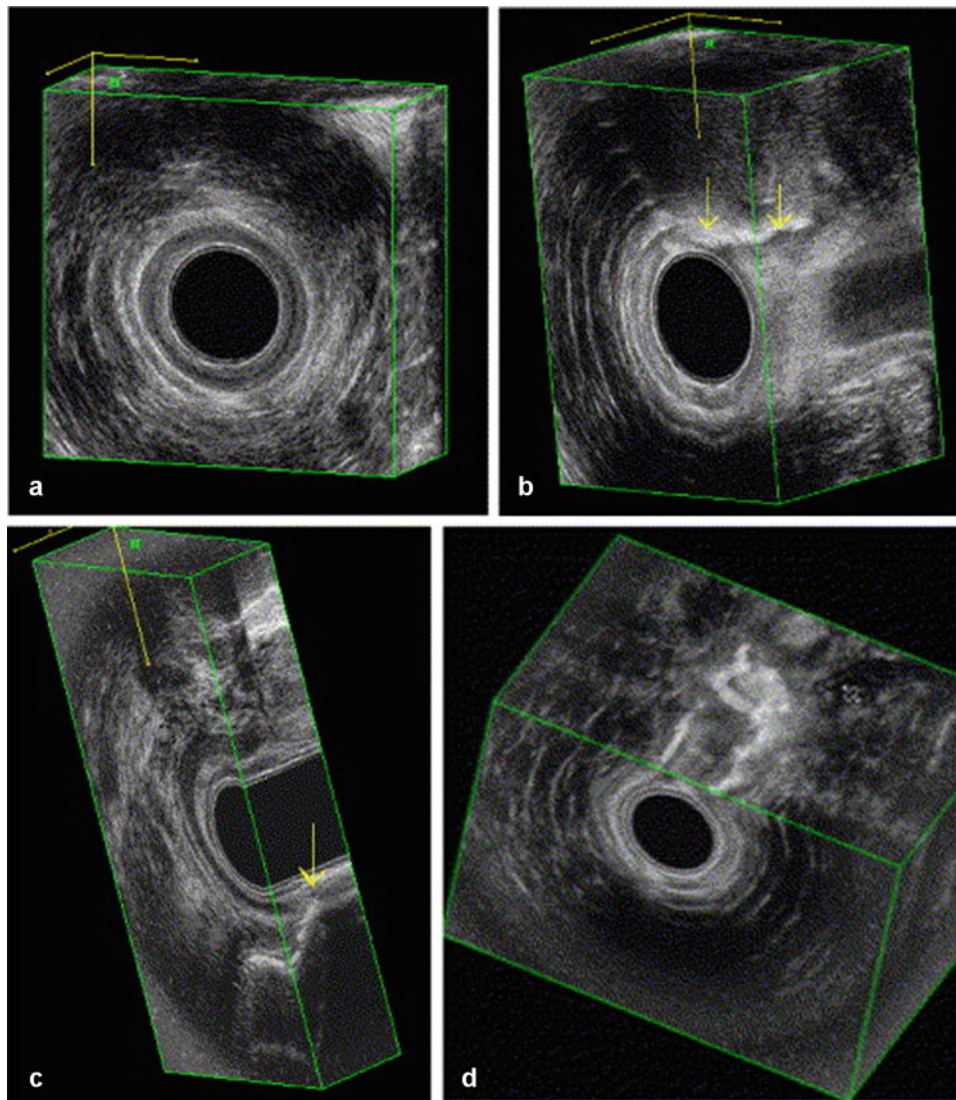
Fig. 19.5 Anal endosonography. Normal anatomy of the anal sphincter and puborectal muscle in 3D imaging: (**a**) frontal view of puborectal muscle (PR); (**b**) frontal view of the anal sphincters; (**c**) lateral view; and (**d**) coronal view. *SM* submucosa, *IAS* internal anal sphincter, *EAS* external anal sphincter. (Adapted from Felt-Bersma RJF. Endoanal ultrasound in perianal fistulas and abscesses. Digestive and Liver Disease 2006;38(8):537–543)

TNFα Inhibitors: Biologics

Monoclonal antibody therapy against T cells has become the mainstay in medical treatment of perianal Crohn's fistulas. Infliximab is a monoclonal antibody with mouse origin against TNFα which was initially approved for the treatment of intestinal Crohn's disease in 1998 [21]. Infliximab is administered intravenously typically at 6–8 week intervals. The first randomized, double blind, placebo-controlled trial of infliximab for the treatment of Crohn's fistulas was done in 1999 by Present and associates [22]. This study included 94 patients with both intra-abdominal and perianal fistulas. At a dose of 5 mg/kg, there was a complete response with fistula closure in 55 % of the patients treated with infliximab vs. 13 % of patients receiving placebo. The most frequent adverse events occurring were headache, abscess, upper respiratory infection, and fatigue.

Adalimumab is a human-derived monoclonal antibody against TNFα. The CHOICE trial evaluated the safety and efficacy of adalimumab in patients who had failed to respond or lost response to infliximab therapy in 673 patients with Crohn's fistula [23]. Approximately 40 % of these patients demonstrated healing of their fistulas by their last follow-up visit (ranging from 4 to 36 weeks). They concluded that adalimumab was an effective treatment for patients who failed therapy with infliximab.

This illustrates the largest problem with trials evaluating medical therapy. The usual follow-up in the study is less than 6 months. Typical follow-up for surgical treatment is greater than a year. This is even too short since fistula recurrence happens up to 5–10 years later. Short follow-up has limited our knowledge regarding medical treatment of fistulas. The true value of medical treatment may be reduction of active Crohn's disease in the rectum and anal canal to allow definitive closure of the internal opening of the anal fistula.

Certolizumab pegol is a monoclonal antibody against TNFα combined with polyethylene glycol to prolong its half-life, allowing the drug to be administered monthly. PRECiSE 2, a multicenter, randomized controlled trial, evaluated the response to certolizumab pegol in 668 patients with moderate to severe Crohn's. This trial showed certolizumab to be effective in inducing a clinical response in 58 of 100 patients with anal fistulas. After 6 weeks, additional analysis was done separately on those patients with draining fistula. These patients were randomized to either maintenance therapy with certolizumab or placebo. A significantly greater number of patients maintained a 100 % fistula closure in the maintenance vs. placebo group (36 % vs. 17 %). The authors concluded that continuous treatment with certolizumab improves outcomes when compared with placebo [24].

Biologic agents are significantly more expensive and have some serious side effects including abscess formation and upper respiratory infections. Nevertheless, there is strong evidence that this group of drugs is more efficacious than antibiotics or immunosuppressants. The 2011 London Position Statement of the World Congress of Gastroenterology provided guidelines for the use of biologic agents in Crohn's disease. Biologic agents are recommended for the treatment of complex fistulas. Infliximab should be regarded as the first line biologic agent for fistulizing Crohn's at this time. All abscesses must be drained prior to initiation of a biologic agent as this can result in worsening perianal sepsis [25]. Adalimumab and certolizumab pegol may be reserved for treatment failures with infliximab.

Surgical Management

If optimum medical therapy fails, the patients may require more definitive surgical management of their disease. The first step in surgical management is to manage and treat perianal sepsis. Abscesses should be appropriately and thoroughly drained. A non-cutting seton using an inert material such as a silastic vessel loop may be placed for continued drainage and to mark the fistula for future surgical procedures. Appropriate antibiotics and medical therapy to control any active Crohn's disease should be initiated. With appropriate drainage and control of perianal sepsis, fistulas may heal without any further surgical treatment, though the

recurrence rates are high. Setons are generally effective in helping to control perianal sepsis but may be associated with recurrence after removal in up to 31 % of patients [26].

There are multiple other techniques for treating fistulas if simple drainage and medical management fails. Choosing the optimal surgical management requires consideration of the type of fistula involved. A proposed treatment algorithm is shown in Fig. 19.6. A low intersphincteric fistula may be treated with fistulotomy or fistulectomy. Excision of the tract leads to larger surgical wounds, and therefore fistulotomy of the superficial fibers of distal internal sphincter is preferred in most circumstances.

High transsphincteric fistula tracts are best treated with the ligation of the intersphincteric fistula tract (LIFT) technique or rectal wall advancement flaps, as the incidence of minor incontinence is less. Suprasphincteric fistulas start out as an intersphincteric abscess with a cephalad extension which then drains through the rectal outer wall and levator ani into the ischiorectal fossa and then to the buttock skin. Unroofing or drainage of the tract lateral to the external sphincter should be performed, and the remaining intersphincteric tract can be incised from the dentate line to the upper extent of the fistula. Setons are not recommended for suprasphincteric fistulas. Final closure with a sliding flap or proximal diversion may be required.

Extrasphincteric fistulas in Crohn's disease are most often the result of a connection with intra-abdominal intestine. In this case, fistulotomy will not definitively treat the disease. Resection of the diseased portion of intestine is the only effective manner to bring about healing and eliminate recurrences of these fistulas.

Fistulotomy and Fistulectomy

The first step in performing a short fistulotomy for the low intersphincteric fistula is to identify the external opening. A probe is then placed through the opening and into the tract in order to try to identify the internal opening within the anal canal and document the amount of muscle encircled by the fistula. Once the probe is in place, the tissue overlying the probe may be divided using a scalpel blade or the cutting current of a cautery device. No external sphincter should be divided. If a diagnosis of Crohn's disease is suspected but not confirmed, curettings from the tract may be sent at this time.

If fistulectomy is chosen, the external opening is located and a stay suture is placed. The tissue around the fistula may be injected with local anesthetic and epinephrine to minimize bleeding. The skin surrounding the external opening is then divided. Scissors are used to core out the tissue surrounding the fibrous tract while the stay suture is retracted downwards. If the tract penetrates the external anal sphincter low, the muscle may be divided; however, if the tract is high
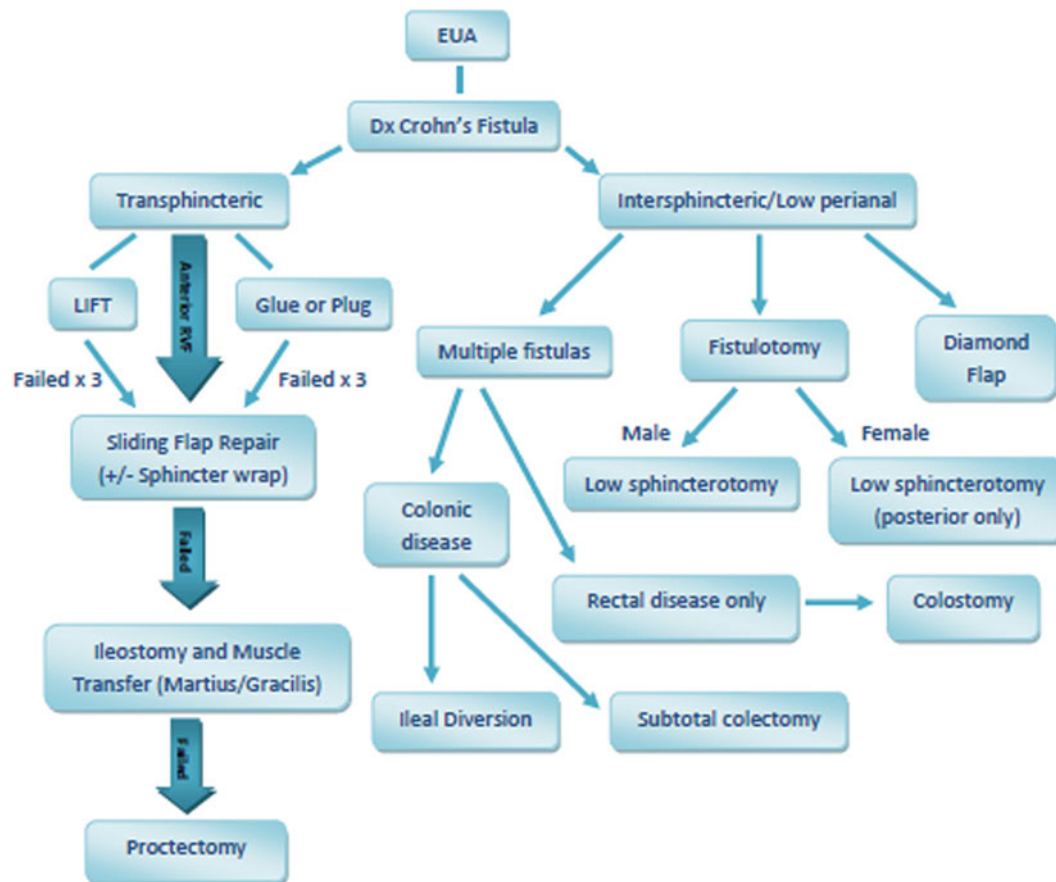
Fig. 19.6 Treatment algorithm for Crohn's perianal fistula

or the patient already has other risk factors for incontinence, dissection should proceed in a meticulous fashion, coring out the track from the muscle and leaving most of the external anal sphincter intact. The defect may then be allowed to heal by secondary intention or may be closed with a suture or an advancement flap. The internal opening should be closed with figure of eight closure.

Fistulotomy or fistulectomy is not appropriate in females with anterior fistulas as the risk of incontinence is very high. Patients with a history of obstetric injury should not undergo either of these procedures. High transsphincteric or suprasphincteric fistulas involve a large portion of the external sphincter. Cutting through the sphincters at this level is associated with high rates of total incontinence. Preexisting scar in the rectovaginal septum which is involved by Crohn's fistula may be injured and result in rectovaginal fistula (RVF) after fistulotomy or fistulectomy.

Postoperative care after fistulotomy or fistulectomy includes appropriate analgesia, tub baths with the water stream hitting the perineum at least three times a day, stool softeners as needed, and frequent follow-up visits. Packing the wound is not necessary. Marsupialization of the edges of the wound rarely lasts and there is very little difference from closure by delayed secondary intention. Some degree of leakage or lack of control may occur, and 90 % of cases will spontaneously resolve. Other postoperative complications include urinary retention, bleeding, pain, pruritis, and poor wound healing due to active Crohn's. Anal stenosis from chronic inflammation may also occur as a late postoperative complication.

Flaps

Coverage of the internal opening with an advancement flap of the rectal wall may be considered for the treatment of anterior low rectal Crohn's fistulas in patients where fistulotomy is not an option. Prior to this procedure any perianal abscess, sepsis, or active intestinal or perianal Crohn's disease must be controlled. Although these flaps are often referred to as endorectal mucosal advancement flaps, various layers of tissue may be used including mucosal, partial thickness rectal, full thickness rectal, or perianal skin. Transanal advancement flaps close the internal opening and leave the external sphincter intact, thus they are associated with a lower risk of incontinence and recurrence. A broad-based U flap
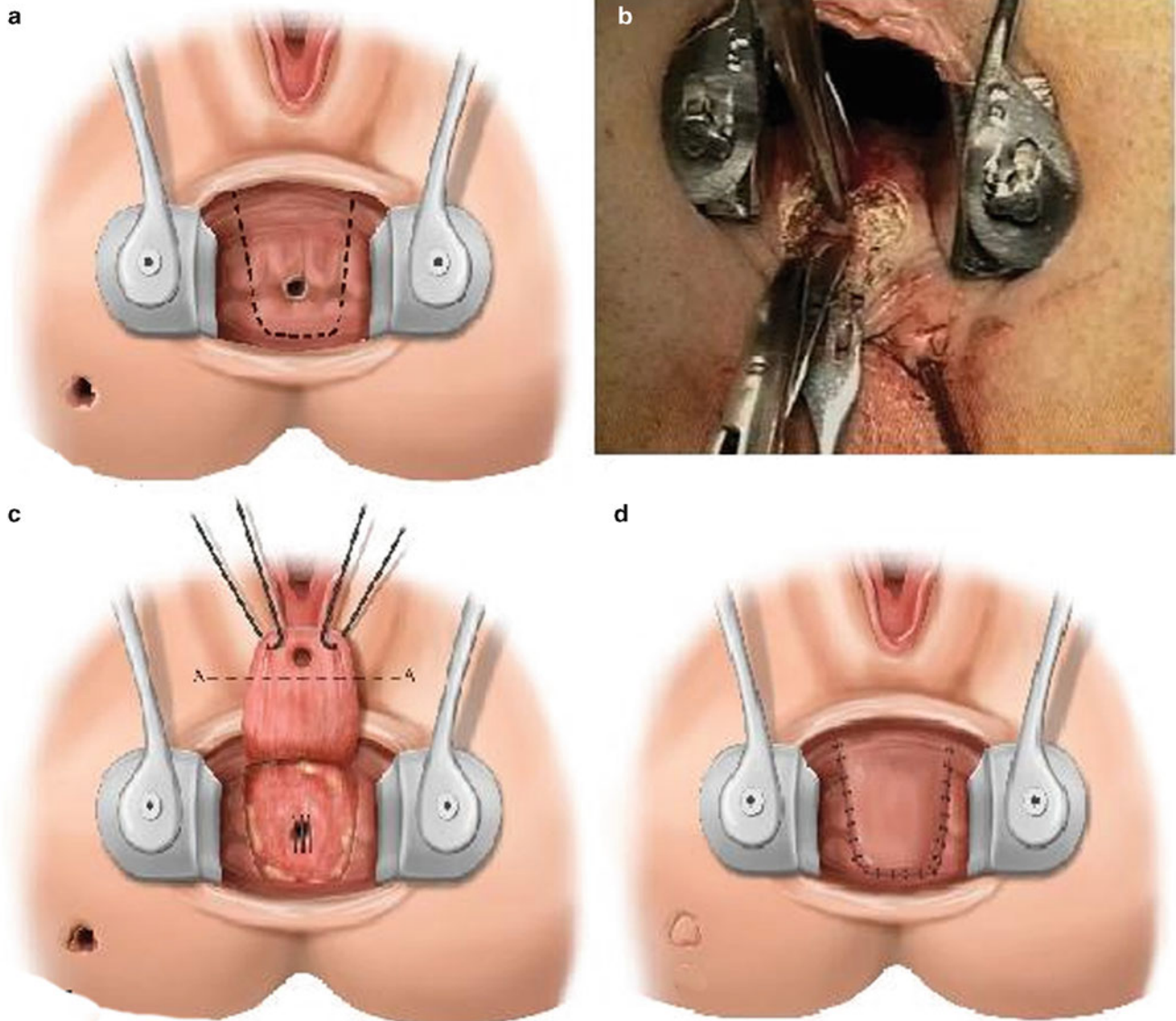
Fig. 19.7 (**a**) Line of incision for a broad-based U endorectal advancement flap (schematic), (**b**) developing the flap, in this case in the intersphincteric plane, raising a full thickness endorectal advancement flap, (**c**) fully mobilized flap retracted using two holding sutures. Internal opening is raised with the apex starting approximately 5–10 mm excised along line A-A. Internal opening defect in the sphincter is closed with interrupted sutures (schematic), (**d**) sutured endorectal advancement flap (schematic). (Adapted from Wexner SD, Fleshman JW. Colon and rectal surgery: Anorectal operations 2012;44–46, with permission)

is raised with the apex starting approximately 5–10 mm below the internal opening and 10–15 mm in width on either side of the opening (Fig. 19.7a). The flap is raised, usually including mucosa and submucosa in the distal portion of the flap, and either partial or full thickness circular rectal wall muscle fibers (Fig. 19.7b). The length of the flap need only be enough to provide a tension-free closure after excising the fistula opening in the flap. The tract opening in the muscle and surrounding tissue is cored out and closed with interrupted absorbable monofilament sutures (Fig. 19.7c). The flap is secured over the top of the internal opening with interrupted absorbable braided sutures (Fig. 19.6d).

The external opening is left open and curetted or drained with a mushroom tip catheter. In patients with low fistulas in the setting of long-standing perianal sepsis or anal stenosis, endorectal advancement flaps are not typically successful. In these cases, an anocutaneous advancement flap may be performed. Full thickness 2×2 cm diamond of perianal skin and subcutaneous fat is elevated adjacent to the fistula internal opening, ensuring there is a broad base with good vascular supply at its lateral aspect. The internal opening and surrounding tissue is once again excised with a vertically directed elipse and the tract closed. The skin flap is advanced into the anal canal and sutured over the internal opening with
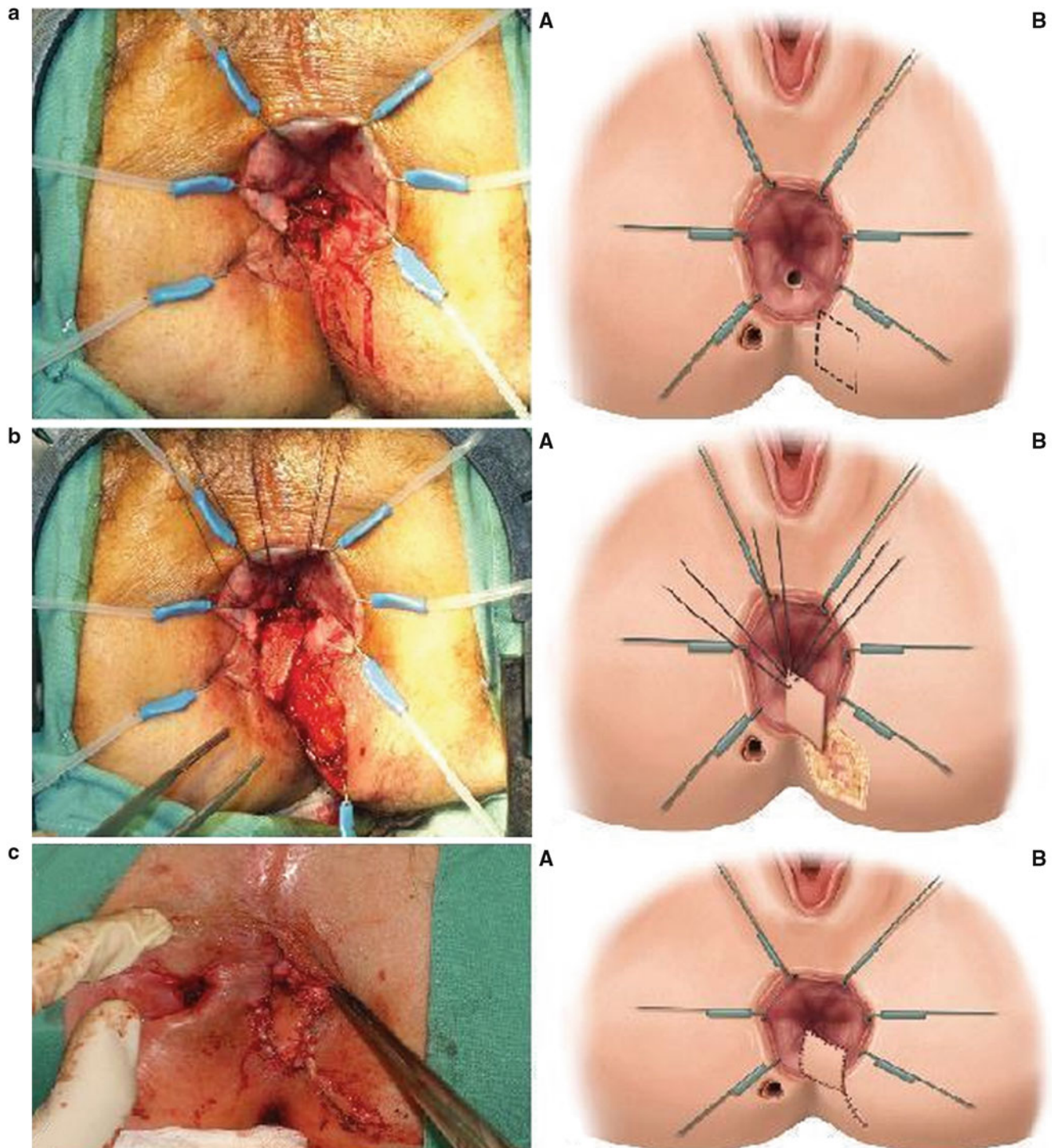
Fig. 19.8 (**a**) Incision for diamond-shaped anocutaneous advancement flap: (*A*) actual view and (*B*) schematic; (**b**) flap being advanced to cover the internal opening: (*A*) actual view and (*B*) schematic; (**c**) sutured anocutaneous advancement flap: (*A*) actual view and (*B*) schematic. (Adapted from Wexner SD, Fleshman JW. Colon and Rectal Surgery: Anorectal Operations: 2012:47–48, with permission)

absorbable braided suture. The skin defect is then closed primarily resulting in a linear suture line with the appearance of a "kite tail" extending from the anal canal (Fig. 19.8).

Postoperative care is minimal. Sitz baths are used to clean the area after a bowel movement. It is important to keep the wound clean and dry, otherwise. Postoperative complications include flap breakdown, incontinence, perianal sepsis, bleeding, ectropion, and iatrogenic fistulas. The reported efficacy rate of this technique varies. Soltani showed a reported efficacy rate of 81 % with cryptoglandular fistulas but only 64 %

with Crohn's fistulas. The rate of incontinence with this procedure in Crohn's fistula patients was nearly 10 % [27]. If the initial flap procedure fails, a second flap procedure may be successful after a period of waiting and the addition of a diverting stoma. The final success rate should be close to 90 % [28].

Glues and Plugs

Two additional options for the treatment of anal fistulas include a fistula plug and fibrin glue. Fibrin glue was first studied in the early 1990s for the treatment of fistulas and approved by the FDA in 1998. The main active ingredient in fibrin glue is fibrinogen, which when combined with thrombin, forms a fibrin clot. This subsequently undergoes fibrinolysis and promotes tissue healing. A recent randomized trial achieved an initial closure rate of 38 % (13/34) in Crohn's patients treated with fibrin glue vs. 16 % for the placebo group. Two of these patients developed recurrence at 16 weeks. Of the 21 patients who did not respond to the initial treatment, five were treated again with the glue. None went into remission [29]. This illustrates the need for long-term follow-up to assess the true efficacy of any method of treating a fistula in Crohn's disease.

Robb and Sklow reported the first use of rolled submucosal "plugs" for the treatment of fistulas. Subsequently, numerous commercial "plugs" have been developed. Initial results using these products were promising, with reported success rates up to 80–90 %. However, eventually it became apparent that recurrence rates were high, especially in patients with Crohn's disease. A recent systematic review by O'Riordan et al. concluded that the rate of closure with the fistula plug was 64 % in patients with cryptoglandular disease. The evidence regarding closure rates in patients with Crohn's disease was insufficient to provide any conclusions [30].

Plugs and glues may be placed after proper drainage of any perianal abscess and fibrosis of the fistula tract has occurred. If any evidence of active infection is present, the procedure should be postponed until this has been controlled. When using fibrin sealant, primary and secondary tracts should be identified, and the fibrin sealant injected into the secondary tracts until seen in the primary tract. Fistula plugs should be fully submerged in sterile saline for rehydration for up to 2 min. A suture may be placed through the seton within the fistula tract. The seton is then pulled out and the suture remains. The suture is then secured to the narrow external opening portion of the plug, and the plug is drawn through the fistula tract inside the rectum and secured at the wide portion of the plug which is trimmed flush to the rectal wall internal opening of the fistula using an absorbable suture. After this is in place, a small mucosal advancement flap may be created to cover the plug at the internal opening.

Postoperative complications are rare and include recurrent abscess or plug extrusion. A controversy exists over whether the fistula tract should be curetted before "setting" the plug. Care should be taken to remove all debris from the tract by repeated flushing with saline or dilute betadine or hydrogen peroxide.

Despite the low rates of remission described in recent literature with the use of anal plugs and glues, they still remain valid treatment options to consider for the treatment of Crohn's fistulas due to their minimally invasive nature and ease of use. A failure with an attempted "plug" closure does not preclude use of another method. This makes the plug an attractive early option for fistula treatment. This is especially true with Crohn's disease given its increased risk for morbidity and recurrence with surgical treatment of anal fistulas.

A recently described technique combining fibrin glue and adipose-derived stem cells (ASCs) has been reported by Garcia-Olmo and colleagues for the treatment of perianal fistulas. A small series of 14 patients with Crohn's fistulas showed healing in 71 % (5/7) of patients treated with fibrin glue and ASCs compared to 14 % (1/7) in the fibrin glue group [31]. Another series of patients treated with ASCs showed a recurrence rate of 42 % after more than 3 years in those patients who were initially treated successfully [32].

Ligation of the Intersphincteric Fistula Tract

Possibly the most innovative recent advance in fistula surgery is the LIFT procedure. This was developed and first described by Rojanasakul et al. in 2007 and has shown promising results since its introduction. The initial report was of a prospective observational study in cryptoglandular disease with 17/18 patients successfully treated and no incontinence [33]. Sileri et al. subsequently showed healing rates of 83 % in patients with cryptoglandular fistulas without recurrence, though median follow-up was only 4 months [34]. However, Tan et al. reported a retrospective comparison of advancement flaps and the LIFT procedure for treatment of cryptoglandular fistulas and found that the advancement flap had a significantly higher success rate (94 % vs. 63 %) [35]. Han reported a series of patients in whom the LIFT technique was used in combination with the "plug" to achieve a 95 % overall success rate with median follow-up of 14 months [36].

The technique isolates and divides the fistula tract between the internal and external anal sphincters by means of an intersphincteric dissection, which begins at the anal verge, thus preserving both anal sphincters. The procedure is performed by identifying the internal and external openings initially and placing a fistula probe to guide the dissection to the fistula tract. The space between the internal and external anal sphincters between the external and internal openings is palpated and a 2–3 cm curvilinear incision is made in the
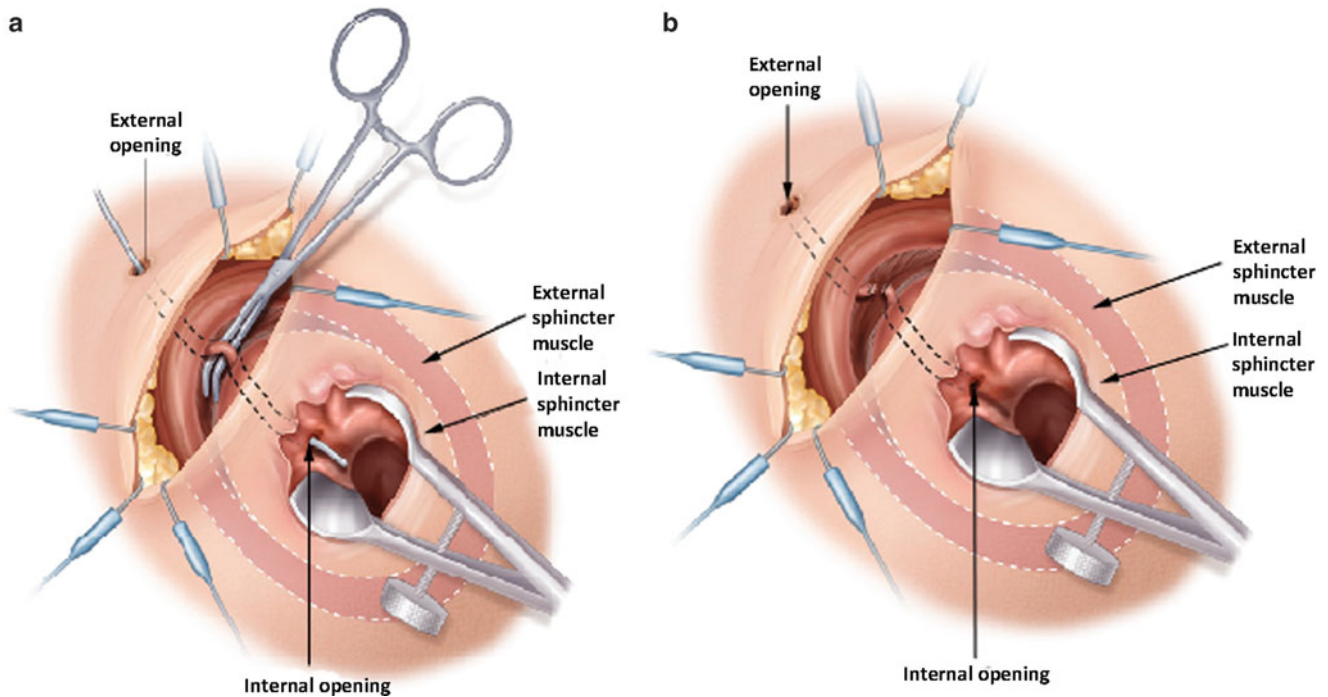
Fig. 19.9 (**a**) The fistula tract, with the probe through it for ease of identification, is dissected free in the intersphincteric space; (**b**) the probe is removed, and the fistula tract is ligated and divided. (Adapted from Wexner SD, Fleshman JW. Colon and Rectal Surgery. Anoretal Operations 2012; 82, with permission)

intersphincteric groove. Intersphincteric dissection is carried out until the fistula tract is identified. The tract is exposed circumferentially. Clamps are placed on either side of the tract as the probe is removed, and the tract is cut (Fig. 19.9). Success seems to be highest when the fistula tract feels like the "spermatic cord during a vasectomy." Alternatively, sutures are placed at each end of the exposed fistula tract to close and expose the tract. A portion of the tract centrally may be removed if desired. Each side is ligated with the absorbable suture. The external opening is generally left open. The internal opening within the rectal lumen is closed with a figure of eight suture. In some instances, such as an anterior fistula in a thin perineal body in a female or in a Crohn's fistula, a square of biomesh can be placed in the intersphincteric space to separate the cut ends of the tract. The outer edges of the muscle are approximated to capture the patch. The skin is closed in an interrupted fashion over a small section of silicone vessel loop as a drain.

The initial results of this technique are good, with minimal postoperative complications and success rates between 60 and 85 %. However, there are currently no studies specifically relating to the treatment of fistulas in Crohn's patients using the LIFT technique. Further studies with long-term follow-up, particularly relating to Crohn's patients, are needed to better evaluate the efficacy of this procedure.

Diversion

In patients with severe perianal disease, diversion coupled with a local surgical procedure may increase the success rate of these local procedures. Rehg et al. reported 85 % of fistulas healed after fecal diversion and local surgical treatment vs. 19 % with local treatment alone. Only 46 % of the diverted patients underwent stoma reversal and of these, half recurred [37]. Galandiuk et al. attempted to identify risk factors which would predict failure of local, sphincter sparing operations in patients with perianal Crohn's disease. Permanent fecal diversion was required in 49 % of this group. Risk factors for failure included anal stricture, the need for ileocolic resection, and the presence of colonic Crohn's disease [38]. For these patients, and patients with complex, high anal fistulas, it may be helpful to construct a diverting stoma. However, it is important that the patient understands that there is a significant chance that this may be a permanent stoma.

Proctectomy

Ultimately between 12 and 20 % of patients with refractory perianal Crohn's disease will eventually undergo a proctectomy [39]. However, 23–79 % of patients who undergo

proctectomy will experience unhealed wounds following proctectomy; especially those with rectal strictures or high anal fistulas [39]. For this reason, it is our opinion that proctectomy should be reserved for situations in which all other treatment options have been exhausted and the patient continues to have debilitating perianal symptoms. This may result in the patient having multiple small procedures to manage symptoms and improve quality of life over the period of many years. In some instances the Crohn's disease will "burn out" or respond to medical therapy and allow the patient to avoid a permanent stoma. In those patients who do not respond or who have worsening disease, their decision to undergo a permanent ostomy will be made much easier and will truly improve their quality of life with the knowledge that all has been tried to avoid this outcome.

Follow-up

As stated previously, the natural history of Crohn's fistulas is such that recurrence is common, and may occur months to years after initial healing. Close follow-up and maintenance with prophylactic medications including metronidazole or ciprofloxacin, immunosuppressants, and biologic agents is imperative. It is also important to be aware that patients with long-standing Crohn's fistulas have an increased risk of anal cancer, both squamous cell and adenocarcinoma. The mechanism is unknown, but is thought to be related to constant inflammation and regeneration of mucosal cells. Ky et al. reported an estimated 0.7 % incidence of carcinoma arising in Crohn's anal fistulas [40]. On average, development of carcinoma in Crohn's fistula has been reported 15–20 years after disease onset [40, 41] in ages 47–51 [40]. Early detection is critical; therefore, patients with Crohn's fistulas must be followed with frequent, thorough physical examinations including EUA if needed.

Rectovaginal Fistulas

Background

RVFs are most commonly associated with a history of rectovaginal trauma (i.e., episiotomy), and have been reported in 3–9 % of women with Crohn's disease [42–44]. Symptoms include dyspareunia, passage of fecal matter or stool from the vagina, or recurrent urinary tract infections. Multiple classification symptoms exist, and may be based on their relationship to the anal sphincter, the complexity of disease, and their etiology. However, no clear consensus has been reached on the usefulness of these classifications except that high fistulas require more complex repair efforts than low fistulas.

Diagnosis

Diagnosis of RVFs includes a thorough physical examination. The rectal opening may be readily visible on anoscopy, though this is not always the case. A methylene blue exam may be done in which a tampon is inserted into the patients vagina, and the patient is given an enema with methylene blue. Staining on the tampon would suggest a RVF is present. Shobeiri et al. described another method of diagnosis using vaginal fistulography. A cone tip catheter is used to locate possible fistula openings within the vagina. Contrast is then injected slowly under fluoroscopy, and if a fistula tract is found, a guidewire is introduced through the vaginal opening into the rectum to delineate the tract. This technique reportedly aided in diagnosing 5 of 9 RVFs which had not been found otherwise [44].

MRI and EUS have also been used for diagnosing RVFs. Stoker compared EUS and MRI for diagnosing RVFs and found that these tests had comparable positive predictive values (100 % and 92 %, respectively) [45]. Maconi et al. evaluated transperineal ultrasound as an alternative diagnostic technique in detecting perianal fistulas and RVFs and found that they had a similar positive predictive value as well [46]. Transperineal ultrasound may be beneficial for patients with anal stenosis or those who are unable to tolerate EUS. No consensus has been reached regarding the superiority of these imaging studies.

Anal manometry, EUS, and pudendal nerve latencies are used in evaluating patients with fecal incontinence and RVFs. Diarrhea is common in active Crohn's disease and must be controlled, as it can cause incontinence even in patients with normal sphincter function. Mean resting pressure in normal individuals is 40–70 mmHg, and is influenced most by the internal anal sphincter [47]. An advancement flap is likely to be effective for treatment of a RVF in a patient with normal sphincter function [48]. Sphincteroplasty and flap advancement with or without diversion is recommended in a patient with abnormal sphincter function. The addition of moving viable muscle across the thin rectovaginal septum adds thickness to the tissue between vaginal and rectal openings. The repair of the sphincter defect may also improve control of stool.

Medical Therapy

RVFs can be very difficult to treat. Similar to perianal Crohn's fistulas, treatment depends on symptoms, and a combination of medical and surgical therapy is commonly warranted. The principles of medical therapy are largely similar to those for all perianal fistulas. The treatment focuses on control of the underlying disease, particularly in the rectum. Unfortunately the contamination of the urethral meatus

requires a more urgent approach to the fistula. There are few studies which specifically evaluate medication ability to close Crohn's RVFs. Sands performed a post hoc analysis after the Accent II trial (a Crohn's disease clinical trial evaluating infliximab in a new long-term treatment regimen in patients with fistulizing Crohn's disease) to determine the effect of infliximab specifically on RVFs. At weeks 10 and 14, 60.7 % and 44.8 % of RVFs were closed, respectively [43]. Duration of closure was longer in patients who were treated with maintenance therapy.

Surgical Therapy

Initial surgical management includes treatment of perianal sepsis, which may include drainage and seton placement followed by appropriate medical management. If the underlying rectal disease has been appropriately treated and controlled but the RVF remains, surgical treatment options should be considered. Fistulotomy is not recommended because of the associated high rate of incontinence. Fibrin glue has not been shown to reliably close Crohn's RVFs [49, 50].

Fistula plugs may be used, though success rates are variable. The button anal fistula plug is a biologically absorbable xenograft made from the submucosa of porcine intestine which has been studied specifically in patients with RVFs. Gajsek et al. prospectively studied the button fistula plug in eight women with Crohn's RVFs, and reported four of eight of these achieved complete closure at 15 weeks. However, these results did not hold up during long-term follow-up with high rates of recurrence, and all repeat procedures failed [51].

Sphincteroplasty

Overlapping sphincteroplasty is used when there is a defect in the external anal sphincter causing incontinence in the setting of a RVF. A curvilinear incision is made at the dentate line in the anterior anal canal which includes anoderm and submucosa, extending cephalad beyond the internal opening of the fistula. The fistula tract is divided and curetted. The edges of the internal and external anal sphincters are located laterally and mobilized away from the ischiorectal fossa fat, overlapped, and sutured with nonabsorbable horizontal mattress sutures. Initial success rates reported were 86–100 % [52–54]; however, long-term maintenance of continence was worse. Gutierrez reported only 40 % of patients treated with sphincteroplasty maintained continence at 10 years [55]. Malouf et al. reported a 50 % continence rate after a minimum of 5-year follow-up in patients with obstetric trauma [56]. Nevertheless, sphincteroplasty is the procedure of choice in patients with RVFs and incontinence (Fig. 19.10).

Ligation of the Intersphincteric Fistula Tract

The LIFT procedure may also be performed for the treatment of RVFs. Ellis described the technique with the addition of a bioprosthetic material. Once the intersphincteric fistula tract is ligated, the tract openings to the vagina and rectum are sutured and closed. A bioprosthetic material is placed between the external sphincter/posterior vaginal wall and internal sphincter/rectal mucosa and sutured to the levator ani laterally, and the external sphincter distally (Fig. 19.11). He reported a 19 % recurrence rate, which was lower than the recurrence rates reported with anodermal and mucosal advancement flaps (27 % and 38 %, respectively) [57]. The most common complications are urinary retention and perianal sepsis.

Advancement Flaps

A diamond skin advancement flap may be used for very low anovaginal fistulas. As previously described, a 2×2 cm diamond of perianal skin and subcutaneous fat is elevated adjacent to the fistula internal opening. The internal opening and surrounding tissue is once again excised. The skin flap is advanced into the anal canal and sutured over the internal opening with absorbable braided suture. A cutaneous flap may also be used on the vaginal side in conjunction with the anal advancement flap [58].

An endorectal advancement flap for RVF may be performed for higher fistulas, with or without sphincteroplasty. A broad-based, U-shaped flap including mucosa, submucosa, and varying thickness of muscle is created with enough length to provide a tension-free repair. The fistula tract is debrided. The opening of the tract in the muscle is closed with figure eight sutures. The flap is sutured into place with absorbable interrupted sutures. The vaginal tract opening is left open to drain. Complications include bleeding, incontinence, perianal sepsis, and flap failure, though the risk of these should be low. Vaginal flaps are performed in much the same way. A flap of vaginal mucosa inferior to the fistula is elevated and the rectal opening of the fistula tract is closed. A levatorplasty is often done to enhance tissue coverage.

Both the transvaginal and transrectal approaches have advantages and disadvantages. One advantage to vaginal repair in patients with Crohn's disease is that non-diseased tissue is used for the repair. An advantage to the transrectal approach is that the repair is done on the high-pressured side of the fistula. Ruffolo et al. systematically reviewed transrectal vs. transvaginal repair of Crohn's RVFs and reported primary closure rates of 54.2 % and 69.4 % with transrectal and transvaginal flaps, respectively. The difference was not significant, and the recurrence rates were similar with each procedure [59].
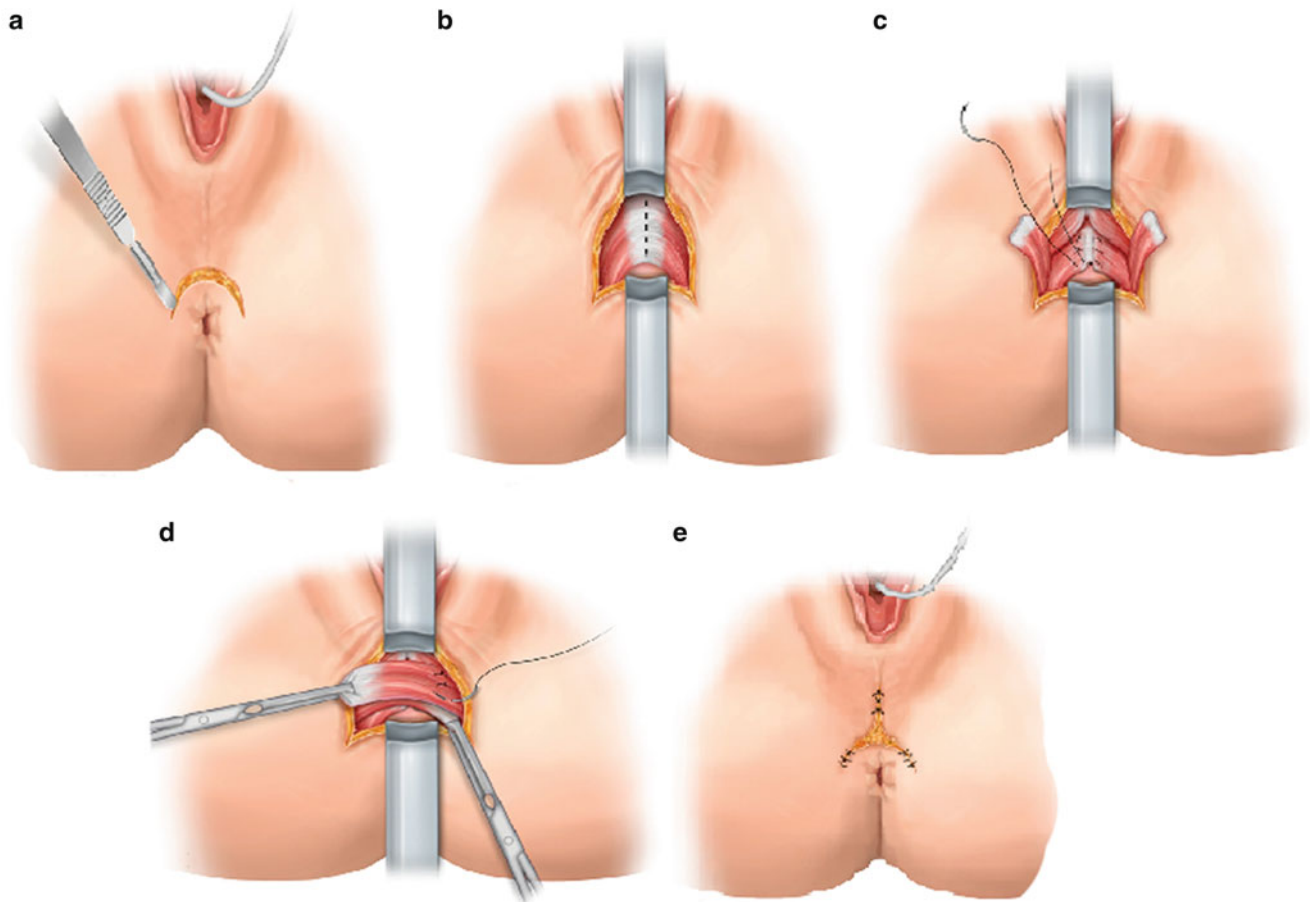
Fig. 19.10 (**a**) Curvilinear incision made along the perineal body; (**b**) the sphincter scar is divided but not excised; (**c**) the internal anal sphincter ins imbricated when a layered repair is performed; (**d**) the external anal sphincter is overlapped; (**e**) the center of the wound is left open for drainage. (Adapted from Wexner SD, Fleshman JW. Colon and Rectal Surgery. Anoretal Operations 2012; 94–97, with permission)

Birman first described rectal sleeve advancement flaps for the treatment of severe anorectal and RVFs. This technique is especially useful in patients with extensive, distal rectal circumferential ulceration or scarring, but with sparing of the more proximal rectum. Patients should undergo bowel prep prior to this procedure. A transperitoneal approach may be needed to sufficiently mobilize the rectum. A circumferential incision is made at the dentate line, extending into the submucosa. The dissection is carried proximally, becoming full thickness at the anorectal ring (at the level of the pelvic floor) and continuing cephalad to obtain mobility. The diseased anal mucosa is excised, and the rectum is pulled caudal to the dentate line and sutured to the anoderm without tension. Marchesa et al. used this technique in 13 patients with severe Crohn's perianal fistulas and RVFs (previously treated unsuccessfully with a transanal rectal advancement flap) and reported a 60 % success rate [60]. Hull reported success in 4/5 patients with Crohn's anovaginal fistulas treated with sleeve advancement flap, three of which were diverted at the time of the procedure [61].

Tissue Interposition

Tissue interposition grafts bring healthy, non-diseased, well vascularized tissue into the diseased region for repair. There are multiple different types of tissue interposition grafts. Gracilis transposition grafts are performed by mobilizing the muscle, detaching it from the tibia, and tunneling the muscle subcutaneously to the perineum. Furst et al. reported fistula closure in 11 of 12 patients with recurrent Crohn's RVFs treated with gracilis transposition, with a mean follow-up of 3.4 years. All patients were diverted, and 11 of 12 were reversed [62]. The gracilis muscle is not ideal for this purpose since the distal end of the muscle is narrow and does not cover a large area.

Martius flaps were initially used for the treatment of vesicovaginal fistulas, and have undergone various modifications over the years. The Martius flap initially referred to tissue interposition using bulbocavernosus muscle, but has more recently been used to describe either a labial fat pad graft, or a combination of muscle and fat pad. The procedure is
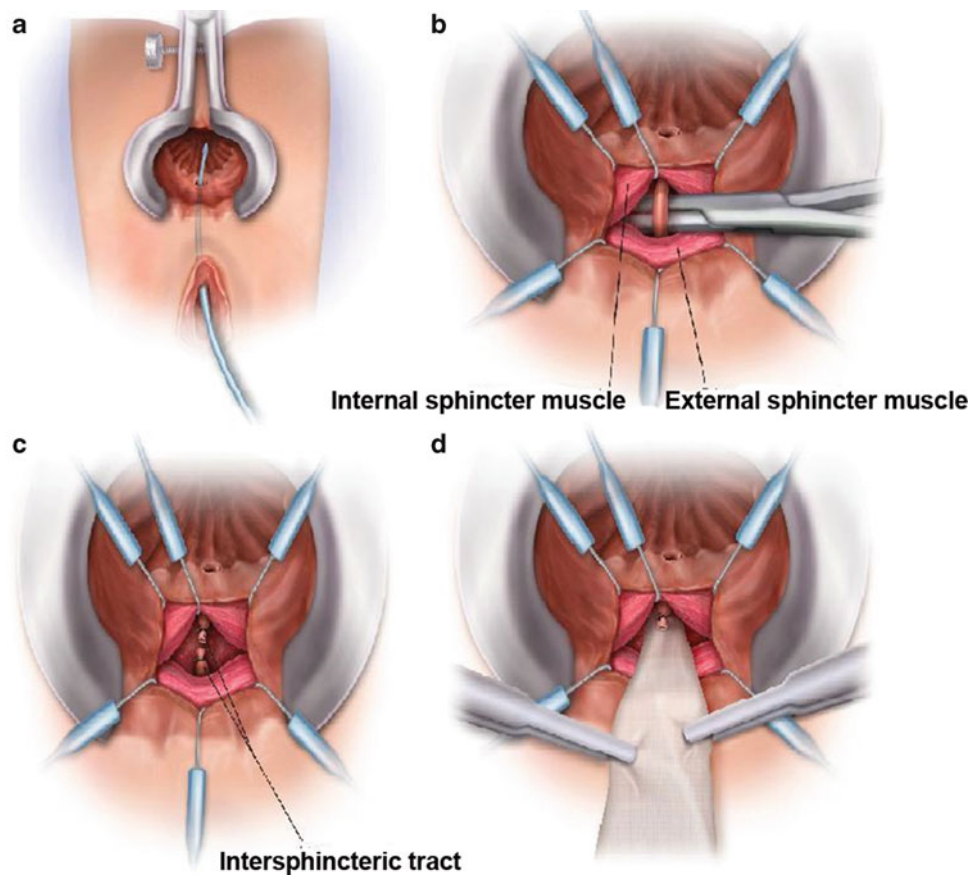
Fig. 19.11 (**a**) Incision for LIFT procedure; (**b**) identification of fistula tract in intersphincteric space; (**c**) ligation and division of fistula tract; (**d**) insertion of bioprosthetic material to separate ends of divided tract.

(Adapted from Wexner SD, Fleshman JW. Colon and Rectal Surgery. Anoretal Operations 2012; 102–103, with permission)

performed by making a longitudinal incision in the labia majora and dissecting out the bulbocavernosus muscle and the labial fat pad. The muscle and fat pad are transected at the ventral extent of the pedicle and tunneled underneath the labia minora to the fistula site and sutured into place. Many of the earlier reports described the Martius flap for the treatment of radiation-induced rectal vaginal fistulas. More recently, McNevin et al. retrospectively reviewed 16 patients with complex, low RVFs with multiple etiologies who were treated with combination bulbocavernosus and labial fat pad grafts, and reported only one fistula recurrence. However, dyspareunia was observed in 31 % [63]. Songne et al. described their experience using a labial fat pad graft in the treatment of RVFs including seven Crohn's patients. All fistulas healed within 3 months, though two of the seven patients with Crohn's ultimately underwent proctectomy for worsening anal disease [64]. Given the close proximity of the graft to the operative field, the Martius flap is an attractive option for patients with low RVFs (Fig. 19.12).

An omental flap may be placed laparoscopically for high intersphincteric or transsphincteric RVFs. The fistula is divided as the cul de sac is exposed to the level of the fistula, and a piece of omentum interposed into the rectovaginal septum between the rectum and vagina. This technique may also be modified for low to mid RVFs using a combination laparoscopic and transperineal approach. The omentum is mobilized 2/3 of the way from the hepatic flexure to the splenic flexure, taking care to ligate the branches of the right gastroepiploic artery but to preserve the arcade. The anterior rectum is then mobilized, exposing the rectovaginal space. The fistula is excised, and the wound edges are approximated. The rectovaginal space is then opened up transperineally, and the omentum is pulled through this space and sutured to the subcutaneous tissue with a single suture (Fig. 19.13). Schloericke et al. reported no recurrences in nine patients treated with this approach, with a median follow-up of 22 months. Eight of these patients were diverted [65]. Though initial results appear promising, this technique is relatively new, and further studies are needed before conclusions are made regarding the efficacy of the procedure.

There are many surgical treatment options for patients with Crohn's RVFs. Unfortunately, recurrence rates are high with virtually all of these procedures. El-Gazzaz et al. looked at predictors for success and failure in women with Crohn's RVFs undergoing repair. They found that the use of immunomodulators was significantly associated with better
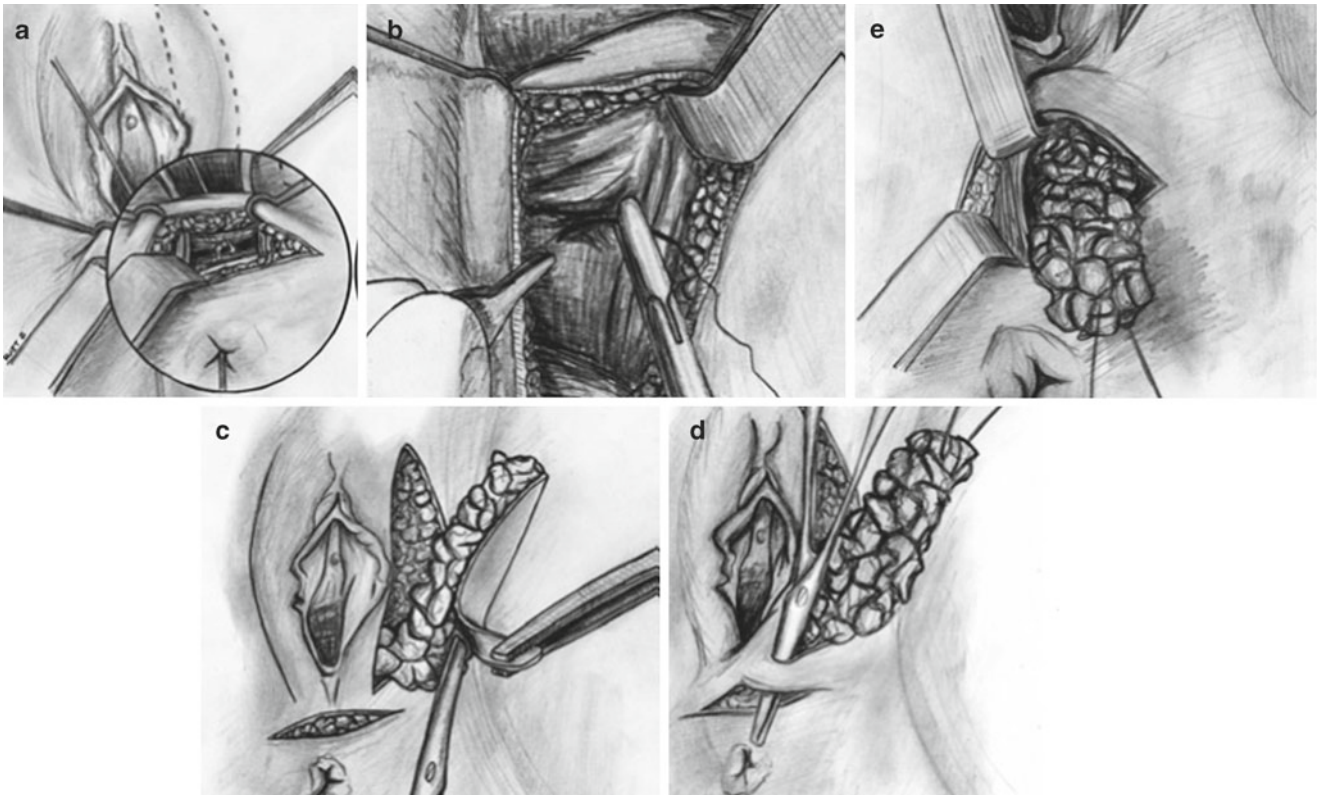
Fig. 19.12 Modified Martius graft procedure. (**a**) Identification of vaginal and rectal defects; (**b**) vaginal and rectal closure; (**c**) graft construction; (**d**) tunneling graft; and (**e**) interposition between the vaginal and rectal closures. (Adapted from Songne K et al. Treatment of anovaginal or rectovaginal fistulas with modified Martius graft. Colorectal Dis 2007;9(7):653–6. Reprinted with permission)
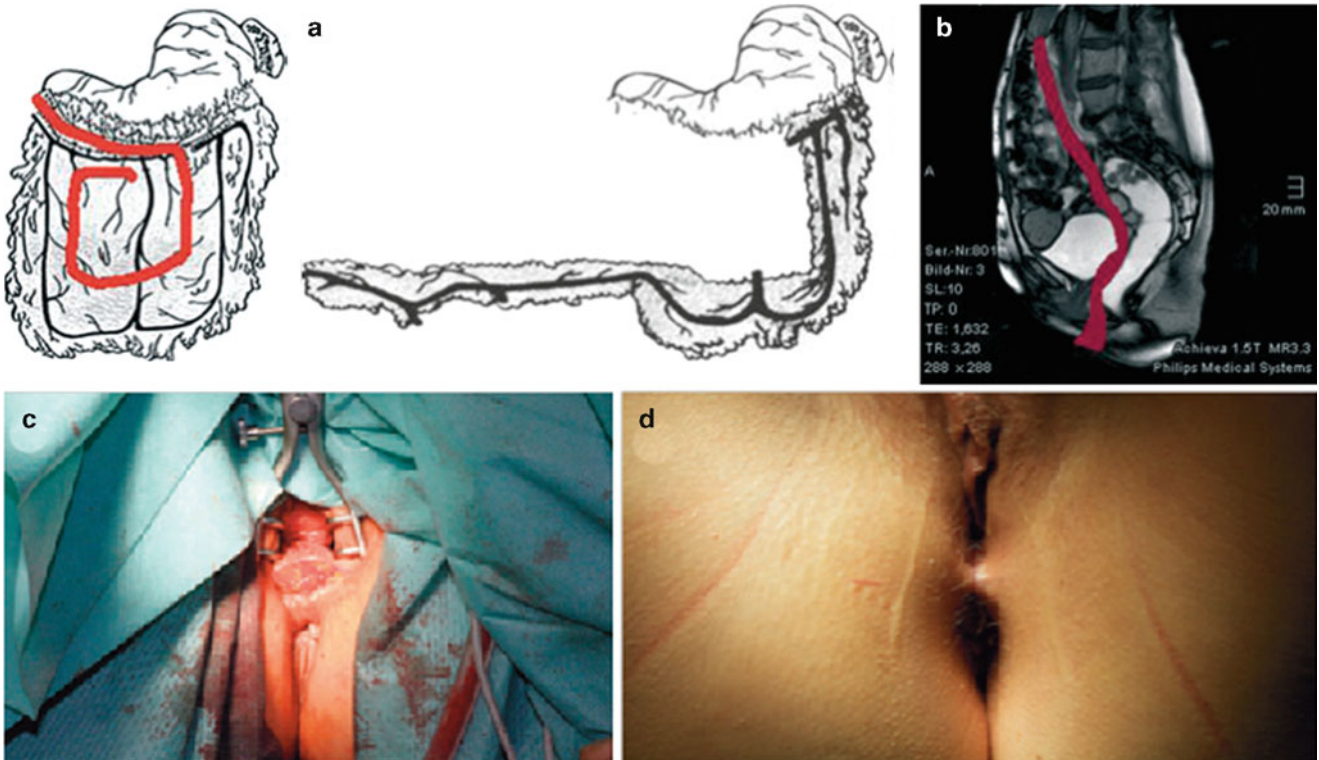

Fig. 19.13 (**a**) Mobilization of the greater omentum; (**b**) transperineal pull-through of the omental flap; (**c**) perineum immediately after fixation of the omental flap; (**d**) perineum 3 months after fixation of the omental flap. (Adapted from Schloericke E et al. Transperineal omentum flap for the anatomic reconstruction of the rectovaginal space in the therapy of rectovaginal fistulas. Colorectal Dis 2012;14(5):604–10. Reprinted with permission)

outcomes, and that smoking and steroid use were associated with higher failure rates [66]. Further studies are needed comparing long-term patient outcomes with each procedure.

Crohn's perianal fistulas and RVFs remain challenging medical and surgical problems. Healing is difficult to achieve and recurrence rates are high. Many advances have been made, particularly with regard to biologic agents, and with newer surgical techniques such as the LIFT procedure. More information is needed with regard to long-term outcome with various treatment modalities so the best option may be chosen for each patient.

References

1. Zawadzki A, Starck M, Bohe M, Thorlacius H. A unique 3D endoanal ultrasound feature of perianal Crohn's fistula: the 'Crohn ultrasound fistula sign'. Colorectal Dis. 2012;9:e608–11.
2. Yousem DM, Fishman EK, Jones B. Crohn disease: perirectal and perianal findings at CT. Radiology. 1988;167:331–4.
3. Guillaumin E, Jeffrey Jr RB, Shea WJ, Asling CW, Goldberg HI. Perirectal inflammatory disease: CT findings. Radiology. 1986; 161:153–7.
4. Leyendecker J, Bloomfield R, DiSantis D, Waters G, Mott R, Bechtold R. MR enterography in the management of patients with Crohn disease. Radiographics. 2009;6:1827–46.
5. Buchanan G, Halligan S, Williams A, Cohen CR, Tarroni D, Phillips RK, et al. Effect of MRI on clinical outcome of recurrent fistula-in-ano. Lancet. 2002;360:1661–2.
6. Law PJ, Talbot RW, Bartram CI, Northover JM. Anal endosonography in the evaluation of perianal sepsis and fistula in ano. Br J Surg. 1989;76(7):752–5.
7. Hildebrandt U, Feifel G, Schwarz HP, Scherr O. Endorectal ultrasound: instrumentation and clinical aspects. Int J Colorectal Dis. 1986;1(4):203–7.
8. Navarro-Luna A, García-Comingo MI, Rius-Macías J, Marco-Molina C. Ultrasound study of anal fistulas with hydrogen peroxide enhancement. Dis Colon Rectum. 2004;47(1):108–14.
9. Lengyel AJ, Hurst NG, Williams JG. Pre-operative assessment of anal fistulas using endoanal ultrasound. Colorectal Dis. 2002;4(6):436–40.
10. Halligan S, Stoker J. Imaging of fistula in ano. Radiology. 2006; 239(1):18–33.
11. Schwartz DA, Wiersema MI, Dudiak KM, et al. A comparison of endoscopic ultrasound, magnetic resonance imaging, and exam under anesthesia for evaluation of Crohn's perianal fistulas. Gastroenterology. 2001;121:1064–72.
12. Sahni VA, Ahmad R, Burling D. Which method is best for imaging of perianal fistula? Abdom Imaging. 2008;33:26–30.
13. West RL, van der Woude CJ, Hansen BE, Felt-Bersma RJ, van Tilburg AJ, Drapers JA, Kuipers EJ. Clinical and endosonographic effect of ciprofloxacin on the treatment of perianal fistulae in Crohn's disease with infliximab: a double-blind placebo-controlled study. Aliment Pharmacol Ther. 2004;20(11–12):1329–36.
14. Bernstein LH, Frank MS, Brandt LJ, Boley SJ. Healing of perineal Crohn's disease with metronidazole. Gastroenterology. 1987;79: 357–65.
15. Thia KT, Mahadevan U, Feagan BG, Wong C, Cockeram A, Bitton A, Bernstein CN, Sandborn WJ. Ciprofloxacin or metronidazole for the treatment of perianal fistulas in patients with Crohn's disease: a randomized, double-blind, placebo-controlled pilot study. Inflamm Bowel Dis. 2009;15(1):17–24.
16. Lecomte T, Contou JF, Beaugerie L, Carbonnel F, Cattan S, Gendre JP, Cosnes J. Predictive factors of response of perianal Crohn's disease to azathioprine or 6-mercaptopurine. Dis Colon Rectum. 2003;46(11):1469–75.
17. Korelitz BI, Present DH. Favorable effect of 6-mercaptopurine on fistulae of Crohn's disease. Dig Dis Sci. 1985;30(1):58–64.
18. Present DH, Korelitz BI, Wisch N, Glass JL, Sachar DB, Pasternack BS. Treatment of Crohn's disease with 6-mercaptopurine. A long-term, randomized, double-blind study. N Engl J Med. 1980; 302(18):981–7.
19. Jeshion WC, Larsen KL, Jawad AF, Piccoli DA, Verma R, Maller ES, Baldassano RN. Azathioprine and 6-mercaptopurine for the treatment of perianal Crohn's disease in children. J Clin Gastroenterol. 2000;30(3):294–8.
20. Ochsenkühn T, Göke B, Sackmann M. Combining infliximab with 6 mercaptopurine/azathioprine for fistula therapy in Crohn's disease. Am J Gastroenterol. 2002;97(8):2022–5.
21. Kornbluth A. Infliximab approved for use in Crohn's disease: a report on the FDA GI advisory committee conference. Inflamm Bowel Dis. 1998;4(4):328–9.
22. Present DH, Rutgeerts P, Targan S, Hanauer S, Mayer L, van Hogezand RA, Podolsky D, Sands B, Braakman T, DeWoody KL, Schaible TF, van Deventer SJH. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med. 1999; 340:1398–405.
23. Lichtiger S, Binion DG, Wolf DC, Present DH, Bensimon AG, Wu E, Yu AP, Cardoso AT, Chao J, Mulani PM, Lomax KG, Kent JD. The CHOICE trial: adalimumab demonstrates safety, fistula healing, improved quality of life and increased work productivity in patients with Crohn's disease who failed prior infliximab therapy. Aliment Pharmacol Ther. 2010;32(10):1228–39.
24. Schreiber S, Lawrance IC, Thomsen OØ, Hanauer SB, Bloomfield R, Sandborn WJ. Randomised clinical trial: certolizumab pegol for fistulas in Crohn's disease—subgroup results from a placebo-controlled study. Aliment Pharmacol Ther. 2011;33(2):185–93.
25. D'Haens GR, Panaccione R, Higgins PD, Vermeire S, Gassull M, Chowers Y, Hanauer SB, Herfarth H, Hommes DW, Kamm M, Löfberg R, Quary A, Sands B, Sood A, Watermeyer G, Lashner B, Lémann M, Plevy S, Reinisch W, Schreiber S, Siegel C, Targan S, Watanabe M, Feagan B, Sandborn WJ, Colombel JF, Travis S. The London position statement of the world congress of gastroenterology on biological therapy for IBD with the European Crohn's and colitis organization: when to start, when to stop, which drug to choose, and how to predict response? Am J Gastroenterol. 2011;106(2):199–212.
26. Takesue Y, Ohge H, Yokoyama T, Murakami Y, Imamura Y, Sueda T. Long-term results of seton drainage on complex anal fistulae in patients with Crohn's disease. J Gastroenterol. 2002;37(11):912–5.
27. Soltani A, Kaiser AM. Endorectal advancement flap for cryptoglandular or Crohn's fistula-in-ano. Dis Colon Rectum. 2010;53(4): 486–95.
28. Kodner IJ, Mazor A, Shemesh EI, Fry RD, Fleshman JW, Birnbaum EH. Endorectal advancement flap repair of rectovaginal and other complicated anorectal fistulas. Surgery. 1993;114(4):682–9.
29. Grimaud JC, Munoz-Bongrand N, Siproudhis L, Abramowitz L, Sénéjoux A, Vitton V, Gambiez L, Flourié B, Hébuterne X, Louis E, Coffin B, De Parades V, Savoye G, Soulé JC, Bouhnik Y, Colombel JF, Contou JF, François Y, Mary JY, Lémann M. Fibrin glue is effective healing perianal fistulas in patients with Crohn's disease. Gastroenterology. 2010;138(7):2275–81.
30. O'Riordan JM, Datta I, Johnston C, Baxter NN. A systematic review of the anal fistula plug for patients with Crohn's and non-Crohn's related fistula-in-ano. Dis Colon Rectum. 2012;55(3):351–8.
31. Taxonera C, Schwartz D, García-Olmo D. Emerging treatments for complex perianal fistula in Crohn's disease. World J Gastroenterol. 2009;15(34):4263–72.

32. Guadalajara H, Herreros D, De-La-Quintana P, Trebol J, Garcia-Arranz M, Garcia-Olmo D. Long-term follow-up of patients undergoing adipose-derived adult stem cell administration to treat complex perianal fistulas. Int J Colorectal Dis. 2012;27(5):595–600.

33. 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.

34. Sileri P, Franceschilli L, Angelucci GP, D'Ugo S, Milito G, Cadeddu F, Selvaggio I, Lazzaro S, Gaspari AL. Ligation of the intersphincteric fistula tract (LIFT) to treat anal fistula: early results from a prospective observational study. Tech Coloproctol. 2011; 15(4):413–6.

35. Tan KK, Alsuwaigh R, Tan AM, Tan IJ, Liu X, Koh DC, Tsang CB. To LIFT or to flap? Which surgery to perform following seton insertion for high anal fistula? Dis Colon Rectum. 2012;55(12): 1273–7.

36. Han JG, Yi BQ, Wang ZJ, Zheng Y, Cui JJ, Yu XQ, Zhao BC, Yang XQ. Ligation of the intersphincteric fistula tract plus bioprosthetic anal fistula plug (LIFT-Plug): a new technique for fistula-in-ano. Colorectal Dis. 2013;15(5):582–6.

37. Rehg KL, Sanchez JE, Krieger BR, Marcet JE. Fecal diversion in perirectal fistulizing Crohn's disease is an underutilized and potentially temporary means of successful treatment. Am Surg. 2009;75(8):715–8.

38. Galandiuk S, Kimberling J, Al-Mishlab TG, Stromberg AJ. Perianal Crohn disease: predictors of need for permanent diversion. Ann Surg. 2005;241(5):796–801.

39. Genua JC, Vivas DA. Management of nonhealing perineal wounds. Clin Colon Rectal Surg. 2007;20(4):322–8.

40. Ky A, Sohn N, Weinstein MA, Korelitz BI. Carcinoma arising in anorectal fistulas of Crohn's disease. Dis Colon Rectum. 1998;41(8):992–6. Review.

41. Korelitz BI. Carcinoma of the intestinal tract in Crohn's disease: results of a survey conducted by the National Foundation for ileitis and colitis. Am J Gastroenterol. 1983;78(1):44–6.

42. Schwartz DA, Loftus Jr EV, Tremaine WJ, Panaccione R, Harmsen WS, Zinsmeister AR, Sandborn WJ. The natural history of fistulizing Crohn's disease in Olmsted County, Minnesota. Gastroenterology. 2002;122(4):875–80.

43. Sands BE, Blank MA, Patel K, van Deventer SJ. Longterm treatment of rectovaginal fistulas in Crohn's disease: response to infliximab in the ACCENT II study. Clin Gastroenterol Hepatol. 2004;2(10):912–20.

44. Shobeiri SA, Quiroz L, Nihira M. Rectovaginal fistulography: a technique for the identification of recurrent elusive fistulas. Int Urogynecol J Pelvic Floor Dysfunct. 2009;20(5):571–3.

45. Stoker J, Rociu E, Schouten WR, Laméris JS. Anovaginal and rectovaginal fistulas: endoluminal sonography versus endoluminal MR imaging. AJR Am J Roentgenol. 2002;178(3):737–41.

46. Maconi G, Ardizzone S, Greco S, Radice E, Bezzio C, Bianchi Porro G. Transperineal ultrasound in the detection of perianal and rectovaginal fistulae in Crohn's disease. Am J Gastroenterol. 2007;102(10):2214–9. Epub 2006 Aug 4.

47. Coller JA. Clinical application of anorectal manometry. Gastroenterol Clin North Am. 1987;16(1):17–33.

48. Tsang CB, Madoff RD, Wong WD, Rothenberger DA, Finne CO, Singer D, Lowry AC. Anal sphincter integrity and function influences outcome in rectovaginal fistula repair. Dis Colon Rectum. 1998;41(9):1141–6.

49. Buchanan GN, Bartram CI, Phillips RK, Gould SW, Halligan S, Rockall TA, Sibbons P, Cohen RG. Efficacy of fibrin sealant in the management of complex anal fistula: a prospective trial. Dis Colon Rectum. 2003;46(9):1167–74.

50. Abel ME, Chiu YS, Russell TR, Volpe PA. Autologous fibrin glue in the treatment of rectovaginal and complex fistulas. Dis Colon Rectum. 1993;36(5):447–9.

51. Gajsek U, McArthur DR, Sagar PM. Long-term efficacy of the button fistula plug in the treatment of ileal pouch-vaginal and Crohn's-related rectovaginal fistulas. Dis Colon Rectum. 2011; 54(8):999–1002.

52. MacRae HM, McLeod RS, Cohen Z, Stern H, Reznick R. Treatment of rectovaginal fistulas that has failed previous repair attempts. Dis Colon Rectum. 1995;38(9):921–5.

53. Khanduja KS, Padmanabhan A, Kerner BA, Wise WE, Aguilar PS. Reconstruction of rectovaginal fistula with sphincter disruption by combining rectal mucosal advancement flap and anal sphincteroplasty. Dis Colon Rectum. 1999;42(11):1432–7.

54. Wise Jr WE, Aguilar PS, Padmanabhan A, Meesig DM, Arnold MW, Stewart WR. Surgical treatment of low rectovaginal fistulas. Dis Colon Rectum. 1991;34(3):271–4.

55. Bravo Gutierrez A, Madoff RD, Lowry AC, Parker SC, Buie WD, Baxter NN. Long-term results of anterior sphincteroplasty. Dis Colon Rectum. 2004;47(5):727–31.

56. Malouf AJ, Norton CS, Engel AF, Nicholls RJ, Kamm MA. Long-term results of overlapping anterior anal-sphincter repair for obstetric trauma. Lancet. 2000;355(9200):260–5.

57. Ellis CN. Outcomes after repair of rectovaginal fistulas using bioprosthetics. Dis Colon Rectum. 2008;51(7):1084–8.

58. Haray PN, Stiff G, Foster ME. New option for recurrent rectovaginal fistulas. Dis Colon Rectum. 1996;39:463–4.

59. Ruffolo C, Scarpa M, Bassi N, Angriman I. A systematic review on advancement flaps for rectovaginal fistula in Crohn's disease: transrectal vs transvaginal approach. Colorectal Dis. 2010;12(12): 1183–91.

60. Marchesa P, Hull TL, Fazio VW. Advancement sleeve flaps for treatment of severe perianal Crohn's disease. Br J Surg. 1998;85: 1695–8.

61. Hull TL, Fazio VW. Surgical approaches to low anovaginal fistula in Crohn's disease. Am J Surg. 1997;173(2):95–8.

62. Fürst A, Schmidbauer C, Swol-Ben J, Iesalnieks I, Schwandner O, Agha A. Gracilis transposition for repair of recurrent anovaginal and rectovaginal fistulas in Crohn's disease. Int J Colorectal Dis. 2008;23(4):349–53.

63. McNevin MS, Lee PYH, Bax TW. Martius flap: an adjunct for repair of complex, low rectovaginal fistula. Am J Surg. 2007; 193(5):597–9.

64. Songne K, Scotté M, Lubrano J, Huet E, Lefébure B, Surlemont Y, Leroy S, Michot F, Ténière P. Treatment of anovaginal or rectovaginal fistulas with modified Martius graft. Colorectal Dis. 2007; 9(7):653–6.

65. Schloericke E, Hoffman M, Zimmermann M, Kraus M, Bouchard R, Roblick UJ, Hildebrand P, Nolde J, Bruch HP, Limmer S. Transperineal omentum flap for the anatomic reconstruction of the rectovaginal space in the therapy of rectovaginal fistulas. Colorectal Dis. 2012;14(5):604–10.

66. El-Gazzaz G, Hull T, Mignanelli E, Hammel J, Gurland B, Zutshi M. Analysis of function and predictors of failure in women undergoing repair of Crohn's related rectovaginal fistula. J Gastrointest Surg. 2010;14(5):824–9.