Treatment Modalities of perianal fistula

Adel Karam Rezk¹, Mohamed Abdelrahman Hasan Sadik ² Abdelrahman Hasan Sadik ², Moustafa B. Mohamed ², Mostafa M Elaidy²

1 Specialist of general surgery Diarb Nigm general hospital

2 General surgery Department, Faculty of Medicine, Zagazig University

Corresponding author: Adel Karam Rezk

E-mail: adelkaram2030@gmail.com

Conflict of interest: None declared

Funding: No funding sources

Abstract

Background: As bacteria continuously enter into the fistula through the internal opening and the inflammation inside the fistula persists, the anal fistula cannot heal spontaneously. So, treatment for fistula-in-ano is almost universally surgical. The goal of surgical treatment of perianal fistula is permanent eradication of the supportive process without compromising anal continence. There are several surgical options for the treatment of perianal fistula, and the best choice is determined by the anatomy of the fistula: fistulotomy with opening and unroofing of the fibrous portion of the tract, fistulectomy with excession of the tract, or seton may be used as a drain placed through a fistula to maintain drainage and/or induce fibrosis. As there is no single technique is appropriate for the treatment of all fistula-in-ano there are variable surgical procedures for the management of anal fistula including fistulotomy, fistulectomy, ligation of intersphincteric fistula tract, setons, fibrin glue, fibrin plug, and endo advancement flap. There are a number of sphincter-sparing methods for the treatment of perianal fistula such as fibrin glue injection, anal fistula plug, endorectal muscular or mucosal advancement flap, core-out fistulectomy, radiofrequency ablation, ligation of the intersphincteric fistula tract.

Keywords: Treatment Modalities, perianal fistula

Tob Regul Sci.[™] 2023;9(1): 7006 - 7017

DOI: doi.org/10.18001/TRS.9.1.495

Introduction:

The goal of surgical treatment of perianal fistula is permanent eradication of the supportive process without compromising anal continence. There are several surgical options for the treatment of perianal fistula, and the best choice is determined by the anatomy of the fistula: fistulotomy with opening and unroofing of the fibrous portion of the tract, fistulectomy with excession of the tract, or seton may be used as a drain placed through a fistula to maintain drainage and/or induce fibrosis **(1)**.

Major causes of recurrence include preoperative causes such as specific fistulas or poor identification of fistulous tract and openings, operative causes such as poor technical aspects of surgery, and postoperative causes such as poor postoperative wound healing (2). As there is no single technique is appropriate for the treatment of all fistula-in-ano there are variable surgical procedures for the management of anal fistula including

fistulotomy, fistulectomy, ligation of intersphincteric fistula tract, setons, fibrin glue, fibrin plug, and endo advancement flap.(3).

There are a number of sphincter-sparing methods for the treatment of perianal fistula such as fibrin glue injection, anal fistula plug, endorectal muscular or mucosal advancement flap, core-out fistulectomy, radiofrequency ablation, ligation of the intersphincteric fistula tract, and, finally, video-assisted anal fistula treatment **Sirikurnpiboon (4)**.

1-Fistulotomy:

In fistulotomy, the tract must be layed open from its termination (external opening) to its source (internal opening); it is the surest way of getting rid of the fistula. It is applied manly to the intersphincteric fistula and trans-sphincteric fistula involving less than 30% of the external sphincter. (5).

Fistulotomy is contraindicated for the treatment of complex fistulas. These include those that lie above the anal sphincter (where there is more muscle), have multiple openings, or are the result of local radiation therapy or inflammatory bowel disease (IBD). Forward-lying (anterior) fistulas in women, typically involving vaginal tissues, are also considered complex. Because vulnerable tissues are involved with these types of fistulas, there is a significant risk of recurrence and fecal incontinence (the inability to control bowel movements). For these same reasons, fistulotomy is avoided in people with recurrent fistulas or those with pre-existing fecal incontinence. **(6)**.



Fig (1), Fistulotomy. (6).

2-Fistulectomy:

Fistulectomy involves coring out of the fistula by either sharp dissection or diathermy cautery. It allows better definition of fistula anatomy than fistulotomy, especially the level at which the tract crosses the sphincters and the presence of secondary extensions (**7**).



Fig, (2) different options for perianal fistula treatment.(7).

A fistulectomy is an invasive procedure that involves medium to large incisions in the anal region. Therefore, it comes with a number of risks and possible complications, the main ones being postoperative pain and infection. Potential risks include, sever scarring, distortion, recurrence of fistula and incontinence.(7).

3-Advancment flap:

Advancement flap may be summarized as elevating a flap, coring out of an infected gland, as well as an epithelized internal opening, suturing of the internal sphincter defect, closing the wound with a flap, and providing effective drainage. **(8)**.



Fig (3), mucosal advancement flap technique (9).

The rectal advancement flap was first described by **Noble** in **1902** for rectovaginal fistulas (**Noble G (10**). Elting (**11**) and Laird **(12)** modified and applied it in the treatment of anal fistulas in 1912 and 1948, respectively. In 1985, Aguilar showed by using this rectal advancement flap in the treatment of anal fistula only a recurrence of 1.5% and a fecal incontinence of 10%. Nowadays, it is a recognized procedure in sphincterpreserving surgery, although the technique presents many variations depending on authors.

Different types of thickness flap have been described: mucosal, partial-thickness (including some fibers of the internal anal sphincter), and full-thickness flaps (including the

entire internal sphincter), without reaching any consensus. There is also no consensus on the issue of treating the fistula tract, by core-out fistulectomy or curettage (**13**).

The endorectal advancement flap involves mobilizing a partial-thickness flap comprising rectal mucosa, submucosa, and some muscle fibers. To ensure adequate blood supply, the base should be wider than the tip with at least a 2:1 ratio. The fistula tract can then be either cored out or curetted to remove epithelial lining and any residual debris, followed by suture closure of the internal opening and placement of the advancement flap over the defect, with care taken to avoid tension. Partial-thickness flaps appear to be better than full-thickness flaps. **(14)**.

Several different flap configurations have been described, including V-Y flaps, Y-V flaps, house flaps, S-flaps, and many more. The typical approach involves debridement of the mucosa overlying the internal opening, debridement of the fistula tract and closure of the internal opening, and mobilization of a pedicled flap from the anal margin with advancement into the anal canal, once again with care taken to avoid tension or tissue devascularization. **(15)**.

Endorectal advancement flaps have been associated with symptomatic mucosal ectropions, and are also thought to be more technically challenging when there is dense scarring within the anal ca nal. (16).

3-Ligation of intersphincteric fistula tract (LIFT) procedure:

Ligation of the intersphincteric fistula tract (LIFT) is a newly introduced technique was first described in 2006 by Rojanasakul since 2007 for treating fistula in the anus, primarily performed for complex or recurrent trans-sphincteric fistula. The technique is implemented by secure closure of the internal and external opening of the tract and removing the infected cryptoglandular tissue. .(**17**).



Fig,(4) LIFT technique .(18).

The common complaint in patients that were dealt with by LIFT technique were perianal discharge in (96.7%), perianal swelling (77%), constipation (35%), perianal pain (32.2%), itching (16%) and incontinence (3%).**(19).**

4-LIFT Modifications :

Modifications was done of original LIFT procedure included LIFT with partial coring out fistulectomy and an additional transanal advancement flap, there was no recurrence and no changes in continence levels. **(14)**.

Coring out of fistula tract from the external opening of the fistula tract to the lateral border of the external sphincter. It was described by Sirikurnpiboon "LIFT PLUS, there was no recurrence and no changes in continence levels. **(4)**.

LIFT Plug, which involve insertion of a plug in the external portion of the track, there was no recurrence only one (5%) patient reported with incontinence for gas. LIFT with partial coring out fistulectomy and insertion of Seton during operation with no recurrence occurred one reported failure in form of wound dehiscence (20).

LIFT-plug procedure for the treatment of trans-sphincteric fistulas is a simple procedure with a high healing rate, minimal invasiveness, quick healiNng, and without disturbance to anal function. LIFT-plug is an ideal procedure for trans-sphincteric fistula. (21).

6-Fistula plug:

Involves plugging the fistula with a device made from small intestinal submucosa. The fistula plug is positioned from the inside of the anus with suture. According to some sources, the success rate with this method is as high as 80%. As opposed to the staged operations, which may require multiple hospitalizations, the fistula plug procedure requires hospitalization for only about 24 hours. Currently, there are two different anal fistula plugs cleared by the FDA for treating ano-rectal fistulae in the United States. This treatment option does not carry any risk of bowel incontinence. In the systematic review published by **Dr Pankaj Garg.(22)**, the success rate of the fistula plug is 65-75%. (The highest series till date for more than 200 plugs, carried out by an Indian surgeon, Dr Ashish Ganatra shows promising results [success rates of more than 90%] with proper technique used to place the plug, with an emphasis on using *MRI*, Maleable probe with gentle delineation of the tract to its internal opening, fixing the plug with 2-0polyglactin *30mm r*ound body needle taking proper bites thru' the internal sphincter while burring the internal end of plug beneath the mucosa and proper post op advice, are shown to be important factor for the better success.



Fig (5), technical steps of anal fistula plug deployment: (A) identification of the fistula tract, (B) the plug being pulled through the internal opening until it is seated, and (C) the plug being secured in the internal opening by using a figure-of-eight suture.(23).

The anal fistula plug (AFP) technique was first described in 2004, with the first case series published in 2006. The technique involves debridement of the fistula tract followed by placement of a bioprosthetic plug within the tract, securing it at the internal opening and

cutting it flush with the skin at the external opening. It was initially described using a rolledup piece of biologic material, but was later studied with the commercially available Surgisis AFP (Cook Medical, Canton, IN), which is a bioabsorbable scaffold made of porcine submucosa. The technique gained instant favor due to its simplicity, ease of performance, lack of disturbance to the surrounding tissue, and relatively high patient tolerance. (24).

The initial reported healing rates for AFP were 85 to 87%. However, these rates did not survive more rigorous study, and subsequent case series were unable to reproduce these high rates of success. Most studies with an adequate period of follow-up reported healing rates below 50%, with some as low as 24%. (Lewis R,2012). There are also data that argue against repeat plug placement after initial plug failure, showing that such an approach is very unlikely to be successful. (25). Success rates for complex fistula ranged from 35 to 87%.

Recently, a second commercially available AFP has been introduced. The Gore Bio-A fistula plug (Gore Medical, Flagstaff, AZ) is a synthetic bioabsorbable scaffold that acts in a manner similar to the Surgisis plug, but for a reportedly cheaper price, and with the addition of several "tentacles" that can be removed or adjusted in a fashion tailored to the size and number of fistula tracts. Initial primary healing with this plug was reported at 69%, but a subsequent multicenter case series reported a 12-month healing rate of 49%. (26).

Overall, the AFP appears to be an acceptable approach to complex anal fistulas, as it is generally well tolerated with minimal side effects. However, failure rates are high, and the patient must be counseled accordingly. (27).

6- Draining Setons:

Draining setons are an effective way to control perianal sepsis. They can serve to prevent blockage of the fistula tract and allow it to mature, and may be particularly useful if a complex repair is planned in the future. It can also be used as a means to shorten the fistula tract to decrease the size of the wound over time, particularly if the external opening is located some distance away from the anal verge. (28).



Fig (6), Draining Seton. (29).

Often, a loose draining seton is placed through a complex fistula during the first evaluation as a means to stent the fistula tract open, and prevent closure of the external opening, which may lead to recurrent abscess. Many different materials can be used as a draining seton. One of the most common approaches is the use of a Silastic vessel loop tied loosely to itself with silk suture. (30).

It should be noted that while the draining seton is often seen as a bridge to a more definitive therapy, it is also an acceptable long-term therapy for complex anal fistulas. For patients with multiple failed repairs or multiple synchronous fistulas, or for those who simply do not wish to undergo any further intervention, a well-constructed draining seton can be kept in the fistula for years, hopefully limiting fistula-associated symptoms and preventing recurrent infection. (28).

7-Cutting seton:

Cutting setons have been used for many years to manage complex fistula-in-ano. In this procedure, the seton is secured tightly within the fistula tract, with intentional pressure placed on the tract itself. The seton can then be serially tightened in the office over time. The theory behind this procedure is similar to that of regelation, where a frozen object melts under pressure, but then freezes again when the pressure is released. This is a common high-school science project, where a wire or paper clip is placed on an ice cube, and the cube retains its form as the wire advances through. **(31)**.

For a cutting seton, the slow division of muscle as the seton becomes more superficial allows buildup of a fibrotic tract, with less muscle separation than if a primary fistulotomy was performed. It is a simple procedure to perform, but takes between 12 and 16 weeks to heal. Also, the regelation is better in theory than in actuality, and fecal incontinence rates range from 12 to 26%, with incontinence to flatus being the most common, followed by incontinence to liquid stool. A review article suggested the average rate of incontinence to be 9.7% for flatus and 5% for solid stool. While some enthusiasts remain, the cutting seton has been abandoned in most centers for use in complex fistulas.(32).

8-Fistula clip closure:

Involves the closure of the internal fistula opening with a superelastic clip made of nitinol (OTSC). During surgery, the fistula tract is debrided with a special fistula brush and the clip is transanally applied with the aid of a preloaded clip applicator. The surgical principle of this technique relies on the dynamic compression and permanent closure of the internal fistula opening by the superelastic clip. Consequently, the fistula tract dries out and heals instead of being kept open by continuous feeding with stool and fecal organisms. This minimally-invasive sphincter-preserving technique has been developed and clinically implemented by the German surgeon Ruediger Prosst. First clinical data of the clip closure technique demonstrate a success rate of 90% for previously untreated fistulae and a success rate of 70% for recurrent fistulae (**33**).



Fig (7), Images showing the through-the-scope clipping devices (A) and their endoscopic deployment for fistula closure by approximating the margins of the fistula opening with multiple clips (C and D).

9-PERFACT Procedure:

Is another latest addition to the armamentarium to treat complex and highly complex fistula-in-ano. It is a minimally cutting procedure as both the anal sphincters (internal and external sphincters) are not cut/damaged at all. Therefore, the risk of incontinence is minimal. PERFACT procedure (proximal superficial cauterization, emptying regularly fistula tracts and curettage of tracts) entails two steps: superficial cauterization of mucosa at and around the internal opening and keeping all the tracts clean. The principle is to permanently close the internal opening by granulation tissue. This is achieved by superficial electrocauterization at and around the internal opening and subsequently allowing the wound to heal by secondary intention. Early results of this procedure are quite encouraging for complex fistula-in-ano (86.4% in highly complex anal fistulae). The procedure is effective even in fistula associated with abscess, supralevator fistula-in-ano and fistula where the internal opening is non-localizable. **(22)**

10-Video-assisted anal fistula treatment (VAAFT):

Video-assisted anal fistula treatment (VAAFT) is a novel minimally invasive and sphincter-saving technique for treating complex fistulas. Key steps are visualization of the fistula tract using the fistuloscope, correct localization of the internal fistula opening under direct vision, endoscopic treatment of the fistula and closure of the internal opening using a stapler or cutaneous-mucosal flap. Diagnostic fistuloscopy under irrigation is followed by an operative phase of fulguration of the fistula tract, closure of the internal opening and suture reinforcement with cyanoacrylate. **(34).**



Fig (8) the fistuloscope (34).

11-BIOLIFT PROCEDURE:

Neal Ellis published outcomes with the BioLIFT technique for the management of transsphincteric fistulae. He reported that the success rate was 94% of 31 patients. The BioLIFT technique is a variation of the LIFT technique in which a bioprosthetic is placed in the intersphincteric plane to reinforce the closure of the fistula tract. The bioprosthetic graft acts as a physical barrier in the intersphincteric space. Actually, the BioLIFT technique utilized a transection of the intersphincteric tract and closure of the fistula opening in the internal sphincter, which is similar to the procedure described by Matos et al. (35), instead of ligating the intersphincteric tract. When compared to the LIFT, the BioLIFT technique has two potential disadvantages. First, it requires a more extensive dissection in the intersphincteric

space because the bioprosthetic must overlap the closure of the fistula tract by at least 1 to 2 cm in all directions. The second disadvantage is the relatively high cost of the bioprosthetic materials

12-EXPANDED ADIPOSE-DERIVED STEM CELLS (ASCs) :

Mesenchymal adult stem cells extracted from certain tissues, such as adipose tissue, can differentiate into various types of cell. **(36)**.

Garcia-Olmo et al. (37) chose adipose tissue as the source of stem cells because of their two biologic properties: their ability to suppress inflammation and their differentiation potential. Moreover, enough fat can be obtained with liposuction, and the fat cells can be harvested with minimal adverse effects on the patient. Their phase I clinical trials show that adipose-derived stem cells are safe for the treatment of a fistula in Crohn's disease, and they published a phase II multicenter, randomized controlled trial to further investigate the effectiveness and safety of ASCs in the treatment of complex anal fistulae compared with the fibrin glue group **(31)**.

The treatment procedures are as follows: 1) tract identification, with special emphasis on the identification of the internal opening; 2) tract curettage, with special emphasis on the intersphincteric tract; 3) closure of the internal opening; 4) injection of a cell suspension through a long fine needle into the tract walls; 5) sealing of the tract with fibrin glue. They reported that fistula healing was observed in 71% of 24 patients who received ASCs in addition of fibrin glue compared with 16% of 25 patients who received fibrin glue alone (relative risk for healing, 4.43; confidence interval, 1.74 to 11.27; P < 0.001). The proportion of patients with healing was similar between the Crohn's and the non-Crohn's subgroups. An advantage of using stem cells to treat an anal fistula is that, because tract resection is not required, the treatment does not injure the anal sphincter. There are, nonetheless, some limitations of the ASCs-based therapy. First, the cost of treatment with ASCs is difficult to evaluate in detail at present. Second, technically, secure closure of the internal opening and complete injection of the cell suspension over the tract may be complicated procedures. Finally, as yet, there are no reports on the long-term effects of using ASCs (**38**).

13-Laser Closure of Anal Fistula (FiLaC):

The FiLaC technique involves the identification of the internal opening, sometimes by the injection of hydrogen peroxide or methylene blue from the external opening, debriding the fistula tract with a curette, closure of the internal opening (usually with a 2-0 Vicryl[®] suture), insertion of a plastic hollow catheter using a guide-wire, insertion of a disposable laser fibre into the catheter with its tip emerging at the internal orifice, and continuous delivery of laser energy (usually a wavelength of 1470 nm and 13 W) circumferentially within the fistula tract while withdrawing it at a rate of 1 cm per 3 s.The parameters of the laser energy can be regulated depending on the width of the tract **(39)**.



Fig (9), FiLaC[™] method: insertion of a disposable laser fibre into the catheter with its tip entering through the external orifice; continuous delivery of laser energy circumferentially within the fistula tract while withdrawing it (38).

References:

- 1. Bullard D., Mary R ., and David B. (2010): colon, rectum, and anus; Schwartz's Principles of Surgery, Vol. 29. 9 th ed; Chicago MacGraw-Hill, 1064-1065.
- 2. Whiteford MH. John Kilkenny . Neil Hyman. et al. (2005): Practice parameters for treatment of fistula in ano. The Standards Practice Task Force, the American Society of Colon and Rectal Surgeons; Dis Colon Rectum. 48:1337-1342.
- 3. Ramachandra M. L. (2018): A comparative study in the management of fistula in ANO using various modalities;Int Surg J.Jun:5(6):2223-2227.
- 4. Sirikurnpiboon S. Burin Awapittaya. and Paiboon Jivapaisarnpong. (2013): Ligation of intersphincteric fistula tract (LIFT) in complex fistula; World J Gastrointest Surg . 5:123-128.
- 5. Kamal ZB. (2012): Fistulotomy versus fistulectomy as a primary treatment of low fistula in ano; Iraqi Postgrad Med J. 11:510-515.
- 6. Knuttinen MG.Johnny Yi . Paul Magtibay. et al. (2018): Colorectal-Vaginal Fistulas: Imaging and Novel Interventional Treatment Modalities; J Clin Med. 7(4).
- Lunniss PJ. (2008). The anus and anal canal. In, Williams NS, Bulstrode CJK, O'Connell PR. Bailey and Love's Short practice of Surgery. 25 th ed. London; UKEdward Arnold (Publishers). Ltd p. 1240-1272.
- 8. Sun MR, Martin P Smith.and Robert A Kane. (2008): Current techniques in imaging of fistula in ano: three-dimensional endoanal ultrasound and magnetic resonance imaging; Semin Ultrasound CT MR. 29:454-471.
- 9. Neil Hyman. (1999):Endoanal advancement flap repair for complex anorectal fistulas; The American Journal of Surgery .Volume 178, Issue 4, October, Pages 337-340.
- 10. Noble G. (1902): New operation for complete laceration of the perineum designed for the purpose of eliminating infection from the rectum; Trans Am Gynecol Soc .27:357–363 2.
- 11. Elting AWX. (1912): The treatment of fistula in ano with especial reference to the whitehead operation;Ann Surg .56:744–752 3.

Adel Karam Rezk et. al

Treatment Modalities of perianal fistula

- 12. Laird DR. (1948): Procedures used in the treatment of complicated fistulas;Am J Surg. 76:701– 708.
- 13. Kodner IJ. A Mazor. E I Shemesh. et al. (1993): Endorectal advancement flap repair of rectovaginal and other complicated anorectal fistulas; Surgery .114:682–689.
- 14. Van Onkelen RS. M P Gosselink.and W R Schouten. (2012): Is it possible to improve the outcome of transanal advancement flap repair for high transsphincteric fistulas by additional ligation of the intersphincteric fistula tract?; Dis Colon Rectum. 55:163–6.
- 15. Farid M. Mohamed Youssef. Ayman El Nakeeb. et al. (2010): Comparative study of the house advancement flap, rhomboid flap, and y-v anoplasty in treatment of anal stenosis: a prospective randomized study; Dis Colon Rectum. 53(5):790–797.
- 16. Emily J. Bubbers.and Kyle G Cologne. (2016): Management of Complex Anal Fistulas; Clin Colon Rectal Surg. Mar; 29(1): 43–49.
- 17. Rojanasakul A, Jirawat Pattanaarun, Chucheep Sahakitrungruang. et al. (2007): Total anal sphincter saving technique for fistula-in-ano, the ligation of intersphincteric fistula tract; Med Assoc Thai. 90: 581-586.
- 18. Wook Ho Kang . H Kyu Yang . H Jeong Chang. et al. (2018): High ligation of the anal fistula tract by lateral approach: A prospective cohort study on a modification of the ligation of the intersphincteric fistula tract (LIFT) technique ; International Journal of Surgery. Volume 60, December, Pages 9-14.
- 19. Nisar A Chowdri1 .Salim Nazki . Z Ahmad Shah. et al. (2020): Ligation of Intersphincteric Fistula Tract (LIFT) For Fistula-in-Ano: Feasibility and Our Experience; World Journal of Surgery and Surgical Research 1. Volume 3 Article 3 : 1209.
- 20. Ahmed M. ,Mahmmad A.,and Hanna H. (2018): Ligation of the intersphincteric fistula tract procedure and its modification ; J Coloproctol (rio j).38(4):324.
- 21. Baocheng Zhao., Zhenjun Wang ., Jiagang Han., et al. (2019): Long-Term Outcomes of Ligation of the Inter-Sphincteric Fistula Tract Plus Bioprosthetic Anal Fistula Plug (LIFT-Plug) in the Treatment of Trans-Sphincteric Perianal Fistula; Med Sci Monit. 25: 1350–1354.
- 22. Garg P. J Song. A Bhatia et al. (October 2010):"The efficacy of anal fistula plug in fistula-in-ano: a systematic review";Colorectal Dis. 12 (10): 965–70.
- 23. Kee Ho Song. (2012): New Techniques for Treating an Anal Fistula; J Korean Soc Coloproctol.28(1):7-12.
- 24. Johnson E K. Janette U Gaw. David N. (2006): Efficacy of anal fistula plug vs. fibrin glue in closure of anorectal fistulas; Dis Colon Rectum. .49(3):371–376.
- 25. Ky A J. Patricia Sylla. Randolph Steinhagen. et al. (2008): Collagen fistula plug for the treatment of anal fistulas; Dis Colon Rectum. . 51(6):838–843.
- 26. Heydari A. G Maria Attinà. Enrico Merolla. et al. (2013): Bioabsorbable synthetic plug in the treatment of anal fistulas; Dis Colon Rectum. 56(6):774–779.
- 27. Wallin U G. Anders F. Robert D. et al. (2012): Does ligation of the intersphincteric fistula tract raise the bar in fistula surgery?; Dis Colon Rectum. 55(11):1173–1178.
- 28. Mushaya C. Lynne Bartlett. Bettina Schulze. et al (2012): Ligation of intersphincteric fistula tract compared with advancement flap for complex anorectal fistulas requiring initial seton drainage; Am J Surg. 204(3):283–289.
- 29. McGee MF. Bradley Champagne. Jonah Stulberg. et al (2010):Tract length predicts successful closure with anal fistula plug in cryptoglandular fistulas; Diseases of the Colon & Rectum. 53(8):1116-20.
- 30. Armen Aboulian ., A H Kaji.,and Ravin Kumar. (2011): Early result of ligation of the intersphincteric fistula tract for fistula-in-ano; Dis Colon Rectum. 54(3):289–292.

- 31. García-Olmo D. M García-Arranz. Dolores Herreros.et al. (2005): A phase I clinical trial of the treatment of Crohn's fistula by adipose mesenchymal stem cell transplantation; Dis Colon Rectum. 48:1416–1423.
- 32. Kamrava A. and J Craig Collins. (2011): A decade of selective use of adjustable cutting seton combined with fistulotomy for anal fistula; Am Surg .77(10):1377–1380.
- 33. Mennigen R. (April 2015): "The OTSC proctology clip system for the closure of refractory anal fistulas"; Tech Coloproctol. 19 (4): 241–6.
- 34. Meinero P. and L. Mori. (2011): Video-assisted anal fistula treatment (VAAFT): a novel sphinctersaving procedure for treating complex anal fistulas; Tech Coloproctol . 15(4): 417–422.
- 35. Matos D. P J Lunniss.and R K Phillips. (1993): Total sphincter conservation in high fistula in ano: results of a new approach; Br J Surg .80:802–804
- 36. Mizuno H. Patricia A Zuk.Min Zhu.et al. (2002): Myogenic differentiation by human processed lipoaspirate cells; Plast Reconstr Surg .109:199–209.
- Garcia-Olmo D. Dolores Herreros. Isabel Pascual. et al. (2009): Expanded adipose-derived stem cells for the treatment of complex perianal fistula: a phase II clinical trial; Dis Colon Rectum. 52:79–86.
- 38. Song KH. (2012): New Techniques for Treating an Anal Fistula; J Korean Soc Coloproctol. 28(1):7-12.
- 39. Altomarc DI. (2015): Anal fistula closure with Filac,New hope or the same old story ? ; Tech Coloprocty. 19:441-2.