Current status and innovations in treatment of perianal and rectovaginal fistulas : are we still in the dark?

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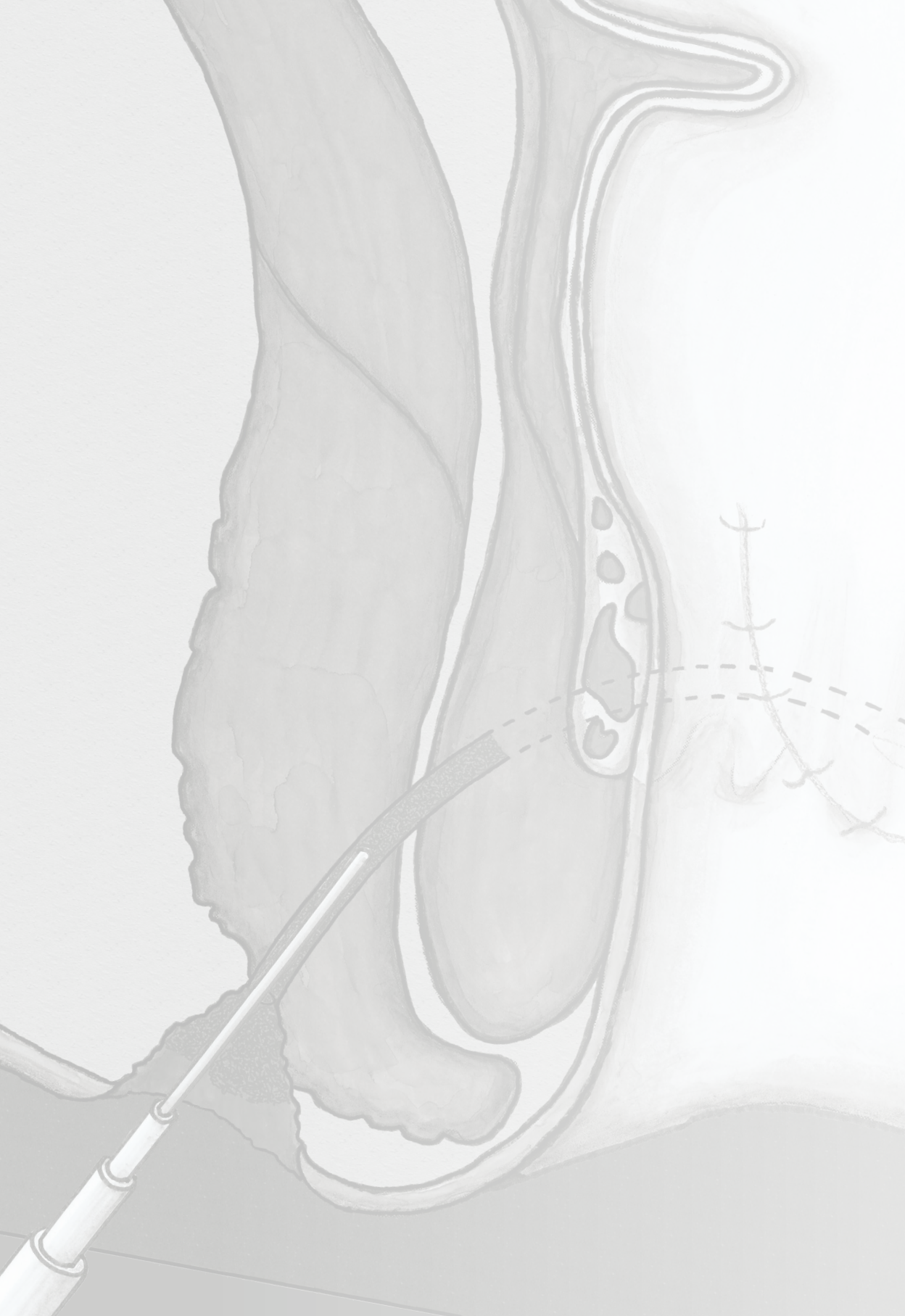

1 Introduction

Perianal fistula

The basics

A perianal fistula (PF) is a non-anatomic canal between the rectum and the skin. PF are first described before the Common Era by Hippocrates.[1] The incidence of PF is relatively low. The largest study performed on the incidence of PF was a population-based study from Finland. A population of 510,000 living in Helsinki showed a mean incidence of 8.6 PF per 100,000.[2] A cohort study by Eglinton showed that 28.3% of patients with Crohn's disease develops a PF eventually.[3]

Symptoms caused by PF are pain and involuntary loss of gas, fluids or faeces. Besides these symptoms, complaints of itching and symptoms of infections are often reported. These complaints often result in social embarrassment and loss of quality of life.[4, 5]

In 1976 Parks published an article suggesting a classification of fistula tracts related to the involvement of the anal sphincter muscle complex.[6] The described fistula tracts running transsphincteric, intersphincteric, suprasphincteric and extrasphinteric. While this classification is still often used, a classification in low and high fistulas might be more useful in deciding which surgical technique is best used for treatment of the PF. Low PF are classified as fistulas running through the lower one-third part of the anal sphincter complex, while high fistulas run through the middle and/or upper one-third parts of the anal sphincter complex.[7]

In 1900 David Henry Goodsall introduced his ideas about the course of the PF being related to the external opening lying anterior or posterior of the transverse anal line. He stated that an anteriorly identified external fistula opening was associated with a fistula tract running in a radial line to the internal opening, while a posterior opening would result in a tract always ending in the posterior midline.[8] His theory is now known as Goodsall's Rule. The accuracy of the rule was tested by Cirocco in 1992, who showed that for posterior external openings the rule is reasonably accurate, but for anterior openings the rule is not reliable.[9]

The diagnosis of a PF is often made by physical examination. The external opening of the fistula can mostly be seen. The internal opening can sometimes be palpated by manual palpation of the anal canal. Magnetic resonance imaging (MRI) scans are often performed to visualize the path of the fistula tract (Park's classification) and to be able to classify the fistula as low or high. Endo-anal ultrasound can be a good substitution of the MRI in specialized centres. Ultimately, in case of doubt about the diagnosis or if it is unclear if an internal fistula opening exists, inspection and probing of the fistula under anaesthesia is a useful method.

The two most occurring aetiologies of a PF are the cryptoglandular PF and the Crohn's disease related PF. A less occurring cause of PF is trauma, including fistulas occurring after external trauma or iatrogenic medical trauma. Two French anatomists first described the cryptoglandular hypothesis in 1880 (Herrmann and Desfosses).[10] They described small glands, which are run through the internal anal sphincter and discharge into the rectum. Infection in these glands could be a cause of PF. Their theories were later confirmed on many occasions by others.[11, 12] In 1956 and 1958 Eisenhammer changed the hypothesis and ascribes anal abscesses followed by fistulas to anal-gland infection between the in- and external anal sphincter muscles.[13, 14] He also suggests internal sphincterotomy is needed to reveal the abscesses. In 1961 Parks performs a histopathology study confirming Eisenhammers theories.[1]

The relation between Crohn's disease and the development of PF was shown before with a high incidence of PF in populations with Crohn's disease. It also seems that the lower the intestinal lesions occur, the higher the incidence of PF.[15]

Treatment

Hippocrates was one of the first to describe the diagnosis and probing of PF. The first extensive descriptions of PF and especially treatments for the disease were described by John Ardenne in 1376 in his book 'Treatises of Fistula in Ano; Haemmorhoids, and Clysters'. From ancient times until the end of the 1800s the basic technique for treatment was to lay-open the fistula, which we now call the fistulotomy. Ardenne also described an extensive use of the seton, and newer techniques aim at closure of the internal fistula opening.

Historical references indicate that Louis the XIV was treated for a PF in the 18th century. In 1835 Frederick Salmon founded The Benevolent Dispensary for the Relief of the Poor Afflicted with Fistula and other Diseases of the Rectum. This hospital is now called St Mark's Hospital and was one of the first specialist hospitals. It has played a major role in the development of treatments for anorectal diseases.

The basic technique we still use for low PF is the fistulotomy, with suggested healing rates over 90%.[16] The good outcomes of this technique resulted in few other techniques being investigated for low PF, this in contrast to the treatment of high PF. The reason why other techniques were needed to treat high PF was the high risk of sphincter muscle damage with resulting postoperative faecal incontinence.

Some of the techniques used for treatment of high PF have already been mentioned, like for instance seton treatment (ranging from sphincter cutting setons to non-cutting setons, and draining setons that are used to drain abscess components and clean the fistula before attempting definitive treatment).[17-19] The first time advancement flaps were introduced for high PF was in 1912.[20] Modifications of this technique included partial and full-thickness rectal wall advancement flaps and modifications on the incision technique.[21]

Fistulotomy has also been used for high PF and the technique was combined with direct sphincter muscle reconstruction in 1991 to lower the risk of postoperative incontinence, but still resulted in incontinence in about 20% of patients.[22] Fibrin glue as a treatment for high PF was introduced in 1991 as well.[23] Other techniques followed in the years coming. In 1996 the island flap anoplasty was introduced,[24] in which a cutaneous flap is transpositioned into the rectum to cover the internal fistula opening.

Stem cells were studied in 2005 in the treatment of PF in a small Phase I trial.[25] It took four more years to publish the larger Phase II trial.[26] In 2006 the absorbable anal fistula plug was introduced, which filled up the complete fistula tract.[27] In the same year a laser technique was described to coagulate the complete fistula tract.[28] In 2007 Rojanuskul showed a novel technique used intensively nowadays. The ligation of the intersphincteric fistula tract (LIFT).[29]

The technique was modified in the years to come, with for instance the LIFT-plug in which the LIFT is combined with an anal fistula plug (2012).[30] Another variation is the LIFT-plus that combines the LIFT with a partial fistulectomy (2013).[31] The BioLIFT is the latest edition to the modification in which a biograft is placed in the intersphincteric space (2014).[32]

Some of the latest additions to the surgical list of interventions were the video assisted anal fistula treatment (VAAFT) that consists of insertion of an endoscope into the fistula tract with electrocoagulation under vision,[33] and a modification of the mucosal advancement flap that combines this technique with PRP.[34]

Many techniques were and are still being developed, indicating that we still do not have an ideal treatment.

Outcome

The most important outcomes for surgical treatment of PF are healing and recurrence rates. The amount of literature on surgical repair of PF is low, but still reasonable. However, the number of high quality randomized controlled trials is limited and comparison of techniques varies widely between these trials.[35-37] Although prospective research is available no clear ideal treatment has therefore been found yet. A typical situation is that initial results of a new technique are far better than those after wider application.

An example is one of the best-known techniques: The advancement flap. Early studies show healing rates over 90%,[38] compared to results nowadays hardly reaching 60%.[39] Whether or not this is due to selection bias in earlier studies, publication bias, better designed studies today, or because of differences between surgeons performing the operations, remains unclear. This could mean we will need to wait several years until larger and more reliable studies are available before a new technique can be implemented in general treatment algorithms or be discarded.

Secondary outcomes are maybe even more important. Especially for high PF a high risk of anal sphincter damage is present during surgery. Many techniques have been designed to save the anal sphincter complex like the LIFT.[29] However, repeat surgery, and also the repeated use of anal retractors, after a fistula recurrence increases the risk of sphincter damage and consequently the risk of postoperative incontinence. These risks are well known from research on the postoperative continence status.[34, 40-43] The following question should be remembered: If patients report actual faecal incontinence postoperatively, while the fistula remains closed, could the surgical intervention be listed as successful?

Rectovaginal fistula

The Basics

A rectovaginal fistula (RVF) is a non-anatomic canal between the rectum and vagina. Alike the PF, first descriptions of the disease are found in literature from before the Common Era. Hippocrates, in the ancient Greek empire, described techniques of rectal and vaginal inspection using a speculum and probing of a fistula. Many centuries later in the 1800s the condition was again relatively often described and treatments were developed. During this period RVF was described as an obstetric fistula. The actual incidence of RVF is difficult to estimate, but is in general very low. We do know that the occurrence of RVF after third or fourth degree childbirth trauma lies between 0.5% and 3%,[44, 45] with the incidence of such trauma estimated at between 1% and 2%.[45, 46] Symptoms associated with RVF include gas, fluid and faeces loss from the vagina. Frequently these symptoms are wrongfully interpreted as faecal incontinence. Vaginal irritation, inflammation, and dyspareunia are often reported symptoms.[47] A RVF is sometimes suspected if the patient presents with recurring urinary tract infections. Besides these physical symptoms the disease has a negative influence on quality of life and is associated with social embarrassment and isolation.[47]

The RVF are difficult to see and even more difficult to palpate because of the often narrow diameter of the fistula. Gynaecologic examination or procto/coloscopy may sometimes prove the existence of the fistula. Nowadays MRI or endo-anal ultrasound can be considered if the RVF is suspected but not clearly found with other techniques. Inspection under anaesthesia is a possibility in case the diagnosis is still unclear and could be combined with surgical repair.

The aetiology of RVF nowadays varies and could be classified in four categories: Traumatic, cryptoglandular, Crohn's disease related and post-malignancy. As explained, in the 1800s the disease was named obstetric fistula, describing only one of the possible causes of a traumatic RVF. Traumatic RVF can be caused by any external or internal trauma, childbirth trauma, or iatrogenic injury. Pouch-vaginal fistulas, occurring after the creation of an ileo-anal pouch could be classified in this category, although some occur after a period of chronic pouchitis.[48] Cryptoglandular RVF are hypothesized to be caused by (chronic) infection of the anal glands, resulting in the formation of an abscess, which may secondly result in the development of a RVF, alike the mechanism for cryptoglandular PF.[1] Crohn's disease is known for the high percentage of patients developing perianal disease. In a recent cohort study more than 29% of patients with Crohn's disease developed perianal disease, of which about 8% had a RVF.[3] Equal results were found in other studies.[15, 49, 50] Patients surgically treated for gynaecologic malignancies or rectal malignancies are susceptible for developing a RVF, especially after treatment with local radiotherapy. The radiation induced RVF incidence is estimate between 0.3% and 6%.[51, 52] Radiotherapy is known to cause poorly vascularized tissue and tissue damage, making the malignancy related fistula very difficult to treat.[53]

Treatment

One of the basic principles of RVF repair, as it is for PF, is closure of the fistula opening(s) to allow the fistula tract to heal. Other techniques are based on the idea that the diseased tissue needs to be replaced by healthy tissue or that the fistula tract needs to be filled up or divided. It remains unclear which of these principles works best.
In the early 1800s the first treatments specifically for RVF were described. In 1828 Nicol describes saucerization (surgical excavation of tissue to form a notch) of the fistula openings allowing for better healing after suturing.[54] In 1836 Walker advised to simply close the fistula openings with sutures.[54] Today, we have a wide range of surgical techniques available to use. Some of these techniques are mostly used for high RVF and others for low RVF. High RVF are classified as fistulas traversing the upper half of the vagina and low RVFs are running through the lower half of the vagina.[54]
Eden described the first transabdominal technique for closure of a RVF in 1914.[55] He described a hysterectomy followed by closure of an otherwise non-accessible high RVF. Only in 1967 was this technique modified by Lawson, who advocated splitting of the cervix to reach the fistula in stead of performing a hysterectomy.[56]
Henri Martius described a bulbocavernosous muscle and labial fat pad graft in 1928 that could be used to close a RVF.[57] This technique is now known as the Martius flap. A modified version of this technique only uses the labal fat pad and is proven to be equally reliable.[58]
The first abdominal repair of a RVF using a transvaginal access was described by Mafouz in 1934.[59] This technique was later modified by Lawson, who combined the repair of the fistula by suturing the anterior rectal wall to the posterior vaginal wall, creating a new posterior fornix.[60]
In 1952 Hofmeister described a technique for the repair of obstetric RVF by first creating a situation alike a third degree childbirth tear and then repairing the tissue by closure in layers.[61] The nowadays well-known gracilis muscle transposition was first described for RVF one year later.[62]
The first description of transabdominal ligation of a RVF combined with omentoplasty was found in a gynaecology and urology textbook from 1960.[63] This technique was described laparoscopically in 2011.[64] A pull-through operation was first described in

1961.[65] The colpocleisis (Closure of the vagina by removing an anterior and posterior mucosal strip and suturing these areas together) was performed for a malignancy related RVF in 1965.[66]
The first time faecal diversion was advocated before the repair of a RVF was in 1966 by Hodgkinson and Baker.[67] Faecal diversion is still discussed nowadays and is still seen as a useful intervention in the surgical repair of RVF. It is still unknown if the faecal diversion aids healing, or if it only results in relief of symptoms.
In 1967 Lescher and Pratt describe the creation of advancement flaps for the closure of simple RVF, which is one of the techniques we still use nowadays.[68] Different types of advancement flaps have been developed over the years, of which the two most important are the endorectal advancement flap and the endovaginal advancement flap.[69]
The first time a transperineal repair was attempted and described was in 1977.[70] By using a transperineal incision the fistula was excised and the rectovaginal septum closed with sutures. Later this approach was among others used for the repair of RVF with mesh placement.[71] Rectal resection was performed in 1986 by Kux.[72]
In the years to follow many more new techniques were developed and advocated. In 1999 fibrin glue was used for the first time in RVF,[73] followed by the used of stem cells in 2003.[74] New muscle flaps and transpositions were also developed, like the gluteal fold flap or the puborectal sling interpositions.[75, 76] In 2008 fistula plugs were introduced for the use in RVF and in the same year endoscopic techniques with clip placement and transanal endoscopic microsurgery were also described.[77-79]
Rectal sleeve advancement and the use of platelet-rich plasma (PRP) were published in 2009.[80, 81] In 2011 Hull advocates the episioproctotomy in which a situation alike a fourth degree childbirth laceration is created and later repaired with closure of the fistula.[82] One of the latest techniques described is the closure of the fistula tract by using a bioglue.[83]
The amount of available techniques and the many recently developed techniques suggest that the perfect treatment has also not been found yet for this type of fistula.

Outcome

The main outcome that is strived for is healing of the fistula and prevention of recurrence. The results of the previously described surgical techniques regarding healing and recurrence rates are unfortunately not ideal. A typical situation is that initial results of a new technique are far better than those after wider application, comparable to the situation for PF. Reasons are equally unclear for this disease, but the hypotheses are the same as for PF.
What makes it even more difficult to assess the true outcome of all the previously mentioned techniques is the lack of high quality data. Randomized trials are simply non-existent for treatment of RVF and the number of prospective trials on surgical outcome is hardly any better.[64, 73, 84-86] This is probably due to the low incidence of RVF, the heterogeneous groups, and because we do not know which techniques to compare in trials.
While we all focus on our healing and recurrence rates, other outcomes might be even more important. As explained before, symptoms of a RVF are comparable to faecal incontinence. Because no decent prospective and randomized trials exist for surgical treatment of RVF our knowledge on postoperative continence status is very limited. If we manage to close a RVF with a certain technique, but afterwards the patient reports symptoms actually accountable to faecal incontinence caused by the operation, then how important are our healing rates? The same could be said about postoperative quality of life and sexual functioning. Studies reporting on these secondary outcomes with standardized techniques are equally rare. 64, 85, 87, 88

Outline of this thesis

The aim of this thesis was to evaluate the efficacy of the currently available surgical treatmens for both PF and RVF, to investigate several new surgical techniques and to show the occurrence and outcome of PF and RVF in a large cohort of patients with Crohn's disease. Most of the studies in this thesis were performed in collaboration with several medical centres in the southern part of the Netherlands and coordinated from the department of general surgery of the Maastricht University Medical Centre (MUMC+).

Chapter 2 was a collaboration of the surgical departments of all medical centres in the southern surgical district (district VIII) of the Netherlands and evaluates the results of fistulotomy for low PF. Specifically investigating healing rates and continence status.

In ***chapter 3*** a systematic review and meta-analysis is presented on the results of available surgical techniques for the closure of high cryptoglandular PF.

Chapters 4 and 5 report on the results of the mucosal advancement flap combined with PRP for high PF. ***Chapter 4*** focuses on the long-term healing and recurrence rates and postoperative incontinence of this technique for cryptoglandular PF and ***chapter 5*** shows the first results of the technique in Crohn's disease related PF.

The Inflammatory Bowel Disease database of the Southern Limburg district (IBD-ZL) was used to perform an epidemiologic study on the occurrence of PF and RVF in patients with Crohn's disease. Results of this study and the outcome of interventions for these fistulas are presented in ***chapter 6***.

Chapter 7 reports on the first results of a new transvaginal and transperineal technique for the closure of RVF. This technique uses a cross-linked collagen matrix biomesh, which is implanted in the rectovaginal septum.

In ***chapter 8*** a series of muscle flaps and transpositions are evaluated as a last resort option for both PF and RVF. This study describes the healing and recurrence rates of these muscle flaps and transpositions in recurring PF and RVF.

Chapter 9 is a systematic review on the outcome of surgical closure techniques for RVF. Specifically, healing and recurrences rates are investigated, but also important secondary outcomes like continence status, sexual functioning and quality of life are evaluated.

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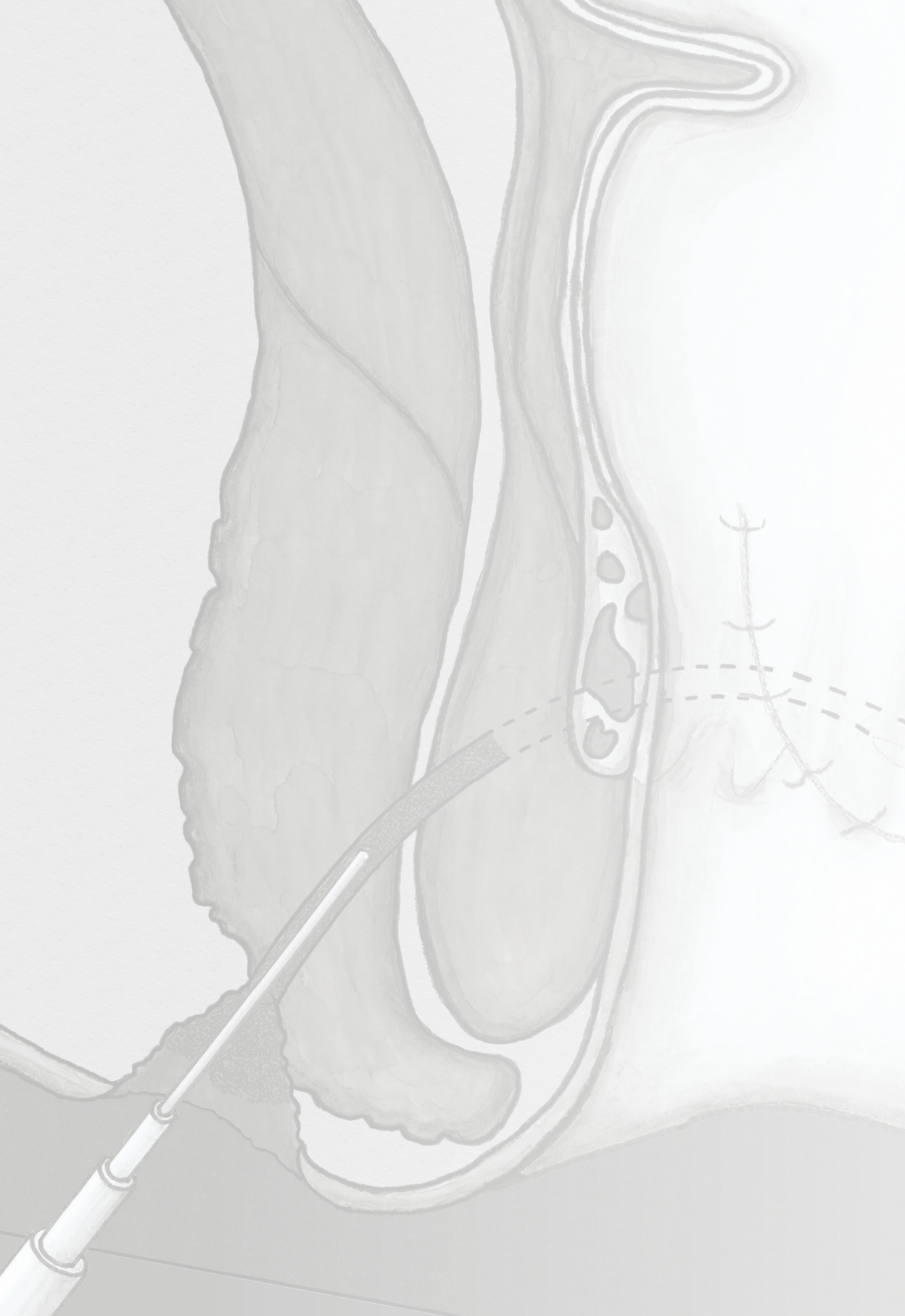

2 Long-term outcome of low perianal fistulas treated by fistulotomy: A multicentre study

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Abstract

Purpose

The fistulotomy is considered to be the golden standard for treatment of low perianal fistula but might have more influence on continence status than believed. This study was performed to evaluate the healing rate after a fistulotomy and to show results for continence status.

Methods

A retrospective database study was performed in one university medical center and its six affiliated hospitals. All patients treated with a fistulotomy for a low perianal fistula were identified. Healing and recurrence of the fistula were identified. Questionnaires on continence status and quality of life were mailed to all patients.

Results

In total, 537 patients were identified. The primary etiology of the fistulas was cryptoglandular (66.5%). Recurrence was seen in 88 patients (16.4%) resulting in a primary healing rate of 83.6%. After secondary treatment for the recurrence, another 40 patients healed. This resulted in a secondary healing rate of 90.3%. The Kaplan-Meier analysis showed that at 5 years, the healing rate was 0.81 (95%-CI: 0.71 – 0.85). The mean Vaizey-score was 4.67 (SD 4.80). Major incontinence, defined as a Vaizey score of >6, was seen in 95 (28.0%) patients. Only 26.3% of the patients had a perfect continence status (Vaizey score 0). Quality of life was not different from the general population.

Conclusions

Fistulotomy seems to be associated with a healing rate of 0.81 (95%-CI: 0.71-0.85) after 5 years. However, major incontinence is still reported by 28.0% of patients and only 26.3% of patients had a perfect continence status.

Introduction

Perianal fistulas (PF) remain a surgical treatment challenge in colorectal practice due to high recurrence rates and the risk of postoperative incontinence. Treatment of PF depends on the relation to the anal sphincter complex. Traditionally, the fistulas are classified according to Parks classification (transsphincteric, intersphincteric, extrasphincteric and suprasphincteric).[1] However, treatment of a PF depends mostly on the amount of the sphincter complex that is involved. Therefore, the classification in high and low fistulas has become more common. High perianal fistulas (HPF) are defined as involving the middle and/or upper third parts of the anal sphincter complex. Low perianal fistulas (LPF) are defined as involving the lower one third of the anal sphincter complex or not involving the sphincter muscles at all. The major disadvantage of surgical treatments for PF is the chance of anal sphincter dysfunction, like soiling, incontinence for gas, liquid stool and/or solid stool.

At first, fistulotomy was the main surgical procedure for all PF. However, in HPF this procedure results in a high risk of anal sphincter dysfunction.[2] Consequently, this led to the development of surgical techniques for HPF aimed at sparing anal sphincter function and improving recurrence rates.[3-5] Nowadays, new techniques are still being developed for HPF, since the ideal treatment has not been found yet.[6-9]

For LPF, fistulotomy is still considered to be the golden standard of surgical treatment. Success rates have been reported as high as 80-100%.[10-12] Unfortunately, incontinence rates after fistulotomy might be higher than we assume. This is indicated by several studies that report on incontinence, ranging from soiling to major incontinence, up to 41%.[11, 13, 14] In contrast to treatments for HPF, development of new treatments for LPF has not been advancing as fast, although some newer techniques have been described.[15, 16] With the development of new techniques lagging behind for LPF and the risks of incontinence being real, we considered the evaluation of our results after fistulotomy appropriate. We therefore assessed healing rate, continence status and quality of life after fistulotomy for LPF in our region.

Methods

We searched the databases and patient files of our university medical center and its six affiliated hospitals for patients with LPF between 2008 and 2013. A LPF was defined as a fistula traversing the lower one third of the anal sphincter complex or a superficial fistula not involving the striated sphincter complex.

Primary outcome of this study was closure rate after fistulotomy. The secondary outcomes were continence levels, quality of life, time to healing, and time to recurrence. Demographic data, disease etiology, type of fistula, fistula anatomy and previous fistula surgery were all extracted from patient files. Fistula type was defined as a primary or a recurrent fistula. Both types of fistula were included. Prior fistula surgery was defined as any surgery regarding the fistula, including seton placement. Abscess drainage was excluded.

Closure of the fistula was defined as a visibly closed wound without external fistula openings and without discharge during manual compression. Recurring of these symptoms was defined as a recurrent fistula. If the fistula did not close within three months it was defined as a persisting fistula. The time from operation to closure of the fistula was defined as time to healing. Time to recurrence was defined as the time from healing to the time that the patient file described recurring symptoms.

Information regarding fistula anatomy (location of internal and external openings,

location of fistula tract, involvement of the sphincter complex, etc.) was obtained from additional imaging like magnetic resonance imaging (MRI) or from descriptions of the fistula tract in operative reports. MRI was generally only performed in case a HPF was suspected preoperatively.
To identify factors associated with a recurrence, patients with a recurrent LPF were compared to the primary healed patients using a cox-regression analysis. A p-value <0.05 was considered statistically significant. Additionally, a Kaplan-Meier analysis was performed to compare cumulative proportions of patients with recurrence.
Long-term postoperative outcome regarding incontinence rate and quality of life were obtained using two questionnaires. To assess the long-term postoperative continence status, we used the Vaizey questionnaire.[17] Quality of life was assessed using the Short Form Health Survey 36 (SF-36).[18]
Telephone interviews were used to evaluate status of the fistula for patients not being in outpatient clinical follow-up anymore. Preoperative and postoperative interviews and examination were performed by the operating surgeons or by the resident surgeon involved with the operation. Either the operating surgeon or the resident surgeon involved with this study performed the telephone interviews. This study was performed according to national and local medical and ethical laws and guidelines. The local medical ethical committees approved this study.

Operative procedure

Patients were positioned in the lithotomy position under general or spinal anesthesia. First, a probe was inserted in the fistula tract, identifying the external and trying to identify the internal fistula openings. An anal retractor was only used if visibility was not good enough to examine the fistula and perform the procedure. The involved medical centers used different types of retractors. If a LPF was confirmed based on the amount of sphincter complex involved after probing the tract, a lay-open procedure of the tract was performed guided by the probe. The fistula track was curetted after the fistulotomy. If a HPF was suspected the fistulotomy was not performed.

Results

Between January 2008 and June 2013, 537 patients were treated by fistulotomy for a LPF. Mean age at time of operation was 45.5 years (range 5-97); 379 (70.6%) patients were male. Median total follow-up was 38.9 months (6.0-74.8).
Of the 537 patients, 369 (68.7%) had a primary fistula, 163 (30.4%) had a recurrent fistula and in 5 (0.9%) patients, the type of fistula was unknown. Fistula anatomy according to Parks' classification is shown in Table 1.
Fistula etiology was cryptoglandular in 357 patients (66.5%). Thirty-six patients (6.7%) had a fistula related to Crohn's disease. For the remaining patients the disease etiology could not be identified.
MRIs were made pre-operatively in 266 patients (49.5%). Of those 266 MRIs, 242

Table 1 - Incontinence levels in relation to previous number of operations

Classification	Number	Percentage
Transsphincteric	164	30.5
Intersphincteric	143	26.6
Superficial (subcutaneous)	211	39.4
Not classified	19	3.5

Table 2 - Number and percentages of recurrence after fistulotomy

	Number	Recurrence	Secondary surgery	Healing after secondary surgery
Type of fistula				
Transsphincteric	164	30 (18.3)	21 (70.0)	5 (23.8)
Intersphincteric	143	18 (12.6)	13 (72.2)	10 (55.6)
Superficial (subcutaneous)	211	40 (19.0)	32 (80.0)	13 (40.6)
Not Classified	19	3 (15.5)	2 (66.7)	2 (66.7)
Previous operations				
0	274	37 (13.5)	27 (73.0)	12 (44.4)
1	121	23 (19.0)	16 (69.6)	13 (81.3)
2	47	11 (23.4)	9 (81.8)	1 (9.1)
>2	29	5 (17.2)	4 (80.0)	1 (25.0)
Crohn's Disease	36	12 (33.3)	7 (58.3)	1 (14.3)

Values given as n (%)

Table 3 - Healing after secondary treatment

Type of treatment after recurrence	Number	Healing after secondary treatment
Conservative treatment	12	9 (75.0)
Seton	16	2 (12.5)
Seton + fistulotomy	1	0 (0.0)
Fistulotomy	47	28 (59.6)
Mucosal advancement flap	4	1 (25.0)
Unknown	8	Unknown

Values given as n (%)

(91.0%) confirmed the presence of a LPF. Fistula tract and sphincter involvement was also described in most of the operative reports.

A recurring fistula was seen in 88 (16.4%) patients of whom 40 (7.4%) had persisting fistulas. In 4 (0.7%) patients it was unclear if a recurrence occurred (Table 2). This resulted in a success rate of 83.6%. The median healing time was 37 days (range 6 – 99). The median time until recurrence was 90 days (range 7 – 1085).

Recurrences were managed by conservative treatment in 12 (13.6%) patients, with a seton in 16 (18.2%) patients, a fistulotomy in 47 (53.4%) patients, a seton + fistulotomy in 1 (1.2%) patient, and a mucosal advancement flap in 4 (4.5%). The method of treatment could not be identified in 8 (9.1%) patients. Results after surgery for recurrent LPF are displayed in Table 3.

After the secondary treatment, another 40 fistula remained closed, reaching a secondary healing rate of 90.3%. The cumulative healing at 5 years is 0.81 (95%-CI: 0.71 – 0.85), as can be seen in the Kaplan-Meier survival curve (Fig. 1).

No significant relation was found between gender, Crohn's disease, an unidentified internal opening or anterior location of the internal opening, and the development of a recurrence. However, a significant relation ($p<0.05$) for the development of a recurrence was found if it concerned a recurring fistula (Table 4).

Pre-operatively, 7 (1.3%) patients had known incontinence problems. Five of these patients had complaints of soiling, one patient was incontinent for gas and one patient was incontinent for solid stool.

The questionnaires were mailed to all 537 patients. After a month, we sent a second questionnaire and contacted the patients that did not respond after the first mailing. In total, 374 patients responded to our questionnaire, resulting in a response rate of

Table 4 - Cox regression analysis for recurrence of fistula

Parameters	Hazard ratio	95% CI	P-value
Female	1.185	0.737-1.907	0.49
Recurrent fistula	2.170	1.427-3.300	<0.05
Crohn's disease	0.329	0.045-2.378	0.27
Unidentified internal opening	1.240	0.684-2.247	0.48
Anterior fistula location	0.547	0.162-1.852	0.33

A hazard ratio >1 shows increased frequency of recurrence

Table 5 - SF-36 outcome: comparison of quality of life

Health score	Fistulotomy	General population	p-value
Physical functioning	85.7 (21.1)	83.0 (22.8)	0.83
Role physical problems	79.2 (37.0)	76.4 (36.3)	0.90
Bodily pain	75.2 (24.3)	74.9 (23.4)	0.99
General health	64.4 (21.6)	70.7 (20.7)	0.61
Vitality	64.3 (20.3)	68.6 (19.3)	0.71
Social functioning	81.8 (21.5)	84.0 (22.4)	0.86
Role emotional problems	83.7 (32.1)	82.3 (32.9)	0.94
Mental health	75.4 (18.7)	76.8 (17.4)	0.90

Values as mean (SD)

Table 6 - Incontinence levels

Vaizey score	Number (%)
0	89 (26.3)
1-6	155 (45.7)
>6	95 (28.0)

Table 7 - Vaizey score related to previous surgery

Vaizey score	No Operations	One operation	Two operations	> Two operations	Unknown
0	53 (32.2)	19 (24.6)	4 (11.1)	2 (10.5)	7 (16.7)
1-6	73 (44.2)	37 (48.1)	19 (52.8)	11 (57.9)	21 (50.0)
>6	39 (23.6)	21 (27.3)	13 (36.1)	6 (31.6)	14 (33.3)

Values given as n (%)

69.6%. Thirty-four (6.3%) patients replied that they were not willing to participate. This resulted in 63.3% completion of the questionnaires. Two (0.4%) patients turned out to be deceased.

We compared the results of our SF-36 survey to the validated values for the general population.19 The results of our SF-36 survey are displayed in Fig. 2. Compared to the national values, no significant difference was found in quality of life (Table 5).

The mean Vaizey-score was 4.67 (SD 4.80). Major incontinence, defined as a Vaizey score of >6,3 was seen in 95 (28.0%) patients. Incontinence levels and their relation to previous surgery are displayed in Tables 6 and 7. We did not find a difference in continence status between patients with and without a preoperative MRI.

Data on the number of vaginal deliveries and nulliparous status were unfortunately not available, and its effect on postoperative continence status could therefore not be evaluated.

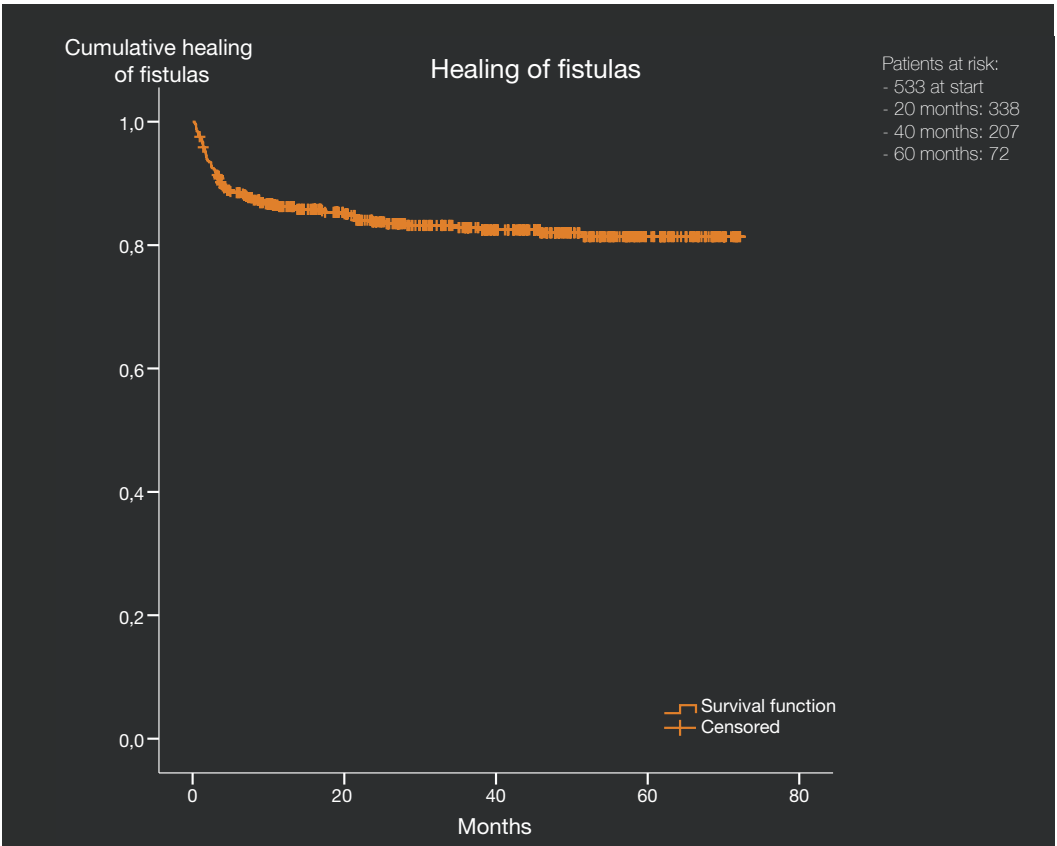

Figure 1 - Healing of fistulas

Discussion

This study on long-term results after fistulotomy for LPF demonstrates a primary healing rate of 83.6%, and a secondary healing rate of 90.3%. This is consistent with other reports that have demonstrated a high healing rate (>90%).[20] Using a Kaplan-Meier analysis we found a healing rate after 5 years of 0.81 (95%-CI: 0.71-0.85).
The healing time after fistulotomy varied widely between several reports, ranging from a median of 3 weeks up to 11.6 weeks.[20, 21] A maximum healing time of 12 weeks is regarded the standard for LPF.[21, 22] The 5 weeks healing time in our study is therefore similar to healing times in other studies.
Although we found a recurrence rate within the reported recurrence range, it cannot go unnoticed that our primary rate (16.4%) was slightly higher than the average total recurrence rate of 10%.[2, 20, 23] By analyzing center-specific data we found the highest recurrence rate in our university medical center. The higher recurrence rate could be explained by the third line referral position for LPF. There might also be a difference in recurrence per surgeon. Furthermore, it cannot be discarded that the inclusion of patients with Crohn's disease might contribute to a higher recurrence rate, although these patients were only treated if the Crohn's disease was in remission. Similar effects are described in reports that also do not exclude Crohn's disease.[10, 24]
Lack of identifying the internal opening,[2] female gender, recurrent fistula surgery,[24] and location off the midline[2] are reported to be factors associated with the development of a recurrence. In our series, the only significant factor associated with a recurrence was a

recurring fistula. The reasons for our different findings are not clear.
Post-operative quality of life results were not significantly different from the general population. Furthermore the long-term incontinence levels were low with a mean Vaizey-score of 4.66 (SD 4.75). However, we did find major incontinence in 95 (28.0%) patients.[3]
Incontinence rates vary significantly between studies from 2.4 up to 64%,[24, 25] but most series report incontinence rates ranging between 30 and 40%.[10, 11, 23] Similar to these reports, most incontinence problems consisted of soiling or flatus. Standardized incontinence scales are unfortunately rarely used in older studies. Reports that do use a standardized scale report average Vaizey-scores of >6.5, which is higher than our series (4.66).[11] Major incontinence is usually described as a Vaizey-score >6.3 The Vaizey questionnaire consists of 6 questions scored 1 (mild incontinence) to 4 (severe incontinence) with a maximum score of 24. If a patient has only minor complaints it may not affect daily functioning, although it may result in a score >6 on the questionnaire. Therefore, it is important to distinguish a very high Vaizey-score from a Vaizey score of just >6 with only minor complaints.
The reason for the high percentage of major incontinence in our study remains unclear; however, several possibilities come to mind. Even though no significant relation was found between the Vaizey score and the number of previous operations, it is likely that previously operated patients have a more damaged sphincter complex and a higher cumulative risk of postoperative incontinence. Secondly, if during the operation a HPF is suspected, even if the MRI contradicts, a fistulotomy is not performed and a seton is placed. This, however, does not exclude the possibility that some of the fistulotomies were performed in patients that had a HPF, making the risk of postoperative incontinence significantly higher. Besides, about half of the patients did not have a preoperative MRI and the surgeon had to rely on operative findings.
As previously described, we unfortunately miss the data on vaginal delivery status for our female patients. It is known that this can negatively affect sphincter function. Unfortunately, we cannot say if this influenced our postoperative results.
Another factor that has to be taken into account is the pre- and postoperative bowel function, specifically for the patients with CD, because irritable bowel with frequent diarrhea may also affect the continence status. However, the number of patients, both pre- and postoperatively, with these symptoms was limited to only a couple. The high level of postoperative continence issues can therefore not contribute to this.
Although we found a major incontinence in 28.0% of the patients, quality of life was not significantly different from the general population. Long-term postfistulotomy quality of life is more likely affected by more recent life-events in stead of a limited surgical procedure years ago.[26] We performed a long-term quality of life survey to assess the current health status of our patients. However, after assessing the results, the usefulness of these quality of life results can be discussed. Either patients are satisfied with their quality of life regardless of their continence status or the quality of life questionnaire is not the right instrument to use.
A limitation of this study was the retrospective design. Due to this design, pre- versus postoperative comparison of secondary outcomes was not possible. Another limitation was the use of telephone interviews to assess long-term follow-up, which may have resulted in bias and maybe missed recurrences.
Fistulotomy is still considered to be the golden standard for the treatment of LPF. However, incontinence rates may be higher than we expected. The amount of sphincter involved by the fistula might be underestimated during operation. Therefore, we believe that it is important to lower the chance of anal sphincter dysfunction as much

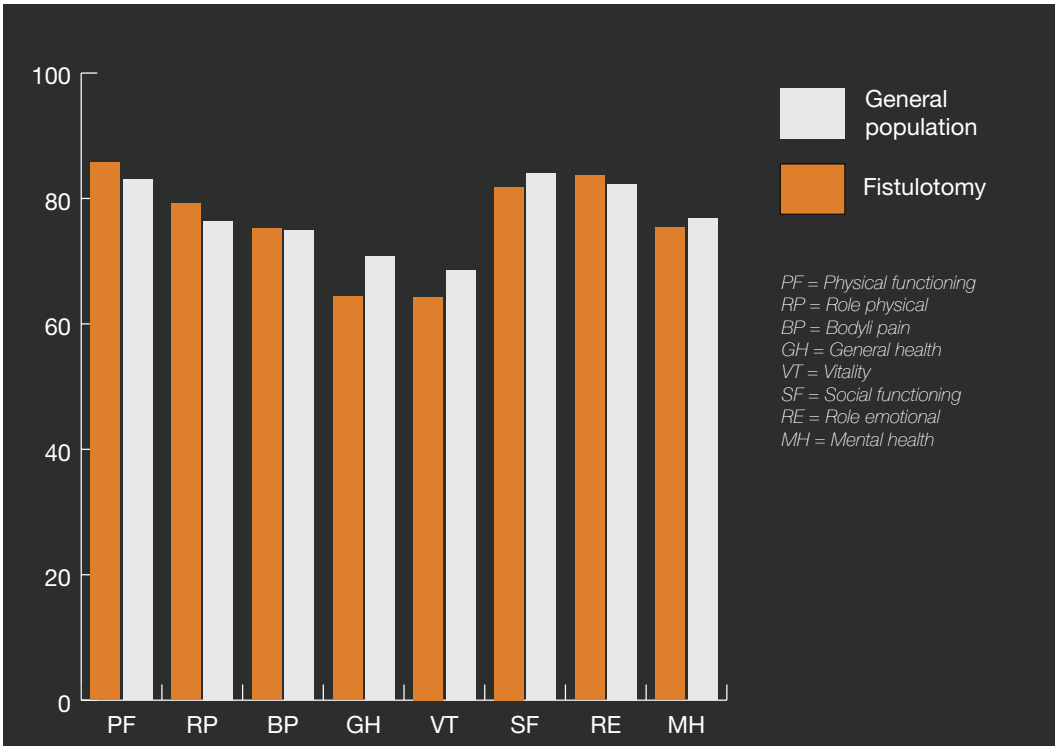

Figure 2 - Outcome SF-36 questionnaire

as possible. Patients should be optimized for the operation to lower the chance of a needed reoperation. Active Crohn's disease needs to be treated first. Besides, patients should be encouraged to stop smoking, since we know smoking influences wound healing,[27] although contradictory results are found for the influence of smoking on the healing of PF.[11, 28]

Preoperative imaging, either using MRI or (endoanal) ultrasound, of the fistula tract might be useful to determine the amount of sphincter muscle involved. This could be advantageous during preoperative planning. Because we know that the higher the internal fistula opening is located, and the more sphincter muscle is involved, the higher the risk of postoperative incontinence. In cases of a relatively high internal opening and large involvement of sphincter muscle, it could be better to change tactics and choose an operative technique that is developed for HPF. However, there is no data supporting this statement.

Conclusion

Fistulotomy seems to be a reasonably good treatment for LPF with a healing rate of 0.81 (95%-CI: 0.71-0.85) after 5 years, and a minimal effect on continence status (Mean Vaizey-score 4.67). However, major incontinence is still reported in 28.0% of patients. Although this rate might be an overestimation on influence in daily functioning, these levels of incontinence are disturbing for a small procedure regarded to be the golden standard for LPF. While many new techniques are being developed for HPF, the development of new LPF treatments is lagging behind when this could lower major incontinence levels.

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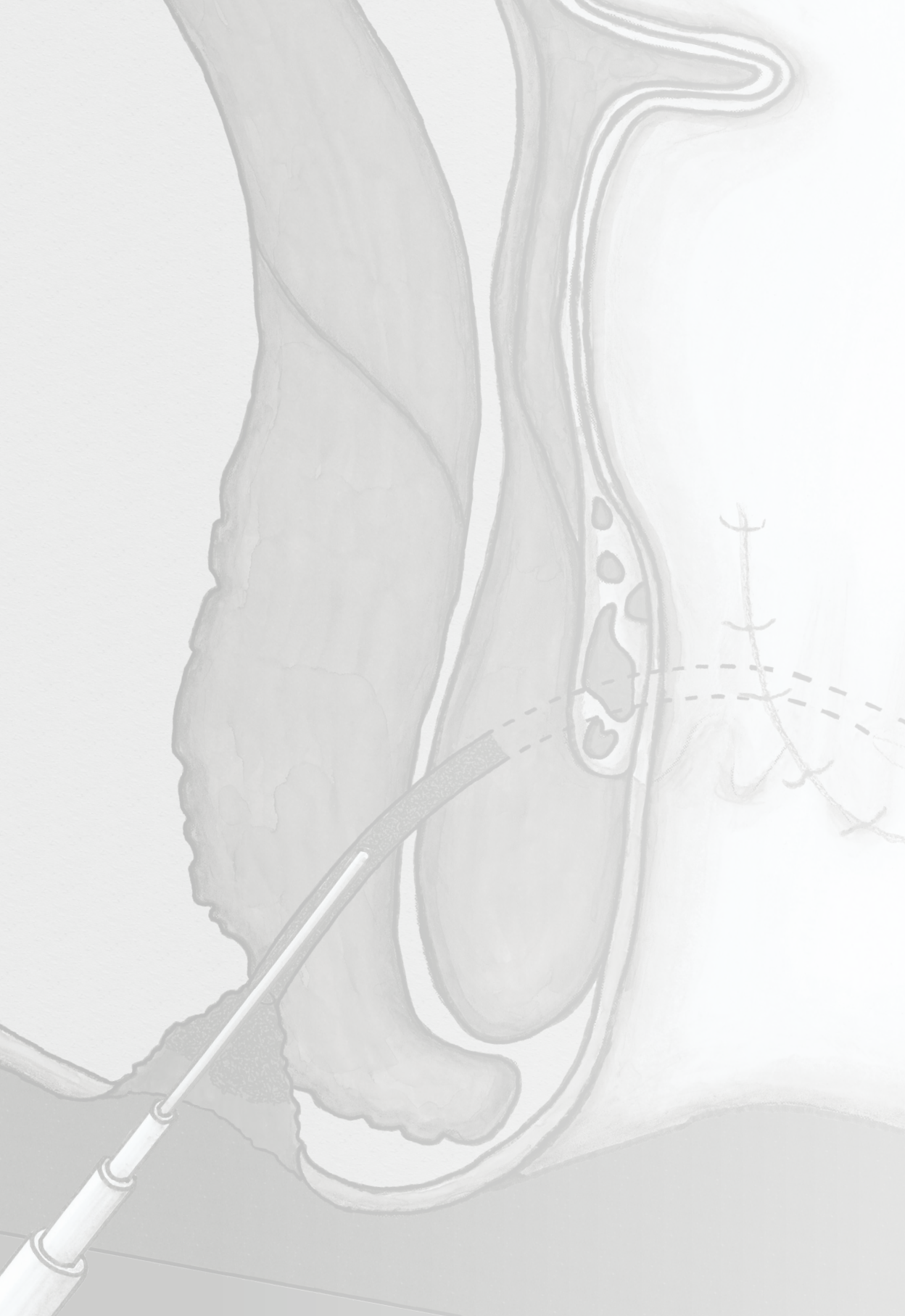

3 Systematic review and meta-analysis of surgical interventions for high cryptoglandular perianal fistula

K.W.A. Göttgens, R.R. Smeets, L.P.S. Stassen, G.L. Beets, S.O. Breukink

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Abstract

Purpose

Perianal fistulas, and specifically high perianal fistulas remain a surgical treatment challenge. Many techniques have, and still are, being developed to improve outcome after surgery. A systematic review and meta-analysis was performed for surgical treatments for high cryptoglandular perianal fistulas.

Methods

Medline (Pubmed, Ovid), Embase and The Cochrane Library databases were searched for relevant randomized controlled trials on surgical treatments for high cryptoglandular perianal fistulas. Two independent reviewers selected articles for inclusion based on title, abstract and outcomes described. The main outcome measurement was the recurrence/healing rate. Secondary outcomes were continence status, quality of life and complications.

Results

The number of randomized trials available was low. Fourteen studies could be included in the review. A meta-analysis could only be performed for the mucosa advancement flap versus the fistula plug, and did not show a result in favour of either technique in recurrence or complication rate. The mucosa advancement flap was the most investigated technique, but did not show an advantage over any other technique. Other techniques identified in randomized studies were seton treatment, medicated seton treatment, fibrin glue, autologous stem cells, island flap anoplasty, rectal wall advancement flap, ligation of intersphincteric fistula tract, sphincter reconstruction, sphincter preserving seton and techniques combined with antibiotics. None of these techniques seem superior to each other.

Conclusions

The best surgical treatment for high cryptoglandular perianal fistulas could not be identified. More randomized controlled trials are needed to find the best treatment. The mucosa advancement flap is the most investigated technique available.

Introduction

Perianal fistulas are a common disorder, estimated to occur in 12.3 per 100.000 men and 8.6 per 100.000 women.[1] In general, the types of perianal fistulas that are known are cryptoglandular fistulas (about 90-95% of perianal fistulas), fistulas related to Crohn's disease (about 1.5%) and traumatic fistulas (about 3.5%).[1] A classification of fistulas was first published by Parks and colleagues, describing the course of the fistula tract (Fig. 1).[2] Nowadays, it is also accepted to classify perianal fistulas in low and high fistulas (Fig. 1). Low fistulas involve only the distal third part of the anal sphincter complex. High fistulas involve the middle and/or upper third part of the sphincter complex.

Treatment for low perianal fistulas usually consists of a fistulotomy (Fig. 2), resulting in closure rates ranging between 80 and 100%.[3-5] Best treatment for a high fistula has not been identified yet. In the last two decades, and even in the last five years, many new techniques have been developed for the treatment of these fistulas. The mucosal advancement flap (MAF) is one of the best-known and oldest techniques (Fig. 3) and results in long-term closure rates between 0 and 75%.[4, 6-8] In the early 1990s fibrin glue (FG) was introduced as a new technique (Fig. 4) to improve long-term closure rates.[9, 10] Anal fistula plugs (FP) were introduced in 2006 and thoroughly investigated in the years after (Fig. 5).[11]

In 2007 Rojanasakul introduced the Ligation of Intersphincteric Fistula Tract (LIFT),[12] which was thought to be a breakthrough in the treatment of perianal fistulas (Fig. 6). However, recently the first study comparing MAF versus LIFT showed comparable results between the two techniques with merely 60% closure.[13] In 2009 the first study using stem cells (SC) was published (Fig. 4),[14] and many studies are still investigating this recent technique. In 2011 an endoscopic technique and a technique using a laser probe were introduced (Fig. 7 and 8).[15, 16] In 2014 Göttgens et al. published an article describing a combination of the MAF with platelet-rich plasma (PRP) resulting in long-term closure rates of 83% (Fig. 4).[17] Currently, a randomized trial is investigating this technique further.

Besides the type of fistula, the aetiology of the fistula is also important because different treatments may be needed. Fistulas related to Crohn's disease are associated with higher recurrence rates and are often treated differently compared to cryptoglandular fistulas. The most occurring fistulas are related to cryptoglandular disease.

As shown, several new techniques have been introduced recently for the closure of high perianal fistulas, but the best technique has not been identified yet. Goal of this study was to perform a systematic review and meta-analysis of all available surgical techniques identifying the superior technique for closure of high cryptoglandular perianal fistulas (HCPF).

Materials and methods

This study was performed according to methodology of the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) group.[18] Besides, the Cochrane Collaboration's tool for assessing risk of bias was used. This review was registered on PROSPERO (CRD42013004570).

Study selection

Searches were performed in Medline (Pubmed and Ovid), Embase (Ovid) and the Cochrane library database for all relevant articles comparing surgical treatments of

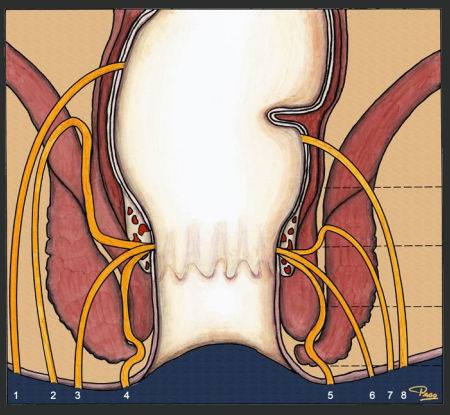

Figure 1 - The Park's classification and the High/Low classification

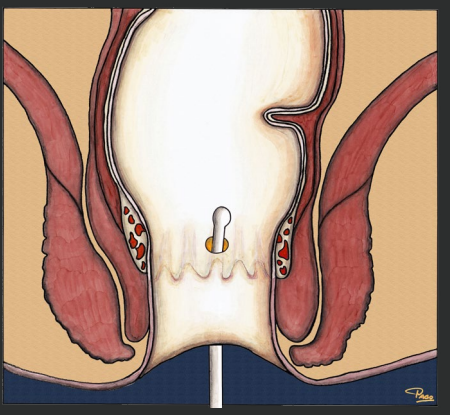

Figure 2a - Fistulotomy for low perianal fistula

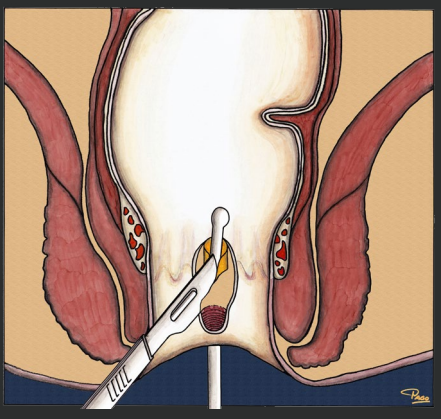

Figure 2b - Fistulotomy for low perianal fistula

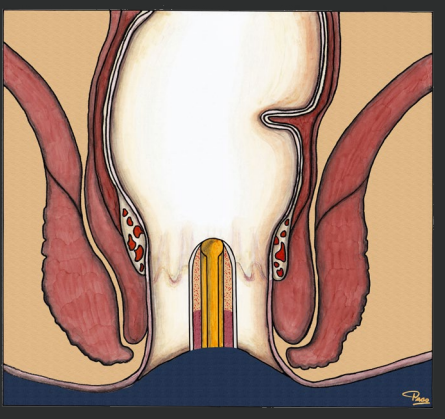

Figure 2c - Fistulotomy for low perianal fistula

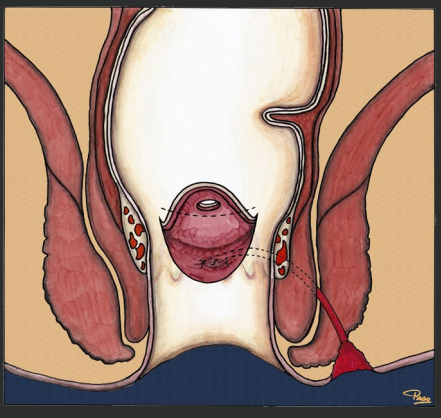

Figure 3a - Mucosa advancement flap

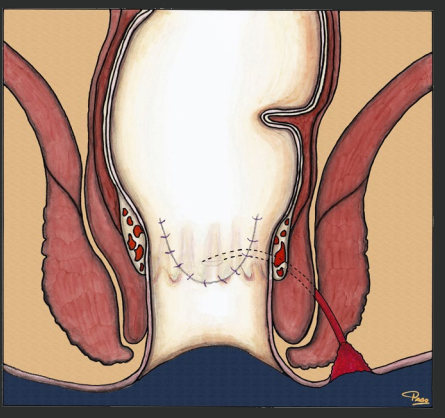

Figure 3b - Mucosa advancement flap

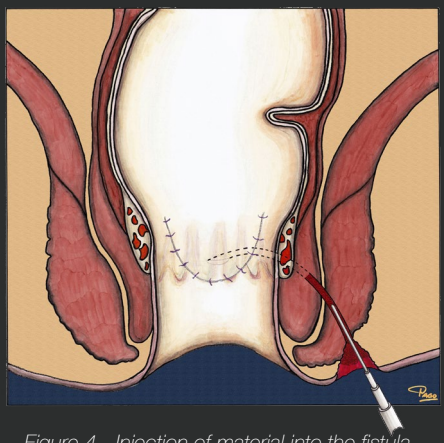

Figure 4 - Injection of material into the fistula tracts

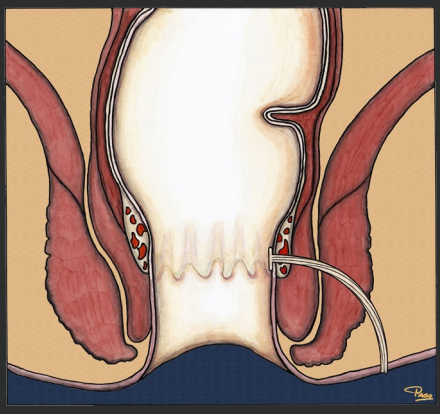

Figure 5 - Anal fistula plug

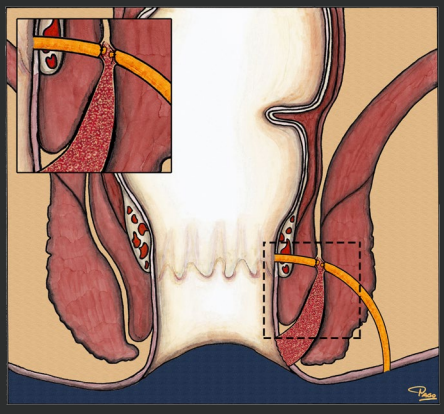

Figure 6 - Ligation of Intersphincteric Fistula Tract

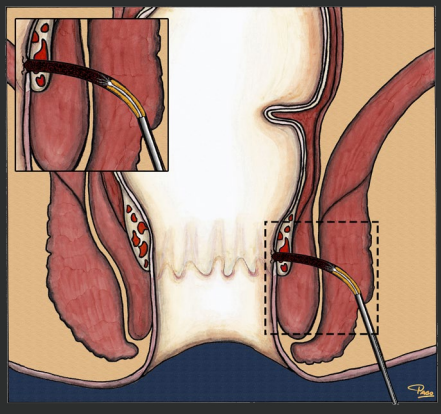

Figure 7 - Video-Assisted Anal Fistula Treatment

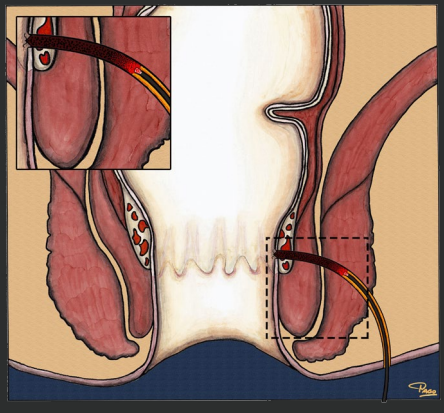

Figure 8 - Laser ablation

Figure 1: Intersphincteric (1); Transsphincteric (2); Suprasphincteric (3); Extrasphincteric (4); Low (5); High (6-8)
Figure 2a: Probing of the fistula
Figure 2b: Starting the fistulotomy and splitting small a amount of sphincter muscle
Figure 2c: Finished fistulotomy
Figure 3a: Fistulectomy up to the sphincter muscle (1); Debriding of the fistula tract (2); Preparing the flap with excision of internal fistula opening (3); Closure of internal opening (4)
Figure 3b: Re-fixation of the mucosa advancement flap
Figure 4: Injection of PRP, fibrin glue or stem cells after mucosa advancement flap
Figure 6: Intersphincteric access with fistula ligation
Figure 7: Insertion of endoscope with electro-coagulation of the fistula tract

HCPF. No language or date limits were instituted. Relevant surgical techniques were: Fistulectomy, MAF, rectal wall advancement flaps (Fig. 9), seton treatment (ST) (Fig. 10), SC, FG, FP, LIFT, PRP, endoscopic techniques, laser probe techniques, radiofrequency techniques and combinations or variations of these techniques.
Two independent reviewers reviewed citations and abstracts and made a selection of articles. Differences in article selection were discussed and a final decision made afterwards. References in articles were searched for other relevant literature. The final search was performed on November 11, 2013.

Inclusion criteria

Only randomized controlled clinical trials (RCT) were eligible for inclusion. The trials had to compare two or more surgical techniques for the closure of HCPF.

Exclusion criteria

Studies only involving patients with other types of perianal fistulas (low fistulas, related to Crohn's disease, traumatic) were excluded. Studies reporting on several types of fistulas were included, but data on these other types of fistulas were not used. Studies were excluded if no outcomes of interest were reported, or if insufficient data were published to extract the necessary data. Studies involving children were excluded.

Outcomes

The primary outcome was the recurrence rate. Secondary outcomes included continence level, quality of life and complications. Complications included: abscess formation, bleeding, urinary tract infections and re-operations.

Data extraction

Two reviewers independently extracted data from the selected articles on predefined forms. Data included name of the authors, year of publication, study design, characteristics of the patient population, characteristics of the included fistula type(s), in- and exclusion criteria, number of patients, and all data related to the defined outcomes.

Study quality

Two reviewers independently assessed the risk of bias in all selected studies. The Cochrane Collaboration's tool for assessing risk of bias was used. Studies were classified as having low risk of bias, high risk of bias and unclear risk of bias. Any disagreement between reviewers was solved by consensus.

Statistical analysis

The standard mean difference (SMD) was calculated as the summary statistic for continuous variables and odds ratios (OR) were calculated for dichotomous outcomes. The meaning of results was described for the different analyses. For p values <0.05, statistical significance was assumed only if the 95 % confidence intervals did not include the value 1 for OR or the value 0 for SMD. Between-study heterogeneity was assessed using the χ^2 and I^2 statistics. A fixed-effects meta-analysis was performed if study homogeneity was confirmed, and a random-effects meta-analysis if significant

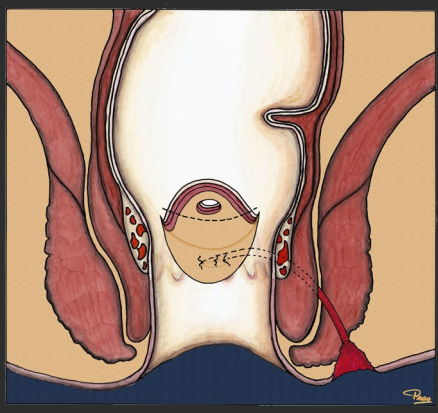

Figure 9a - Rectal wall advancement flap

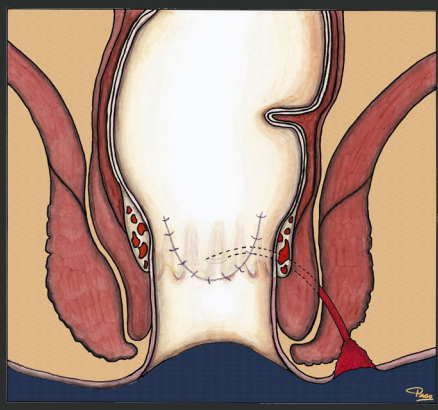

Figure 9b - Rectal wall advancement flap

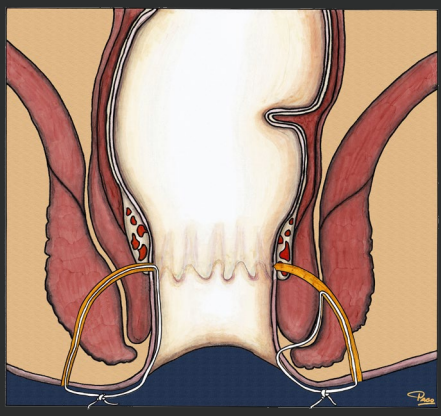

Figure 10 - Seton treatment

Figure 9a: Technique equal to mucosa advancement flap, except for the creation of full rectal wall advancement flap
Figure 9b: Re-fixation of the rectal wall advancement flap
Figure 10: Standard seton treatment (1); Internal sphincter preserving seton with creation of new intersphincteric tract (2)

heterogeneity was found.
Review Manager (RevMan) 5.27 (The Nordic Cochrane Center, Copenhagen, Denmark) was used for the statistical analyses.

Results

In total 111 publications were found in the initial search. Finally 14 publications fulfilled the inclusion criteria and were included in this review. Figure 11 shows the flow diagram of study selection. The two most occurring reasons for excluding a study were Non-RCT studies and studies not investigating HCPF.
Table 1 shows the included studies and techniques.

Fistula plug versus mucosa advancement flap

Three RCTs were identified comparing FP and MAF.[19-21] Risk of bias was defined as

low for all three studies as is shown in Fig. 12. The same FPs were used in all studies and the technique of creating a MAF was comparable. Thus, a meta-analysis was performed for the primary outcome measure. The forest plot can be seen in Fig. 13. The random-effects model was used, which did not show an advantage for either technique concerning recurrence rate with an Odds ratio of 1.7 (95% CI 0.12 – 23.41), p=0.69.
Regarding the secondary outcomes comparison using a meta-analysis was only possible for the complication rate. A fixed-effects model was used for this outcome, which did not show an advantage for either technique (Fig. 14) with an Odds ratio of 0.32 (95% CI 0.08 – 1.21), p=0.09.
Continence levels were objectified pre- and postoperatively using the Vaizey scale in two studies;[20, 21] however, for one study the results are not extractable.[20] Both studies do not report a significant difference in continence levels between the techniques. The third study does not report on continence status.
Only two studies report on quality of life.[20, 21] Both use a different questionnaire (respectively the Life quality scale system and the SF-36 questionnaire) and do not show a difference in quality of life between techniques.

Seton treatment versus fibrin glue

Only one RCT was identified comparing ST (n=25) and FG (n=39).[22] Risk of bias in this study was regarded as low. Duration and type of ST was not clearly described. They used a cutting or a loose latex seton. They show a significant advantage of the ST over FG in recurrence rate with respectively 12.5 and 62.0% recurrence, p<0.05.
Complication rate and quality of life are not measured in this study. Continence status was pre- and postoperatively objectified using the Wexner continence score. Pre-operatively, no significant difference was seen between both groups, but postoperatively, a significant rise in the incontinence score was seen in the ST group. The mean score was 5.1 in the ST group and 0.49 in the FG group, p<0.05, postoperatively.

Advancement flap versus advancement flap + fibrin glue

Ellis et al. report on their RCT comparing an advancement flap (n=30) with an advancement flap + FG (n=28).[23] This study was classified as low risk of bias (Fig. 12). Advancement flaps were either a MAF or an anodermal advancement flap depending on previous treatment failure or technical difficulty. This study only reports on recurrence rates and does not mention any secondary outcomes. Recurrence rates are not reported separately for primary and recurring fistulas.
A recurrence rate of 20.0% was seen for the advancement flap group compared to 46.4% for the advancement flap combined with FG, p<0.05. A sub-group analysis showed no significant difference between the types of advancement flap used.

Mucosa advancement flap versus mucosa advancement flap + gentamicin

One study was found comparing the MAF (n=41) and the MAF with a gentamicin collagen sponge (n=42) placed under the advancement flap.[24] The risk of bias in this study was estimated to be low (Fig. 12). The recurrence rate for the patients receiving the gentamicin sponge compared to the MAF alone was 38.1 and 48.8% respectively, not significantly different.
No secondary outcomes are reported in this study.

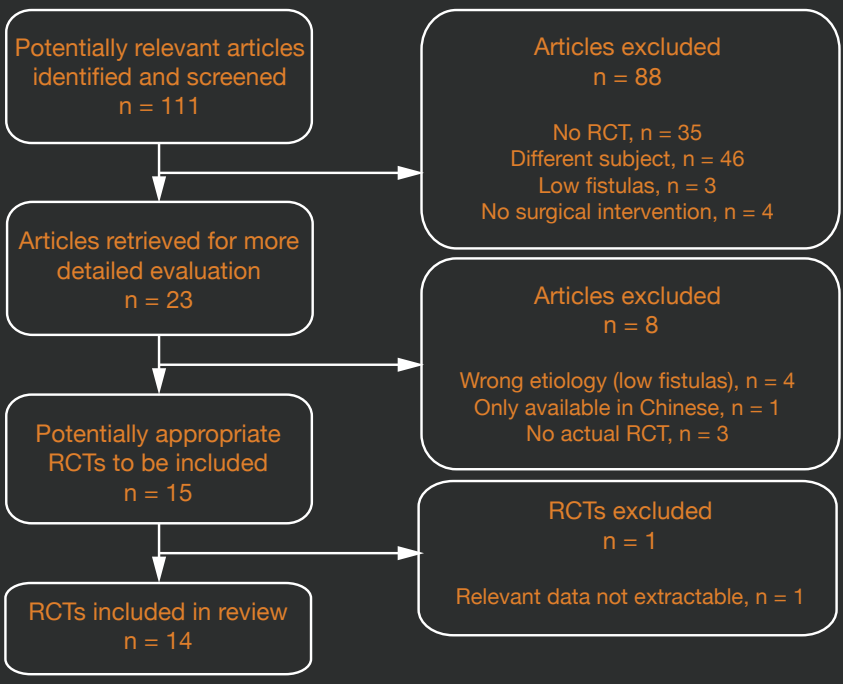

Figure 11 - Flow diagram of study selection

Autologus stem cells versus autologus stem cells + fibrin glue versus fibrin glue + placebo

We identified one study investigating ASC for the treatment of HCPF.[25] It was a phase III RCT investigating safety of ASC treatment. This study had three arms: ASC injection into the fistula (n=64) was compared to ASC injection combined with FG injection (n=60) and also with FG injection combined with a placebo (n=59). All fistula tracts were identified and curetted, and the internal fistula opening was closed before injections. The quality of this study was high and it was classified as having a low risk of bias (Fig. 12). No significant differences were seen in recurrence rates with respectively, 57.1%, 52.4% and 37.3% healing after one year, p=0.13.
Secondary outcomes reported were continence levels and quality of life, respectively measured using the Wexner incontinence score and the SF-36. No significant differences in these outcomes were seen between groups and between pre- and postoperatively.

Island flap anoplasty versus seton treatment

The island flap anoplasty involves a cutaneous advancement flap into the rectum (Fig. 15). There was only one RCT found describing this technique.[26] The authors compared it to ST. Risk of bias in this study was deemed high (Fig. 12). They included only 2 patients in both groups with HCPF. All other included patients had LCPF and were not treated with ST, but with a fistulotomy. Due to the poor quality and very low number of patients the recurrence rates of 0% in both groups are not reliable. Data regarding the secondary outcomes quality of life and continence status were not extractable.

Table 1 - Included studies with primary outcome

Author	Year	Techniques compared			Number of patients			Recurrence rate (n (%))			Follow-up duration	
A Ba-bai-ke-re[20]	2010	FP	MAF		45	45		2 (4.4)	13 (28.9)		6 months	
Altomare[22]	2010	ST	FG		25	39		3 (12.0)	23 (59.0)		1 year	
Ellis[23]	2006	AF + FG	AF		28	30		13 (46.4)	6 (10.0)		22 months	
Gustafsson[24]	2006	MAF	MAF + gentamicin		41	42		20 (48.8)	16 (38.1)		1 year	
Herreros[25]	2012	ASC	ASC + FG	FG + placebo	64	60	59	37(57.8)	36 (60.0)	36 (61.0)	26 weeks	
Ho[26]	2005	IFA	ST		2	2		0	0		63 weeks	
ICMR[27]	1991	Kashaarasootra seton	Fistulectomy		40	33		28 (70.0)	26 (78.8)		1 year	
Khafagy[28]	2010	RWA	MAF		20	20		2 (10.0)	8 (40.0)		1 year	
Mushaya[29]	2012	LIFT	MAF		25	14		2 (8.0)	1 (4.0)		16.4 months	30.0 months
Ortiz[19]	2009	FP	MAF		16	16		12 (75.0)	2 (12.5)		1 year	
Perez[30]	2006	MAF	Fistulotomy + SR		27	28		2 (7.4)	2 (7,1)		3 years	
Singer[31]	2005	FG + AB	FG + surgical closure	FG + AB + surgical closure	23	23	22	18 (78.3)	13 (56.5)	14 (60.9)	27 months	
Van Koperen[21]	2011	FP	MAF		31	29		22 (71.0)	15 (51.7)		11 months	
Zbar[32]	2003	SPS	ST		18	16		2 (11.1)	1 (6.3)		12 months	

FP: Fistula plug; MAF: Mucosal advancement flap; ST: Seton treatment; FG: Fibrin glue; AF: Advancement flap (Anodermal flap or MAF); ASC: Autologous stem cells; IFA: Island flap anoplasty; RWA: Rectal wall advancement flap; LIFT: Ligation of intersphincteric fistula tract; SR: Sphincter reconstruction; AB: Antibiotics; SPS: Sphincter-preserving seton

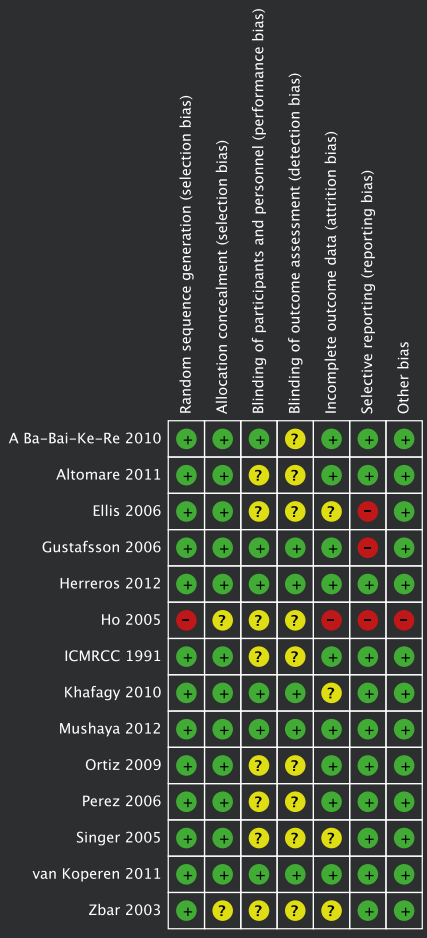

Figure 12 - Risk of bias table

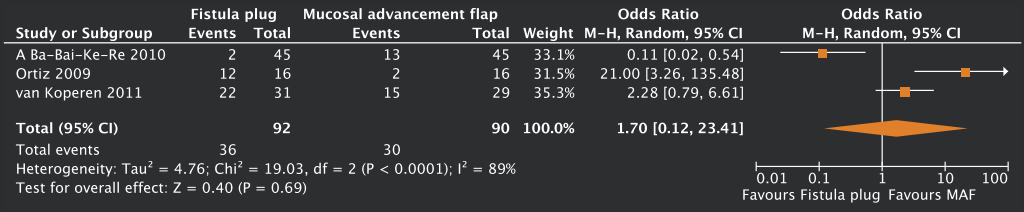

Figure 13 - Forest plot Fistula plug versus Mucosa advancement flap - Recurrence

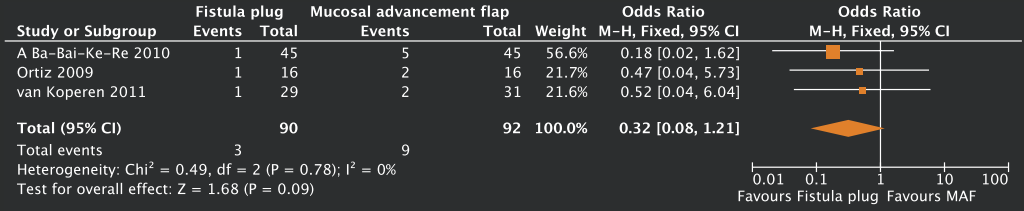

Figure 14 - Forest plot Fistula plug versus Mucosa advancement flap - Complications

Kashaarasootra seton versus fistulectomy

A study performed by a collaboration of surgical centres in India was found comparing fistulectomy against a seton coated with Ayurvedic (called a Kshaarasootra seton).[27] The fistulectomy was performed for the tract below the anal sphincter complex (Fig. 3). The upper part of the tract was curetted. Ayurvedic is a combination of several vegetal materials and is as far as we know only used in India. The seton was changed regularly in the outpatient clinic and eventually removed. It was a well-organized and well-performed study with a low risk of bias (Fig. 12). They included 40 HCPF in the Ayurvedic group and 33 in the fistulectomy group. The closure rates are poor with recurrence rates of 70.0 and 78.8% respectively, but not significantly different between the two procedures. Levels of incontinence were described to be low, but no standardized questionnaires were used.

Rectal wall advancement flap versus mucosa advancement flap

The rectal wall advancement flap (RWA) (n=20) is compared to the MAF (n=20) in only one study.[28] The RWA included mucosa, submucosa and the circular muscle layers, while the MAF did not include the muscle layers. Risk of bias in this study was low. The authors found a significant higher success rate in the RWA group with a recurrence rate of 10.0 versus 40.0% in the MAF group, $p<0.05$. The level of incontinence was higher in the RWA group, 10% compared to 0%, but this was not significantly different. The complication rate was higher in the MAF group. The complications were mostly disruption of the advancement flap and occurred in 30% in the MAF group and in 5% in the RWA group, $p<0.05$. Quality of life is not reported.

Ligation of intersphincteric fistula tract versus mucosa advancement flap

The LIFT is a relatively new technique for treatment of HCPF. We found only one RCT involving the LIFT,[29] which compared the technique to the MAF. All patients were treated with ST first for 6 months to reduce sepsis. Risk of bias was low (Fig. 12). However, the number of patients included in the trial was small with 25 patients in the LIFT group and 14 in the MAF group, and follow-up was much shorter for the LIFT group (16.4 months versus 30.0 months, respectively). No significant differences were seen for recurrence rates, with 8.0 and 4.0% recurrence respectively. The Wexner incontinence score was used to evaluate continence status. No differences were seen for pre- and postoperative continence, nor were differences found between both groups. Complication rates were not significantly different for the techniques. Quality of life was not measured. The only differences the investigators found between both groups were a higher satisfaction rate, a lower postoperative pain score and shorter time to resuming normal activities after the LIFT.

Mucosa advancement flap versus fistulotomy + sphincter reconstruction

Perez et. al. compare the MAF against a fistulotomy with sphincter reconstruction (FSR) (Fig.16).[30] They included 27 patients in the MAF group and 28 patients in the FSR group. Risk of bias was defined as low (Fig. 12). Recurrence rates were 7.4 and 7.1% respectively, not significantly different. Continence levels were measured using the Wexner incontinence score, which did not show significant differences in continence status pre- and postoperatively or between both interventions. The authors specifically reported incontinence in previously fully continent patients, which was 9.5 versus 17.4%, $p=0.26$. Complication rates were not different between both techniques. Quality of life was not measured.

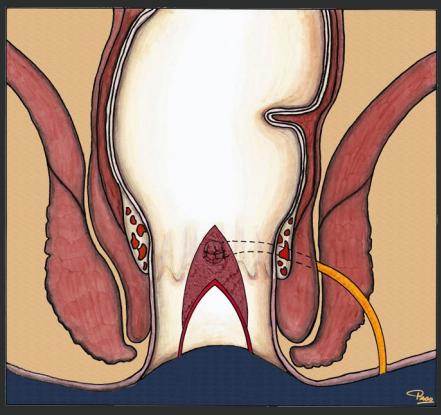

Figure 15a - Island flap anoplasty

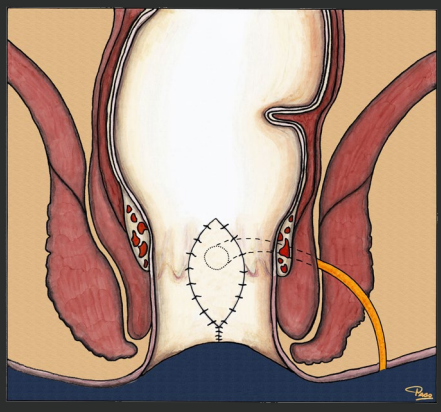

Figure 15b - Island flap anoplasty

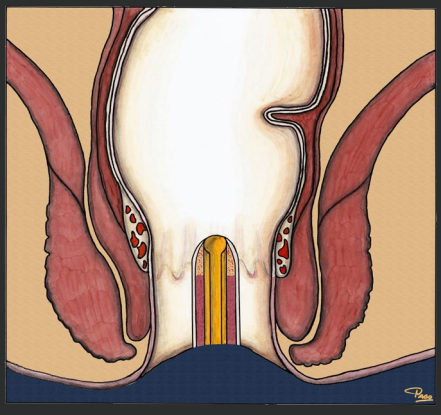

Figure 16a - Fistulotomy with sphincter reconstruction

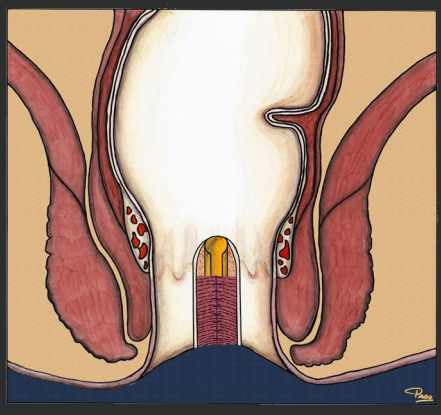

Figure 16b - Fistulotomy with sphincter reconstruction

Figure 15a: Creation of skin flap and excision of mucosa with closure of internal fistula opening
Figure 15b: Re-fixation of created flap
Figure 16a: Fistulotomy with large amount of split sphincter muscle
Figure 16b: Reconstruction of sphincter muscle

Fibrin glue + antibiotics versus fibrin glue + surgical closure versus fibrin glue + antiobitiocs + surgical closure

We found one study comparing different treatments with FG.[31] Patients were randomized into three groups: FG + antibiotics (n=23), FG + surgical closure (n=23) and FG + antibiotics + surgical closure (n=22). Surgical closure was defined as placing one suture over the internal fistula opening. The antibiotic used was Cefoxitin. Risk of bias in this study was low (Fig. 12). Recurrence rates in all groups were high, with 78.3, 56.5 and 60.9%, p=0.38. Complication rates were not different and no changes in continence status were observed (although no standardized score was used). Quality of life was not reported.

Sphincter-preserving seton versus seton treatment

Zbar et al. report on their technique with a sphincter-preserving seton (SPS) (Fig. 10).[32] They compare this technique with conventional ST. The SPS procedure is described as performing a MAF with closure of the internal opening and then dissecting an intersphincteric tract for the seton without injuring the internal anal sphincter. Eighteen patients were treated with the SPS and 16 with the ST. The recurrence rate was 11.1% and 6.3% respectively, not significantly different. No differences were found in pre- and postoperative continence levels and neither were differences found between both groups. Quality of life was not reported and complication rates were not significantly different between both procedures.

Discussion

A relatively low number of RCTs investigating surgical procedures for closure of HCPF were identified making it difficult to compare all available techniques. Only two techniques could be compared in a meta-analysis: the FP and the MAF. This meta-analysis did not show a difference in recurrence rate nor in complication rate. Continence levels and quality of life were not different between both techniques, but not comparable using a meta-analysis because of different measurement tools. However, the three RCTs that were compared in this meta-analysis showed significant heterogeneity in inclusion criteria, methodology, and postoperative management. One study included all HCPF,[19] another only transsphincteric fistula,[21] and the third both transsphincteric and intersphincteric fistulas.[20] A single study mentioned inclusion of patients from 12 years old up to only 60 years old.[20] Only one of the studies was a blinded study,[21] Regarding postoperative management one study used intravenous antibiotics for three days postoperatively instead of only prophylactic preoperative antibiotics, and the same study required sitting baths and mandatory laxatives for a significant period.[20] These differences make the result of this meta-analysis less convincing, especially taking into account that many non-randomized studies show far less favourable results for the FP.[33]

For all other techniques only one RCT could be found making it impossible to perform meta-analyses. Most available randomized studies on surgical treatment of HCPF investigate the MAF, making this technique the best investigated surgical procedure for this disease. The results of these studies do not show an advantage of the MAF over other techniques. The MAF is still the most used technique for treatment of HCPF, and most (colorectal) surgeons are well familiar with this procedure. The technique is widely adopted, and could probably still be considered the golden standard for HCPF treatment. Newer techniques like the LIFT are gaining followers and might show advantages over the MAF in the future. Up to now, there is no high level evidence favouring any surgical technique over the others.

The main limitation of our systematic review is the limited number of RCTs that could be included. This makes it difficult to identify the best technique available to close HCPF. Newer techniques, for instance video-assisted anal fistula treatment or closure with a laser probe, have not yet been investigated widely and results should be awaited in the future.[15, 16]

As far as we are aware of, there is only one other systematic review and meta-analysis comparing all available surgical interventions for PF.[34] This study does not focus specifically on HCPF or even HPF and was updated last in 2010. It seems that currently there is not much more high-quality data available compared to then, resulting in comparable findings.

However, other review articles were published in the last years, most focussing on one of the available techniques.[7, 33, 35-37] These reviews show reasonable results for healing and recurrence. The main difference with our study and the mentioned review from 2010 being that all other reviews include non-randomized and non-comparative studies. The level of evidence in these reviews is obviously less high compared to a systematic review only including randomized controlled trials. Whether our purist approach is best in this case remains questionable. We were not able to shed light on the best technique for HCPF. It would perhaps be more useful, but with less high-level evidence, to systematically show all available data on the surgical techniques and let these numbers guide us in the right direction. If no clear winner would arise from a comparison like this, it could show us which techniques would be best studied in a comparative randomized controlled trial based on available results.

Conclusion

We were not able to identify the best surgical technique for HCPF due to the many techniques available and the low number of RCTs. More RCTs are needed to show us the information we are seeking to define a best-treatment algorithm for HCPF. The MAF is the most investigated and most used technique. Whether or not the MAF is the best technique to use in the treatment of HCPF remains unclear until more comparative studies are available.

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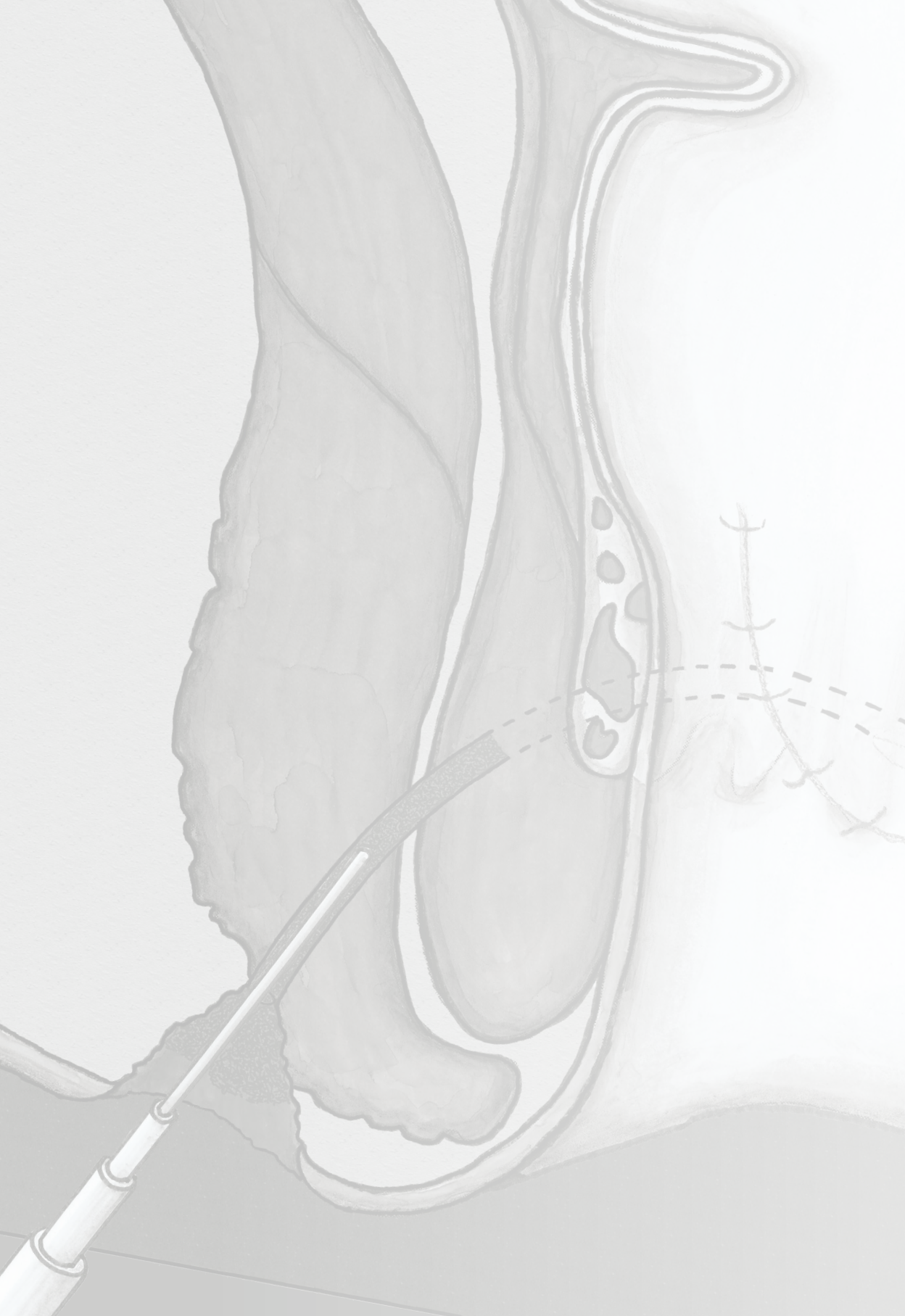

4 Long-term results of mucosal advancement flap combined with platelet-rich plasma for high cryptoglandular perianal fistulas

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Abstract

Background

The long-term closure rate of high perianal fistulas after surgical treatment remains disappointing.

Objective

The goal of this study was improving the long-term closure rate of high cryptoglandular perianal fistulas combining mucosal advancement flap with platelet-rich plasma.

Design

This study was retrospective in design.

Setting

This study was conducted at two secondary and one tertiary referral hospitals.

Patients

Patients presenting with high cryptoglandular perianal fistulas involving the middle/upper third of the anal sphincter complex were included.

Interventions

A staged surgical treatment was performed; After seton placement a mucosal advancement flap was combined with platelet rich plasma.

Main Outcome Measures

Recurrence was the main outcome, incontinence the secondary outcome.

Results

We operated 25 patients between 2006 and 2012. Thirteen (52%) patients had previous fistula surgery. The median follow-up period was 27 months. One patient (4.0%) was lost to follow-up after four months. Freedom from recurrence at two years was 0.83 (95% CI 0.62 – 0.93). Two of the four patients with a recurrence (8%), had a repeated treatment and healed. One patient (4.0%) refused another treatment, but agreed to stay in follow-up. One patient (4.0%) requested a colostomy, resulting in closure of the fistula. Complications occurred in 1 patient (4.0%). Incontinence numbers were low with a median Vaizey score of 3.0 out of a maximum of 24.

Limitations

The study was limited by its retrospective design, lack of preoperative incontinence data, selection bias and phone interview follow-up.

Conclusion

The long-term outcome results of patients with primary and recurrent high cryptoglandular perianal fistulas treated with a seton followed by mucosal advancement flap and platelet-rich plasma, show low recurrence, complication and incontinence rates. Therefore, this technique seems to be a valid option as treatment. Larger and preferably randomised controlled studies are needed to further explore this surgical technique.

Introduction

Perianal fistulas can be classified in a simple way as low and high fistulas, depending on the extent of the sphincteric complex that is involved. Low fistulas involve only the lower third part of the sphincteric complex whereas high fistulas involve the middle and/or the upper third part. The classification by Parks et al divides fistulas based on the route of the fistula tract: Transsphincteric, suprasphincteric, intersphincteric and extrasphincteric.[1] Some prefer the simplified classification as low and high fistulas; others prefer the classification by Parks.

With the use of the simplified classification mentioned, low cryptoglandular perianal fistulas (LCPF) are generally easy to treat by a fistulotomy, resulting in a high closure rate of 98%.[2] The definitive closure of high cryptoglandular perianal fistulas (HCPFs) remains a challenge. The staged mucosal advancement flap (MAF) with noncutting seton is one of the developed techniques for closure of HCPF adopted by many colorectal surgeons.[3] Unfortunately the recurrence rate after treatment with a MAF varies widely between 0 and 75%.[4-7] Patients with recurrent fistulas have an even higher recurrence rate, and are at greater risk for continence problems if several MAFs need to be performed. This is most likely caused by either damaging the internal sphincter while making the MAF or the recurrent introduction of an anal spreader.

Van der Hagen et.al describe an operative technique combining a MAF with the injection of platelet-rich plasma (PRP) in the fistula tract, resulting in a closure rate of 90%.[8] PRP is hypothesized to improve wound healing and may therefore also improve closure of perianal fistulas.

This study describes the long-term closure rates and incontinence of patients with primary and recurrent HCPF treated by MAF with PRP and is a continuation of the pilot study by van der Hagen et. al.[8]

Materials and Methods

Between 2006 and 2012, 25 patients with primary and recurrent HCPF, defined as involving the middle or upper third of the anal sphincter complex, were treated with a 2-staged technique. This study consisted of a retrospective analysis of collected data. First a non-cutting seton was inserted. After a minimum of 3 months, the second operation was performed, consisting of a MAF combined with injection of PRP in the external fistula tract. Patients with inflammatory bowel diseases, bleeding disorders, haematological or local malignancies, or who were pregnant were excluded.

Patient characteristics as age, sex and previous operations were also recorded. Magnetic resonance imaging (MRI) was performed in addition to clinical examination to confirm an open high fistula and to classify the route of the tract. Both the surgeon and radiologist carefully examined the MRI. The primary outcome measure was recurrence of the HCPF. The secondary outcome was incontinence.

This study was conducted according to national medical ethical laws and guidelines, and written informed consent was obtained from all patients to allow long-term follow-up in the outpatient clinic.

Procedure

During the first procedure, a seton was placed under general or spinal anaesthesia. At least 3 months after placement of the seton, a second examination under spinal or general anaesthesia, also in the lithotomy position, was performed. Fifty-five millilitres

of whole blood was collected from the patient before transfer to the operating room and PRP was prepared in the meantime, as is described under Platelet-rich plasma preparation. Before the start of anaesthesia, prophylactic intravenous antibiotics were administered according to local hospital protocol. If no more inflammatory activity was present the seton was removed.
The next steps in the procedure were probing the fistula tract, excising the external opening and curetting the complete fistula tract using a sharp spoon and gauze. When the fistula tract was debrided, a MAF was placed over the internal opening. The MAF was performed as follows: A trapezoid-formed mucosal flap was prepared starting just distal from the internal fistula opening. The internal opening in the flap was excised, and the flap positioned distally over the internal opening in the rectum. The flap was secured using absorbable sutures. The prepared PRP was injected in the external opening while the patient was in a slight Trendelenburg position to ensure the PRP stayed in place by using gravity. After some minutes, the PRP had transformed into a clot. Now, the patient was returned to normal supine position because leakage of PRP out of the external fistula opening was minimized.

Platelet-rich plasma preparation

Before the operation, 55 millilitres whole blood is collected into a 60-mL syringe that contains 6mL of sodium citrate. A peripheral complete blood count is also collected at the time of the initial blood draw. The blood is then prepared according to the Gravitational Platelet Separation III (GPS-III) system instructions (Cell Factor Technologies, Biomet, Warsaw, Ind, US). This device is a desktop-size centrifuge with disposable cylinders for the blood. Platelet concentrate is obtained for each patient. Autologous platelet concentrate contains concentrated white blood cells and platelets that are suspended in plasma. Because an acidic anticoagulant is introduced to the whole blood used to produce the platelet concentrate, the platelet concentrate must be buffered to increase the pH to normal physiological levels. This is accomplished with 8.4% sodium bicarbonate solution added at a ratio 0.05mL of sodium bicarbonate solution to 1mL of platelet concentrate. The resulting buffered platelet concentrate contains approximately a 6 to 8 times the concentration of platelets compared with baseline whole blood. The total time from blood draw to injection in the patients is about 30 minutes. No specialized equipment, other than the GPS-III equipment, is required. The thrombin-coated syringe activates the PRP during injection.

Follow-up

Regular outpatient follow-up visits were scheduled for all patients up to 1 year postoperatively. A fistula was considered closed if the symptoms disappeared and the external opening was visually closed. This was further assessed by physical examination with finger compression on the external opening to visualize fluid release from a not clearly visible fistula opening. A MRI scan was ordered if there was doubt about closure of the fistula tract. All patients underwent a telephone interview at the end of this study to check if the fistula was still closed, with the exception of patients still in follow-up at the outpatient clinic. In case of doubt, we invited the patients in the outpatient clinic for a physical examination.
If the fistula was not closed 3 months after the operation, it was considered a treatment failure. A new fistula occurring after a symptom-free period of 3 months was defined as a recurrence.
During the phone call at the end of follow-up or during visits at the outpatient clinic,

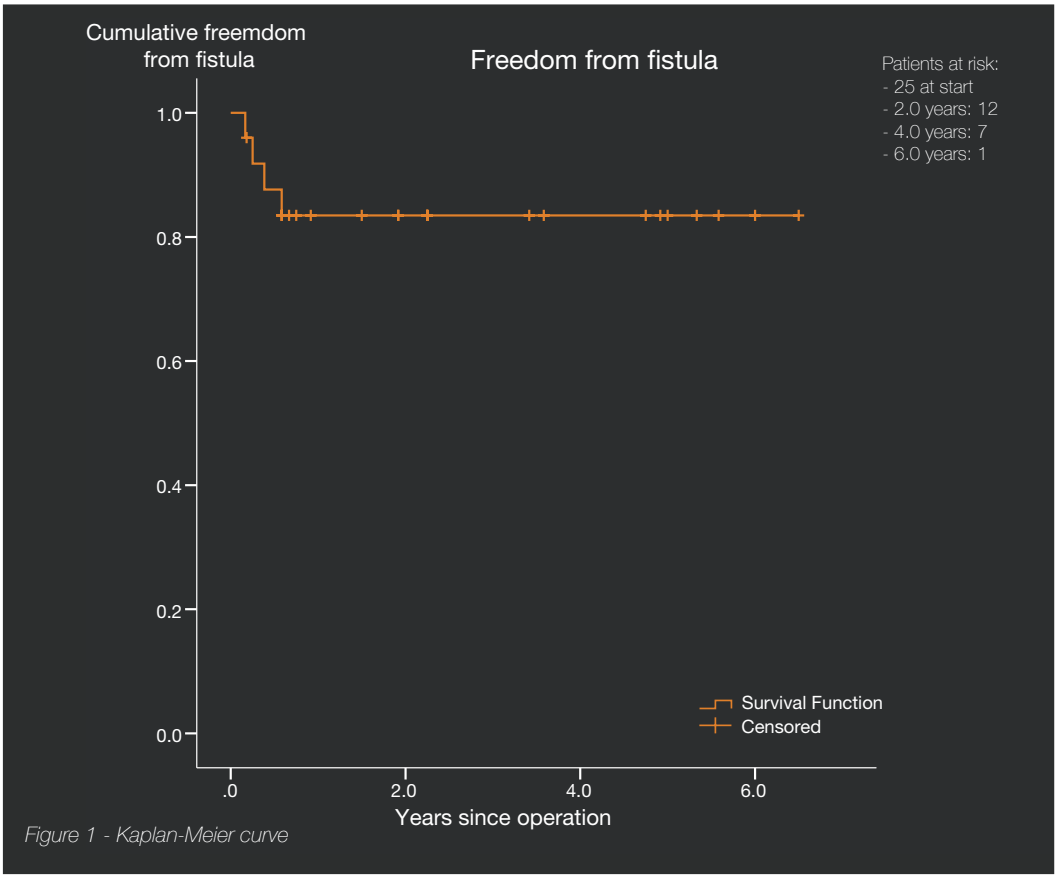

Figure 1 - Kaplan-Meier curve

patients were also asked if they were willing to complete a series of questionnaires about continence. If they agreed, the questionnaire was mailed. Continence was classified by using the Vaizey-score.

Results

Twenty-five patients, of whom 17 (68%) were male, were treated according to protocol. Median age was 49 years, ranging from 23 to 75. The complete patient characteristics are listed in Table 1. One patient was lost to follow-up after 4 months. Median duration of seton placement was 3 months (range, 3-12). All patients underwent an MRI scan preoperatively. All fistulas closed within 3 months after operation. A Kaplan-Meier curve was created to show Freedom of fistula (Figure 1). Freedom from recurrence at 2 years was 0.83 (95% CI, 0.62 – 0.93). In total, 4 recurrences were seen of which 1 had a primary fistula. Median time from operation until recurrence was 115.5 days (range, 66-216). Median follow-up was 27 months (range, 4-77) for all patients and 27 months (range, 8-77) for the patients free from recurrences. Two (8%) of these patients achieved healing after a second identical procedure. One patient (4%) repeatedly developed an abscess in the fistula tract. The abscess and the fistula eventually healed after repeated drainage and a temporary colostomy. One (4%) patient refused further treatment for the recurrence and was lost to follow-up after 4 months of follow-up. No other complications were seen.

One (4%) patient developed a low perianal fistula about 1.5 years after treatment for

Table 1 - Patient characteristics & results

	Value
Male	17 (68%)
Age	49 (23 - 75)
Smokers	5 (20%)
BMI	27.6 (19.1 – 35.3)
Fistula location	Suprasphincteric: 2 (8.0%) Extrasphincteric: 1 (4.0%) Intersphincteric: 3 (12.0%) Transsphincteric: 19 (76%)
Previous operations	None: 12 (48%) One operation: 6 (24%) Two Operations: 3 (12%) > Two operations: 4 (16%)
Duration of seton placement	3 (3 – 12) months
Residual inflammation and prolonged seton placement	0 (0%)
Recurrences	4 (16%)
Primary closure rate	21 (84%)
Secondary closure rate	23 (92%)

Values given as n (%) or as median/mean (range)

Table 2 - Incontinence levels

Vaizey-score	n (%)
0	11 (44)
1-6	10 (40)
>6	4 (16)

Table 3 - Incontinence levels in relation to previous number of operations

Vaizey score	No operations	One operation	Two operations	> Two operations
0	3 (25.0)	4 (66.6)	2 (66.6)	2 (50.0)
1-6	7 (58.3)	1 (16.6)	1 (33.3)	1 (25.0)
>6	2 (16.7)	1 (16.6)	0	1 (25.0)

Values given as n (%)

which a small fistulotomy was performed and the fistula healed. This fistula was also not located in the area of the previous HCPF and was therefore not defined as a recurrence. The response rate to the questionnaire was 88%. The median Vaizey-score was 3 (range, 0-18). Table 2 and 3 show the Vaizey scores. We did not find higher incontinence levels in patients with more previous operations. No preoperative continence data were available.

Discussion

The results of this study combining PRP with the MAF show a low recurrence rate with a freedom from recurrence at two years of 0.83 (95% CI, 0.62 – 0.93). Besides, the postoperative incontinence levels after using this technique are low.
The median follow-up of our study was 27 months, which implicates that long-term results and therefore more reliable recurrence numbers are shown. Besides being a much-used and well-known technique by colorectal surgeons, the MAF is used as the basis of treatment for HCPF, averting a learning curve for surgeons in future

Figure 2 - Showing the clotting of PRP after activation

studies and the already started randomised controlled study. This will hopefully benefit reproducibility of our results.

Unfortunately, this is only a retrospective analysis of a small group. Another limitation of this study is the lack of preoperative data on incontinence prohibiting a comparison of pre- and postoperative incontinence. Besides these limitations, we believe some selection bias might have occurred during the long inclusion period, due to fewer patient referrals from other centres between the years 2008 and 2009. However, during the periods of inclusion, all patients eligible for treatment were included. Finally, telephone interviews are not ideal during follow-up and some complications might have been missed.

Compared to the pilot study by Van der Hagen et al using PRP in addition to MAF for HCPF, the number of patients in this study is higher, the follow-up longer and continence has been assessed.[8] Our success rate confirms the results found before in this study. The Vaizey scores we found are comparable to reported incontinence levels after MAFs as described by Dubsky et al who report a Vaizey-score >6 to be major incontinence.[5] Preoperative continence data were unfortunately not available for comparison.

As stated before, only 1 study is known to combine the MAF with PRP.[8] In this article, the authors describe the success of PRP in other clinical applications, such as maxillofacial,[9] plastic,[10] orthopaedic surgery and spinal fusion and that it has been used for the treatment of chronic wounds and ulcers.[11-14] Platelet-released factors have been used to treat wounds since 1985. PRP contains numerous growth factors that promote healing by attracting undifferentiated cells in the newly formed matrix and triggering cell division. PRP may suppress cytokine release and limit inflammation and interacts with macrophages to improve tissue healing and regeneration.[15, 16] It also promotes

new capillary growth and accelerates epithelialisation in chronic wounds.[15] Platelets in PRP also play a role in the host-defence mechanism at the wound site by producing signalling proteins that attract macrophages. PRP may contain a small number of leukocytes that synthesize interleukins as part of a nonspecific immune response.[17, 18] PRP seems to improve wound healing at varies sites, and may therefore also improve the closure of perianal fistulas.

PRP, and, for instance, fibrin sealants, are initially fluids, ensuring that even very small fistula tracts are fully filled. When PRP is combined with thrombin it becomes glue. When it transforms into glue, the PRP will stay inside the fistula tracts (even the very small tracts) when the patient is mobilized (Figure 2). This glue now contains activated thrombocytes that release growth factors. A difference between PRP and fibrin sealants is that fibrin sealants have no additional effect on wound healing because no growth factors are released and no immunomodulation occurs after clotting.

The current price of manufacturing PRP for 1 patient is €703 or $924. We believe that the high closure rate justifies this price in patients with a high recurrence rate, because it results in fewer subsequent operations that sometimes use more expensive techniques. Treatment with, for instance, mesenchymal stem cells seem to be far more expensive as described by Garcia-Olmo et al, who estimate the cost of stem cell production between €8,000 and €12,000 or $10,500 and $15,750.[19]

Conclusion

Treatment with MAF combined with PRP will have to be further investigated in a randomized and controlled setting to show the actual benefit of adding PRP, its actual affect on incontinence and its reproducibility by other surgeons in the future. The authors have registered a randomized controlled trial at clinicaltrials.gov under registration number NCT01615302; this trial has already started.

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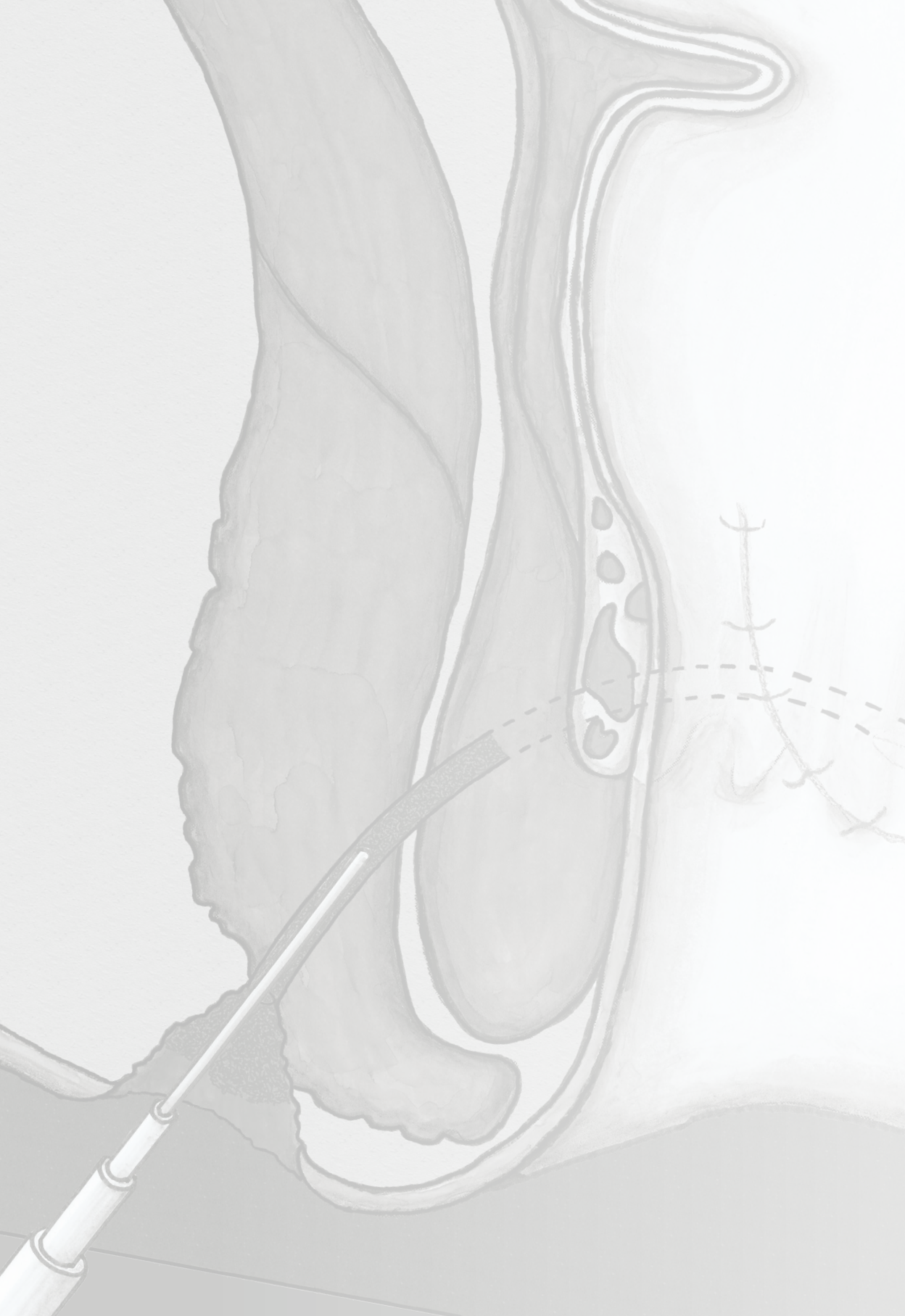

5 Treatment of Crohn's disease related high perianal fistulas using platelet-rich plasma. A pilot study

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Abstract

Background

Healing rates after surgical closure for high perianal fistula in patients with Crohn's disease are even more disappointing than in patients with cryptoglandular fistulas. The objective was to improve healing rates by combining the well-known mucosal advancement flap with platelet-rich plasma.

Methods

A prospective pilot study was conducted in one tertiary referral centre. Consecutive patients with primary or recurrent Crohn's disease-related high perianal fistulas, defined as involving the middle and/or upper third parts of the anal sphincter complex, were included. A staged procedure was performed with non-cutting seton treatment for 3 months first, followed by a mucosal advancement flap with injection of platelet-rich plasma into the fistula tract.

Results

Ten consecutive patients were operated between 2009 and 2014. Half (50.0%) of patients had undergone previous fistula surgery. Mean follow-up was 23.3 months (SD 13.0). Healing of the fistula was 70% (95% CI, 33–89%) at one year. One (10.0%) patient had a recurrence and in two (20.0%) patients, the fistula was persistent after treatment. An abscess occurred in one (10.0%) patient. The median Vaizey score was 8.0 (range 0-21), indicating a moderate continence impairment.

Conclusion

The results of combining the mucosal advancement flap with platelet-rich plasma in patients with Crohn's disease related high perianal fistulas are moderate with a healing rate of 70%. Further investigation is needed to determine the benefits, and risks on continence status, for this technique in this patient population.

Introduction

High perianal fistulas (HPFs) are difficult to treat, and many techniques have been developed in recent years to reduce recurrence rates and to maintain optimal post-operative continence status.[1-6] Up to know, there is no consensus regarding the best technique for treatment of this disease.

The high cryptoglandular perianal fistulas (HCPF) and the Crohn's disease-related high perianal fistulas (CDRF) are the most common subtypes of HPF.

In a population-based cohort study, the cumulative frequency of perianal Crohn's disease (CD) complications was 12% at 1 year, 15% at 5 years, 21% at 10 years and 26% at 20 years, and other population-based studies report incidence rates from 20 to 28%.[7-10] Thus perianal fistulas occur frequently in CD patients and significantly affect the patients' quality of life. According to the European Crohn and colitis organisation (ECCO) guidelines for complex perianal fistula, drainage of all abscesses, seton placement and dilatation of strictures are recommended first. Active luminal disease should be treated. Thiopurines in combination with antibiotics are the first medical choice.[11] Infliximab or adalimumab should be used as a second-line medical treatment.[12-15] Combining anti-tumour necrosis factor (TNF) treatment with ciprofloxacin may improve the outcome.[16] The recurrence rate of complex fistula after medical treatment is high, and therefore, combination with surgery is recommended. No surgery should be performed if active proctitis is still present.

Similar surgical techniques are used for both HCPF and CDRF. However, healing rates are lower for CDRF. For example, the mucosal advancement flap (MAF), one of the most frequently used techniques, shows healing rates of about 60-80% for HCPF compared to only 40-50% for CDRF.[17-20]

Other techniques for closure of CDRF show similar disappointing results, with long-term healings rates of around 55% for fistula plugs,[21] about 40% for fibrin glue,[22] and about 33% after ligation of the intersphincteric fistula tract (LIFT).[23]

We have developed a technique in which the MAF is combined with the injection of platelet-rich plasma (PRP) into the fistula tract. PRP is hypothesized to improve wound healing and might improve fistula closure of HPF. Compared to fibrin glue, PRP in addition to clotting releases many growths factors, which are not present in fibrin glue. Long-term results using this technique for treatment of HCPF were previously published and show favourable results with healing of the fistula after two years of 83% (95% CI, 62-93%).[3] We hypothesized that the MAF in combination with PRP can also improve outcome of complex CDRF. To the best of our knowledge, this treatment regimen has not been studied in CD patients before. We therefore performed an open-label prospective pilot in primary and recurrent CDRF.

Materials and methods

Between November 2009 and March 2014, 10 consecutive patients with primary or recurrent high CDRF were included in this pilot feasibility study. HPFs were defined as fistula involving the middle and / or upper one-third of the anal sphincter complex. Rectovaginal fistulas were excluded. Initial assessment of the fistula was done with clinical examination and magnetic resonance imaging (MRI). MRI was used to confirm a HPF and to classify the route of the fistula tract. Patients were only deemed fit for surgery if the luminal CD was in clinical and endoscopic (mucosal) remission after medical treatment according to ECCO guidelines.

The first part of the surgical procedure included no-cutting seton treatment for at least

3 months to reduce inflammation and drain sepsis, followed by a MAF with injection of PRP in the fistula tract. Patients on corticosteroids were first tapered off this medication. Patients with HPF not due to CD were excluded, as well as patients with bleeding disorders, local or haematological malignancies, and pregnant patients.
The primary outcomes of the study were healing and recurrence rates of the CDRF. The secondary outcome was continence status.
This study was conducted according to national medical ethical laws and guidelines, and written informed consent was obtained from all patients for the procedure long-term follow-up in the outpatient clinic. The local medical ethics committee approved the study.

Procedure and preparation of PRP

The surgical procedure and preparation of PRP were previously described for treatment of HCPF and were not changed for the treatment of CDRF in this study.[3]
In short, patients were first treated with a non-cutting seton for drainage of the fistula tract and treated with a MAF combined with injection of PRP at least 3 months after placement of the seton. The PRP was made from 55mL of the patients' own blood, resulting in PRP with a 6-8 times higher concentration of platelets compared to baseline whole blood. A thrombin-coated syringe activated the PRP during injection in the fistula tract. The Gravitational Platelet Separation III (GPS-III) system instructions (Cell Factor Technologies, Biomet, Warsaw, IN, US) were used for the preparation of the PRP.

Follow-up

All patients were seen at the out patient clinic for follow-up up to 1 year postoperatively. Follow-up moments were at 6 weeks, 3 months, 6 months and 1 year after surgery. If needed, patients were invited in between these follow-up visits. Fistula healing was defined as no more symptoms, a macroscopically closed external fistula opening and no drainage during manual compression. In case of doubt about closure, an MRI scan was performed to visualize a possible fistula tract. At the end of the study, patients that were not in clinical follow-up anymore, were contact by phone to check if the fistula was closed. If this phone interview resulted in a suggestion of a recurrent fistula, the patient was invited to the outpatient clinic for physical examination. At 6 months post-operatively the Vaizey-score was used to evaluate continence status.
If the fistula was not closed three months after the operation, it was considered a persisting fistula or treatment failure. A new fistula occurring after a symptom free period was defined as a recurrence.

Results

Ten consecutive patients with CDRF were treated according to protocol and were followed up prospectively. There were three (30.0%) males and seven (70.0%) females. Median age was 47.5 years (Range 30-67 years). Patient characteristics with previous treatments and study outcomes are shown in Table 1 and 2. All patients were treated with a seton for at least 3 months first before the second operation was performed. All had a preoperative MRI scan. Five (50.0%) patients had a recurrent fistula.
Eight (80.0%) patients' CDRF healed, with a median healing time of 52.5 days (range 12-114 days), although one (10.0%) patient showed delayed healing with a time to healing of 114 days (without any additional intervention). One (10.0%) of these healed patients developed a recurrence 44 days after complete closure of the fistula. The other

two (20.0%) patients' fistulas did not heal after operation.
A Kaplan-Meier curve was created to show healing of the fistulas (Figure 1). Healing at 1 year was 70 (95% CI, 33–89%). Mean follow-up was 23.3 months (SD 13.0).
The patient with the recurrence was treated with a MAF + PRP again after another 3 months of seton treatment and developed another recurrence. One of the patients with a persisting fistula chose to have a colostomy and did not want other treatment for the CDRF. This fistula closed several months after colostomy placement. The other patient with a persisting fistula was treated with a MAF + PRP after another three months of seton treatment. This fistula is still not closed to date.
An abscess occurred in one (10.0%) patient post-operatively. This was the patient with a persisting fistula, who later received a colostomy. No other complications occurred.
Seven (70.0%) patients completed the Vaizey-score questionnaire 6 months post-operatively. The median Vaizey score was 8 (range 0-21). No preoperative data on continence status were available.

Discussion

We report data of the first study combining the MAF with injection of PRP in the fistula tract for high CDRF. The healing rate was moderate with a healing of the fistulas at 1 year of 70% (95%CI, 33–89%). The median Vaizey score of 8.0 indicates a fairly severe impairment of continence status.
There were some limitations to this study. It was a small single-centre prospective pilot study to evaluate the effectiveness of adding PRP to the MAF in this patient group. Besides, data on preoperative continence status were not available, making it difficult to determine influence of the surgical procedure on continence status. Patients in follow-up for more than 1 year were evaluated using telephone interviews, which might have resulted in some bias in results.
As previously explained,[3] our surgical procedure is based on the MAF, which is a well-known and much performed operation for HPF. The rationale behind using the MAF as the basis of our technique was to avoid long learning curves for surgeons and to make results reproducible. The results of our technique, as published previously, showed promising for HCPF with healing at 2 years of 83% (95% CI, 62-93%).[3] The results for the treatment of CDRF are less favourable than hoped, although our healing rates seem higher compared to the MAF alone.[19, 20]
The reason for these less favourable results, compared to the treatment of HCPF, is not clear. However, it is known that the Vascular Endothelial Growth Factor (VEGF) response is defective,[24] and Platelet-Derived Growth Factor might be responsible for maintenance of damaged vasculature in patients with CD.[25] Both growth factors have, respectively, functions in angiogenesis, and protein and collagen synthesis, and are released when using PRP as described by van der Hagen et. al,[26] thus improving wound healing. This, however, might not be true for patients with CD. Furthermore, platelets in patients with inflammatory bowel disease show higher levels of some interleukin receptors,[27] which might change the effects of PRP. The function of PRP, concerning wound healing, in patients with CDRF might therefore be different. Unfortunately, no studies on the use of PRP in patients with Crohn's disease are available.
Regarding continence impairment, it is difficult to draw conclusions. Our previous study in patients with HCPF did not show much impairment of continence status. This study in patients with CDRF resulted in a higher median Vaizey score of 8.0, which would be classified as major incontinence according to Dubsky et. al.[28] It is, however, shown that the prevalence of faecal incontinence in patients with CD is high, with rates between 25

Table 1 - Patient characteristics & results

	Value
Male	2 (20.0%)
Age	47.5 (30.0 – 67.0)
Smokers	4 (40.0%)
BMI	25.7 (21.1 – 32.4)
Fistula location	Extrasphincteric: 1 (10.0%) Intersphincteric: 2 (20.0%) Transsphincteric: 7 (70.0%)
Previous operations	None: 5 (50.0%) One operation: 0 (0%) Two operations: 1 (10.0%) > Two operations: 3 (30.0%) Unclear: 1 (10.0%)
Residual inflammation and prolonged seton placement	0 (0%)
Recurrences	1 (10.0%)
Persisting fistulas	2 (20.0%)
Primary healing rate	7 (70.0%)
Secondary healing rate	7 (70.0%)

Values given as n (%) or as median (range)

Table 2 - Patient history and outcome

Patient	Current treatment for Crohn's disease	Fistula type	Previous high fistula treatment	Stoma	Persisting fistula	Recurrence
1	Mesalazine; Azathioprine	Primary	-	No	No	No
2	Adalimumab	Primary	-	No	No	Yes
3	Azathioprine; Infliximab	Recurrent	Fistulotomy; Seton treatment	No	No	No
4	Azathioprine; Infliximab	Recurrent	Seton treatment (4x)	No	No	No
5	None	Recurrent	MAF, other treatments unknown	No	Yes	No
6	Infliximab	Recurrent	Seton treatment (3x), MAF + stem cells	No	No	No
7	Infliximab; 6-mercaptopurine	Primary	-	No	No	No
8	Adalimumab	Primary	-	No	No	No
9	Mesalazine; Infliximab	Primary	-	No	Yes	No
10	6-mercaptopurine	Recurrent	Seton treatment (3x), deviating colostomy	Yes	No	No

MAF: Mucosal advancement flap

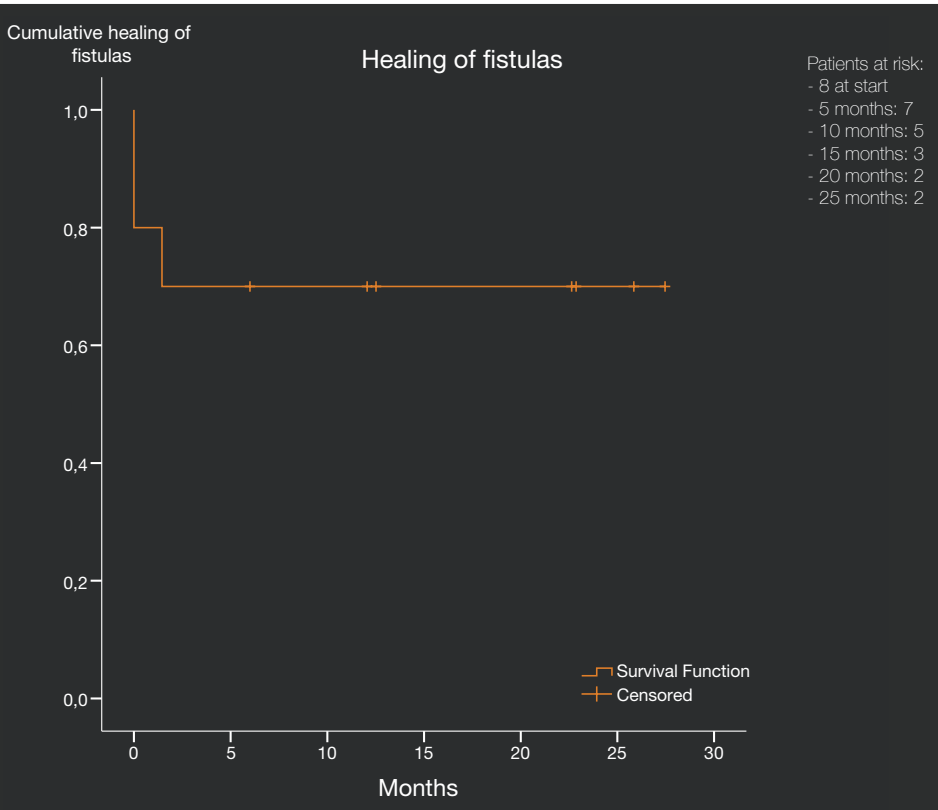

Figure 1 - Kaplan-Meier curve - Healing of fistulas

and 74%, even without anal fistula surgery.[29] This would make it even more important to clarify the influence of our surgical procedure on, the perhaps already impaired, continence status of patients with CDRF.
Previous surgery, and specifically previous MAF, might also have had a significant influence on continence status. We use curettage for the fistula tract before performing the MAF, and other surgeons use only mild abrasive de-epithelialization or even resect and core-out the tract. Since all the previously treated patients were referred from others centres, we are unsure what the influence of the prior surgery was on their continence status.

Conclusion

The healing rate of CDRF treated using our technique is 70% and favourable compared to the 40-50% for the MAF reported in other studies. Further investigation, preferably as a randomized study, into the usefulness of combining the MAF with PRP in patients with CDRF is needed to see whether healing rates can actually be improved, and especially to show the influence on continence status post-operatively in a patient population with an already high risk of faecal incontinence.

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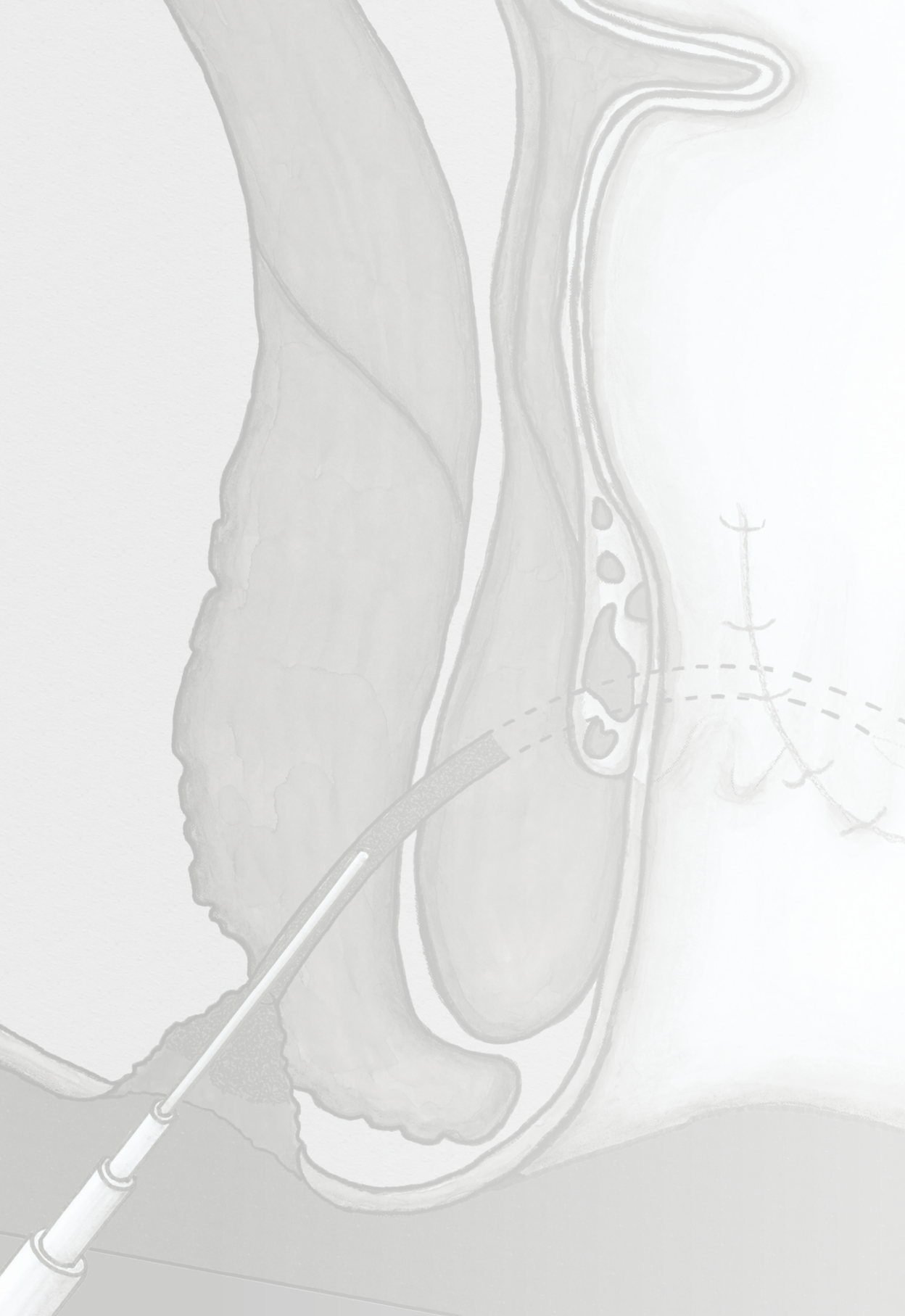

6 Time trends in incidence and outcome of perianal and rectovaginal fistulizing Crohn's disease in a population-based cohort

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Submitted

Abstract

Background

Perianal fistulas (PF) and rectovaginal fistulas (RVF) frequently occur in Crohn's disease (CD) patients. Fistulas can be very invalidating and are often refractory to treatment. Despite their obvious relevance, little is known about the incidence of and risk factors for these conditions.

Methods

Since 1991, incident IBD cases are included in the population-based IBDSL cohort. All CD patients were included for this study. The cumulative probability of fistula development was determined by Kaplan-Meier survival analysis, and hazard ratios (HR) of potential risk factors were calculated using a Cox regression model.

Results

In total, 1162 CD patients were included with a mean follow-up of 8.7 years (SD 5.7). In 161 cases a PF developed, corresponding to a cumulative probability of 21.5% after 20 years. Ninety-nine patients (61.5%) underwent fistula surgery. Cumulative probability of a PF recurrence was 73.2% after 20 years. In 17 cases, a RVF developed, corresponding to a cumulative probability of 3.9% after 20 years. In contrast to patients diagnosed between 1991 and 1998, patients diagnosed between 1999 and 2011 had a lower risk of RVF (1.4% vs. 5.1%, $p<0.05$). The risk of PF did not differ between groups (17.6% vs. 14.5%, $p=0.39$), although the recurrence risk was higher in the latter cohort (45.2% vs. 30.0%, $p<0.05$).

Conclusion

This population-based study showed that the incidence of RVF decreased over time, while PFs are still common and often recur, despite changes in CD management. These findings underline the importance of improving medical and surgical treatment strategies for these invalidating conditions.

Introduction

Crohn's disease (CD) is a chronic inflammatory disease that can affect the entire gastrointestinal tract including the anus. Perianal CD is present in 10% of patients at the time of diagnosis,[1] and may be the presenting symptom.

Perianal CD, as classified by the American Gastroenterological Association, is an umbrella term for perianal abscesses, skin tags, hemorrhoids, fissures, strictures and fistulizing disease.[2] The latter entity is probably the most difficult to treat. The two most common forms of perianal fistulizing disease are the perianal fistula (PF) and the rectovaginal fistula (RVF), which both heal difficult after medical and surgical treatment, and are prone to recur. The combination of debilitating symptoms and poor therapeutic outcome make perianal CD a difficult entity in CD management.[3, 4]

According to the European Crohn and Colitis organisation (ECCO) guidelines it is recommended to drain abscesses, place setons and dilate strictures first. Active proctitis should be treated medically and no other surgery should be performed if active proctitis is still present.[5] For both PF and RVF many different surgical treatments are available. Previous studies showed that treatment outcome is worse in CD-related fistulas compared to cryptoglandular fistulas and some patients end up with a proctectomy or definitive faecal diversion. The mucosal advancement flap for instance, one of the most frequently used techniques for PF, shows healing rates of about 60-80% for cryptoglandular PF, compared to only 40-50% for PF related to CD.[6-9] Treatment results for RVF are even more disappointing.[10]

Several cohort studies have investigated the incidence of perianal CD and some specifically focused on fistulas. The incidence of PF is estimated to be 13-28%.[1, 11-14] Unfortunately PFs and RVFs are not described separately in these studies. The risk of developing a RVF is therefore unknown. Risk factors for the development of PF in CD are only reported in three studies and the results were contradicting.[11, 12, 14]

The number of recurrences of CD associated fistulas are also only reported in two studies, and treatment strategies were not specified.[1, 14] Moreover, patients included in these studies were often recruited in eras in which immunomodulator therapy was not as commonly used as nowadays, and biological therapy was not available. Updated information on PF and RVF incidence, risk factors and recurrence from a large population-based cohort is therefore warranted.

The aim of this study was to assess the incidence of PF and RVF in a population-based IBD cohort. In particular, we studied fistula incidence over time, with special attention to the incidence in the current era, characterized by a common use of immunomodulators and biological availability. Secondary, we aimed to identify clinical risk factors for the development of PF or a RVF.

Materials and methods

Cohort description

The IBD South-Limburg (IBDSL) cohort is a population-based IBD cohort in the South-Limburg area of the Netherlands, with a completeness of more than 93%.[15] Since 1991, incident IBD cases in area are prospectively included in the population-based IBDSL cohort to study epidemiology, disease outcome, and, more recently, molecular epidemiology, and pathophysiology of IBD with a population-based biobank. IBDSL has been approved by the Ethics Committee of the Maastricht University Medical Centre and is registered in ClinicalTrial.gov (NCT02130349).

Data collection

For this study, all 1162 CD patients in the IBDSL registry were included. Data on fistula occurrence, fistula recurrence, and data on medical treatments and surgical treatments for fistulizing disease were extracted from patients' medical records.

Definitions and outcomes

PF and RVF were assessed and classified with either radiologic imaging (Magnetic resonance imaging (MRI) or endoanal ultrasound) or physical examination. PF were classified as low or high fistulas, depending on the level of sphincter muscle that is involved. A fistula in the lower one third of the sphincter complex was classified as low, and a fistula traversing the middle and/or the upper third parts was classified a high fistula. The fistulas were also described using the Park's classification when available.[16] PFs in patients with CD can also be divided in simple and complex. A simple fistula is a low superficial, intersphincteric or transsphincteric fistula, without complicating factors like multiple tracts, abscesses or strictures. A complex fistula is a simple fistula with the mentioned complications, a high fistula or a RVF.[2] In this study RVFs were described separately. RVFs were divided in low or high fistulas, of which the low fistulas involve the lower half of the rectovaginal septum and the high fistulas, the upper half.
A recurrence of a fistula was defined as a visible new fistula at the same location or the returning of symptoms after a symptom-free period. In this study both persisting and recurring of the fistula were described as recurrence, as the data, due to its retrospective nature, did not allow discriminating these two outcomes.

Statistical analyses

An independent Student's t-test or Mann-Whitney U test, depending on normality of the underlying distribution, was used to compare continuous data. Dichotomous data were compared by Fishers's exact test.
Kaplan-Meier survival analyses were used to calculate cumulative incidences of perianal and rectovaginal fistulizing disease over time. Log-rank analysis was used to compare survival curves. Cox-regression analysis was used to assess time trends in fistula incidence and to identify risk factors for the development of perianal and rectovaginal fistulizing disease. All parameters were first tested in a univariate model. Parameters with a p-value <0.10 were subsequently tested in a multivariable Cox regression model. A p-value lower than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 21 (SPSS, Chicago, IL).

Results

In the IBDSL database, 1162 patients with CD, diagnosed between 1991 and 2011 were identified. The patient group consisted of 728 (62.7%) female patients. The current mean age was 49.5 years (SD 16.5) and the mean age at time of CD diagnosis was 37.7 years (SD 15.9). No significant differences in current age and age at time of diagnosis were seen between female and male patients. Mean follow-up after CD diagnosis was 8.7 years (SD 5.7).
We identified 283 (24.4%) patients with fistulizing disease (including RVF, PF, enterocutaneous and entero-enteral fistulas). The number of patients with RVF and/or PF was 163 (14.0%). Of these patients 161 (13.9%) had a PF, 17 (1.5%) women had a RVF, and 15 (1.3%) women had both a PF and RVF. Patient characteristics of CD patients with and without a PF and/or RVF are shown in Table 1.

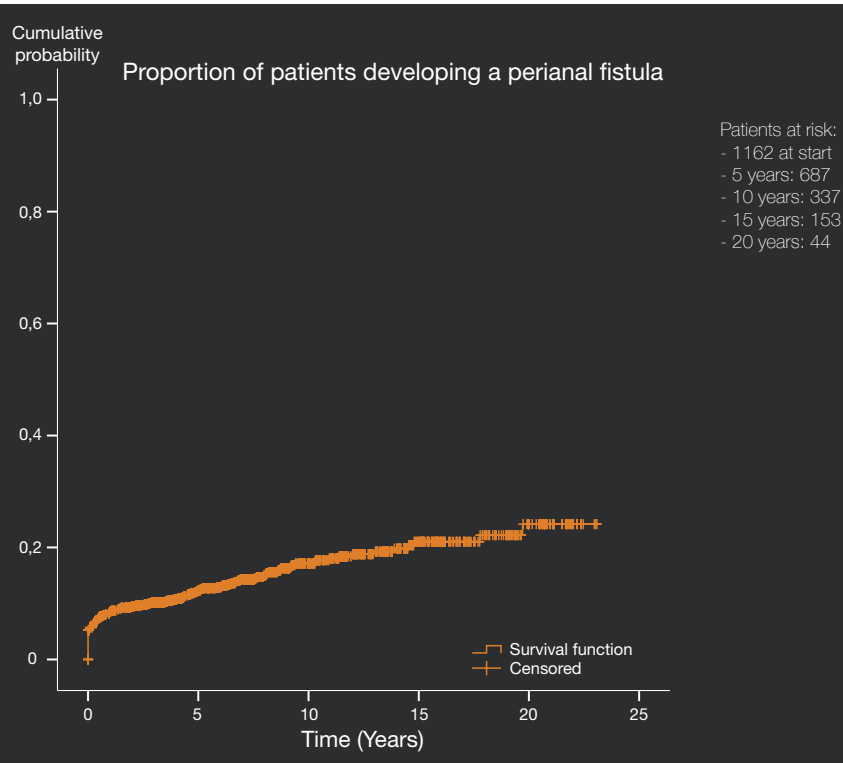

Figure 1 - Kaplan-Meier curve showing proportion of patients developing perianal fistulas

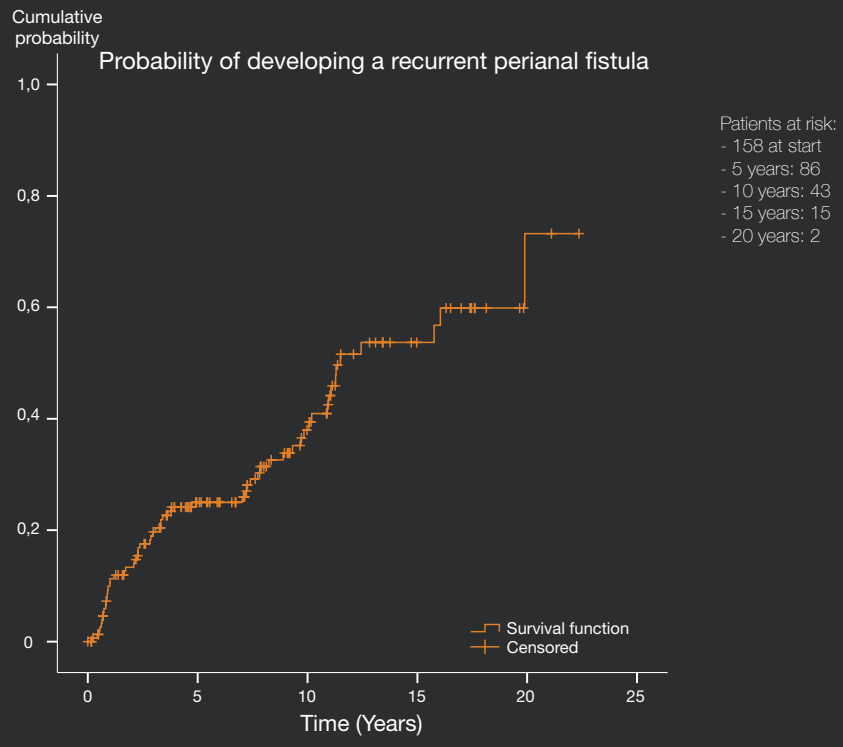

Figure 2 - Kaplan-Meier curve showing proportion of patients developing recurrent perianal fistulas

Perianal fistula

In total, 161 CD patients ever had a PF. The PF classifications are shown in Table 2. Forty-nine patients (30.4%) had developed the fistula prior to CD diagnosis, at a median time of 0.8 (IQR 0.2-2.7) years before diagnosis. The majority (n=112, 69.6%) developed a PF during CD disease course, at a median time of 2.1 (IQR 0.4-6.3) years after diagnosis. Thirty-one (27.7%) primary PFs developed under immunosuppressive treatment and six (5.4%) under anti-TNF treatment. The other 75 PF (67.0%) developed in patients on mesalamine or steroid treatment, or in CD patients not receiving any form of medical therapy at time of fistula diagnosis.

The overall cumulative probability of developing a PF was 8.2% after one year, 11.6% after 5 years, 15.7% after 10 years, and 21.5% after 20 years follow-up (Figure 1). The cumulative 20-year probability of developing a PF was not significantly different between CD patients diagnosed between 1991 and 1998 and CD patients diagnosed between 1999 and 2011 (17.6% vs. 14.5%, adjusted HR 0.81; 95%CI 0.58-1.12, respectively, p=0.39). Medication use differed between the two time eras. Patient diagnosed between 1999 and 2011 more often used immunomodulating agents than patients diagnosed between 1991 and 1998 (77.4% vs. 49.0% after 10 years, respectively, p<0.01) and commenced treatment earlier in their disease course (42.7% vs. 14.3% within the first year, p<0.01). Anti-TNF agents were also more often used in more recently-diagnosed patients (47.9% vs. 16.5% after 10 years, respectively, p<0.01) and initiated earlier in disease course (16.3% vs. 0.8% within the first year, p<0.01). Clinical risk factors were identified by using a multivariable Cox regression model (Table 3). A history of a perianal abscess was strongly associated with the development of a PF (adjusted HR 18.60; 95%CI 13.22-26.16). Colonic localization of CD was also associated with a higher risk of developing a PF in comparison to ileal localization (adjusted 2.18; 95%CI 1.33-3.58).

Antibiotics were administered to 133 (82.6%) patients for the treatment of a PF. Surgical treatment was performed in 99 (61.5%) patients. Thirty-four (63.0%) of the patients with a low PF were operated (all fistulotomy) and 32 (88.9%) of the patients with a high PF. In total, 59 CD patients (36.6%) developed a PF recurrence, of which 48 were patients that underwent surgery for their primary PF. Twenty-four (40.7%) patients were on immunomodulating therapy and two (3.4%) on anti-TNF therapy at time of recurrence PF diagnosis. Cumulative probability of either a persisting fistula or PF recurrence was 10.9% after one year, 25% after five years, 38.0% after ten years, and 73.2% after 20 years (Figure 2). The cumulative probability of developing a recurrent PF was significantly higher in the group diagnosed between 1999 and 2011 compared to the group diagnosed between 1991 and 1998 (45.2% vs. 30.0% after 10 years, p<0.05). The median duration between the first PF diagnosis and diagnosis of the recurrent PF was 2.9 years (IQR 0.9-8.9). No risk factors could be identified for developing a recurrent PF (Table 3).

Rectovaginal fistula

In total, 17 of the 728 female CD patients (2.3%) had a RVF. Two patients (11.8%) already suffered from RVF before CD diagnosis and had a time to CD diagnosis of 0.2 and 6.7 years. Six (42.9%) RVFs developed under immunomodulator treatment and none under anti-TNF treatment. In one patient, current medication status could not be retrieved as the date of occurrence RVF could not be retrieved. The overall cumulative probability of developing a RVF was 0.6% after one year, 1.6% after 5 years, 3.0% after 10 years, and 3.9% after 20 years follow-up (Figure 3).

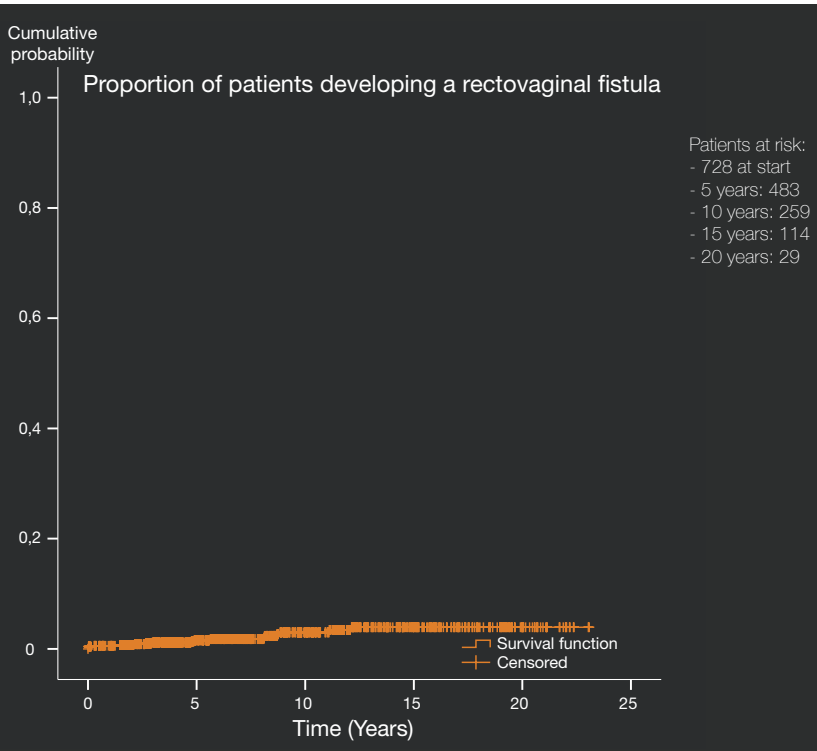

Figure 3 - Kaplan-Meier curve showing proportion of patients developing rectovaginal fistulas

The cumulative 20-year probability of developing a RVF was significantly lower in CD patients diagnosed between 1999 and 2011, compared to CD patients diagnosed between 1991 and 1998 (1.4% vs. 5.1%, adjusted HR 0.19; 95%CI 0.05-0.68, respectively, $p<0.05$). Due to the limited number of events, only univariable analyses could be performed for assessing risk factors for developing a RVF. A history of perianal abscess is associated with a higher risk of developing RVF (HR 8.59; 95%CI 3.30-22.36).

Discussion

This population-based cohort study showed a 20-year cumulative incidence rate of 21.5% for PF and 3.9% for RVF in CD. A significant number of patients were diagnosed with PF or RVF prior to CD diagnosis. The number of patients requiring surgical treatment for their PF was high with 61.5%. The cumulative recurrence risk after 20 years was 73.2%.

Several other population-based cohort studies on CD are available, with some partially focusing on perianal disease and anorectal fistulas (Table 4).[1, 11-14] Cumulative probability of a PF after 20 years in these studies varies between 21.3% and 28.3%.[1, 13] This however, is the only study to date that reports on the incidence of and risk factors for PF and RVF separately. The present study is also the first that assessed time trends in fistula incidence

For PF no trend could be seen, but for RVF the cumulative 20-year incidence probability was significantly lower in CD patients diagnosed between 1999 and 2011 in contrast to patients diagnosed between 1991 and 1998. In the last two decades, treatment options

Table 1 - Patient characteristics

	All patients	Patients without fistula	Patients with PF	Patients with RVF
Age	49.5 years (16.5)	50.0 years (17.0)	45.8 years (12.5) ^	55.0 years (14.1)
Sex	62.7% female	62.5% female	63.4% female	-
Smoking	42.5%	49.8%	49.7%	46.7%
Age at diagnosis of CD*	37.7 years (15.9)	38.5 years (16.3)	32.3 years (12.3) ^	37.3 years (15.1)
Follow-up duration*	8.7 years (5.7)	8.3 years (5.6)	11.4 years (5.9) ^	13.6 years (5.8) ^

** Mean (SD), PF: Perianal fistula, RVF: Rectovaginal fistula, CD: Crohn's disease, ^ p<0.05*

Table 2 - Fistula classifications

	Perianal fistula	Operated perianal fistulas	Recurrent perianal fistulas	Rectovaginal fistula
High fistula	36 (22.4%)	32 (88.9%)	11 (18.6%)	2 (11.8%)
Low fistula	54 (33.5%)	34 (62.9%)	14 (23.2%)	6 (35.3%)
Unknown	71 (44.1%)	33 (46.5%)	34 (57.6%)	9 (25.9%)
Park's Classification				
Intersphincteric	36 (22.4%)	23 (63.9%)	14 (23.7%)	
Transsphincteric	30 (18.6%)	20 (66.7%)	4 (6.8%)	
Extrasphincteric	12 (7.5%)	11 (91.7%)	3 (5.1%)	
Suprasphincteric	7 (4.3%)	7 (100%)	3 (5.1%)	
Superficial	15 (9.3%)	8 (53.3%)	2 (6.9%)	
Unknown	61 (37.9%)	30 (49.2%)	33 (55.9%)	
Simple	39 (24.2%)	21 (53.8%)	12 (20.3%)	
Complex*	39 (24.2%)	29 (74.4%)	9 (15.35)	
Unknown	83 (51.6%)	49 (59.0%)	38 (64.4%)	

** Excluding rectovaginal fistulas*

and strategies for CD have changed. Immunomodulating treatment is more frequently used and initiated earlier in the disease course.[17] We also found a more frequent use of immunomodulators and anti-TNF agents in more recently-diagnosed patients in our cohort. Of particular interest is the availability of anti-TNF treatment as from 1999. Anti-TNF agents are proven to be effective for fistula closure.[18-20] The present study showed similar cumulative probabilities of developing a PF in patients diagnosed in the first (1991-1998) and diagnosed in the second decade (1999-2011). Although no causative relation can be made, the present study suggests that anti-TNF availability has not led to a lower incidence of PF in our cohort under current treatment strategies at a population level.

Only a few studies looked into the recurrence of PFs after treatment, and report absolute recurrence rates between 33.3 and 63.6%.[1, 14] In our cohort the treatment outcome for PFs is also disappointing with a cumulative recurrence rate over 70% after 20 years. More-recently diagnosed patients seem to have a higher cumulative probability of developing a recurrence, even though the use of immunomodulators and anti-TNF agents is higher in this group. This observation might be explained by a higher clinical awareness for fistula and increased use of MRI in CD more recently diagnosed

CD patients. Although the use of thiopurines, antibiotics and anti-TNF agents is advised for perianal fistula in CD nowadays and several new surgical treatments have been developed have been developed in recent years, like the ligation of intersphincteric fistula tract,[21] treatment results shown in studies are not improving using newer techniques.[7] Randomized controlled trials are rare, but are needed to compare the available treatment options to see what treatment is best.
Although information on medication and surgical technique is available further, analyses to asses what was the most effective treatment was not performed due to confounding by indication and reversed causation, as is the problem with many studies.
Risk factors for the development of PFs are reported in several studies.[11, 12, 14] Unlike other studies we also studied risk factors for RVF specifically. Young age of CD onset was found to be a risk factor for the development of a PF by other studies and is confirmed by the present study. In line with other studies we found colonic disease involvement to be related to PF development.[12, 14] We did not find gender to be related to the development of any fistula, which may be related to the fact that we analyzed RVF separately.
The strengths of this study reside in the large sample size, the population-based character and the length of follow-up of the patients. Some limitations have to be addressed. The identification of the fistulas based on medical files in our cohort-study might have resulted in an underrepresentation of the fistula incidence. Its presence may not have been registered in the medical record and could thereby have been missed. The same goes for fistula recurrence or persistence. Secondly, although information on medication and surgical technique is available further analyses to asses what was the most effective treatment was not performed due to confounding by indication and reversed causation.

Conclusion

PFs are still common nowadays, and the recurrence rate remains high, despite changes in treatment options and strategies for CD in the last two decades. RVF occur less frequently in CD and its incidence has decreased over time. The findings of the present study underline the importance of improving medical and surgical treatment strategies for these invalidating conditions.

Table 3 - Cox regression analysis for fistula development and recurrence

	Primary perianal fistula		Recurrence perianal fistula		Primary rectovaginal fistula
	Unadjusted hazard ratio HR (95% CI)	Adjusted hazard ratio HR (95% CI)	Unadjusted hazard ratio HR (95% CI)	Adjusted hazard ratio HR (95% CI)	Unadjusted hazard ratio HR (95% CI)
Era - 1991 – 1998 - 1999 – 2011	Reference 0.81 (0.58-1.12)		Reference 1.67 (0.95-2.94)	Reference 1.60 (0.91-2.83)	Reference 0.19 (0.05-0.68)
Age at diagnosis	0.98 (0.97-0.99)	0.99 (0.98-1.00)	0.99 (0.97-1.02)		1.01 (0.97-1.04)
Sex - Male - Female	Reference 1.02 (0.74-1.41)		Reference 0.97 (0.57-1.66)		** **
Disease location - L1 Ileal - L2 Colonic - L3 Ileocolonic - L4 Upper GI only	Reference 2.70 (1.68-4.34) 2.83 (1.84-4.37) 2.43 (0.58-10.21)	Reference 2.21 (1.37-3.57) 1.30 (0.82-2.05) 3.77 (0.89-15.94)	Reference 1.47 (0.61-3.52) 1.42 (0.63-3.21) 4.73 (0.58-38.77)		**
Upper GI disease	0.95 (0.64-1.41)		1.46 (0.80-2.67)		**
Disease Behavior - B1 non-stricturing/non-penetrating - B2 stricturing - B3 penetrating	Reference 1.01 (0.69-1.48) 1.30 (0.88-1.92)		Reference 1.49 (0.80-2.76) 1.25 (0.67-2.33)		**
Perianal Abscess	19.40 (14.14-26.61)	18.70 (13.31-26.25)	1.57 (0.89-2.77)	1.70 (0.96-3.00)	8.76 (3.37-22.79)

Table 4 - Available data on perianal and rectovaginal fistula in Crohn's disease

	This study	Hellers (1980)[14]	Schwartz (2002)[1]	Lapidus (2006)[11]	Tang (2006)[12]	Eglinton (2012)[13]
Patients with CD	1162	826	169	1389	1595	715
Follow-up	7.6* / 8.7# years	9.4 years#	-	-	-	6.3 years*
RVF rate	1.5%	-	5.3%	-	-	2.1%
PF rate	13.9%	23%^	19.5%	13.7%$	9.9-14.0%^	11.2%
20 year probability of RVF	3.9%	-	-	-	-	-
20 year probability of PF	21.5%	-	26.0%	-	-	28.3%^
Recurrences of PF	37.3%	63.6%^	33.3%	-	-	-
20 year probability of PF recurrence	73.2%	-	-	-	-	-
Operated for PF	61.5%	53.8%^	71%	-	-	-
Occurrence of RVF related to CD diagnosis	3.9 years#	-	-	-	-	-
Occurrence of PF related to CD diagnosis	2.0 years#	-	5.5 years#^	-	-	
Risk factors for RVF	PA	-	-	-	-	-
Risk factors for PF	PA; C	Female^; C^	-	Male$; Low AD$	Low AD^; C^	-
Risk factors for PF recurrence	None identified	-	-	-	-	-

*PF: Perianal fistula; RVF: Rectovaginal fistula; CD: Crohn's disease; AD: Age of diagnosis; PA: Perianal abscess; C: Colic involvement of CD; *: Median; #: Mean; ^: All anorectal fistulas combined; $: All anorectal fistulas and abscesses combined*

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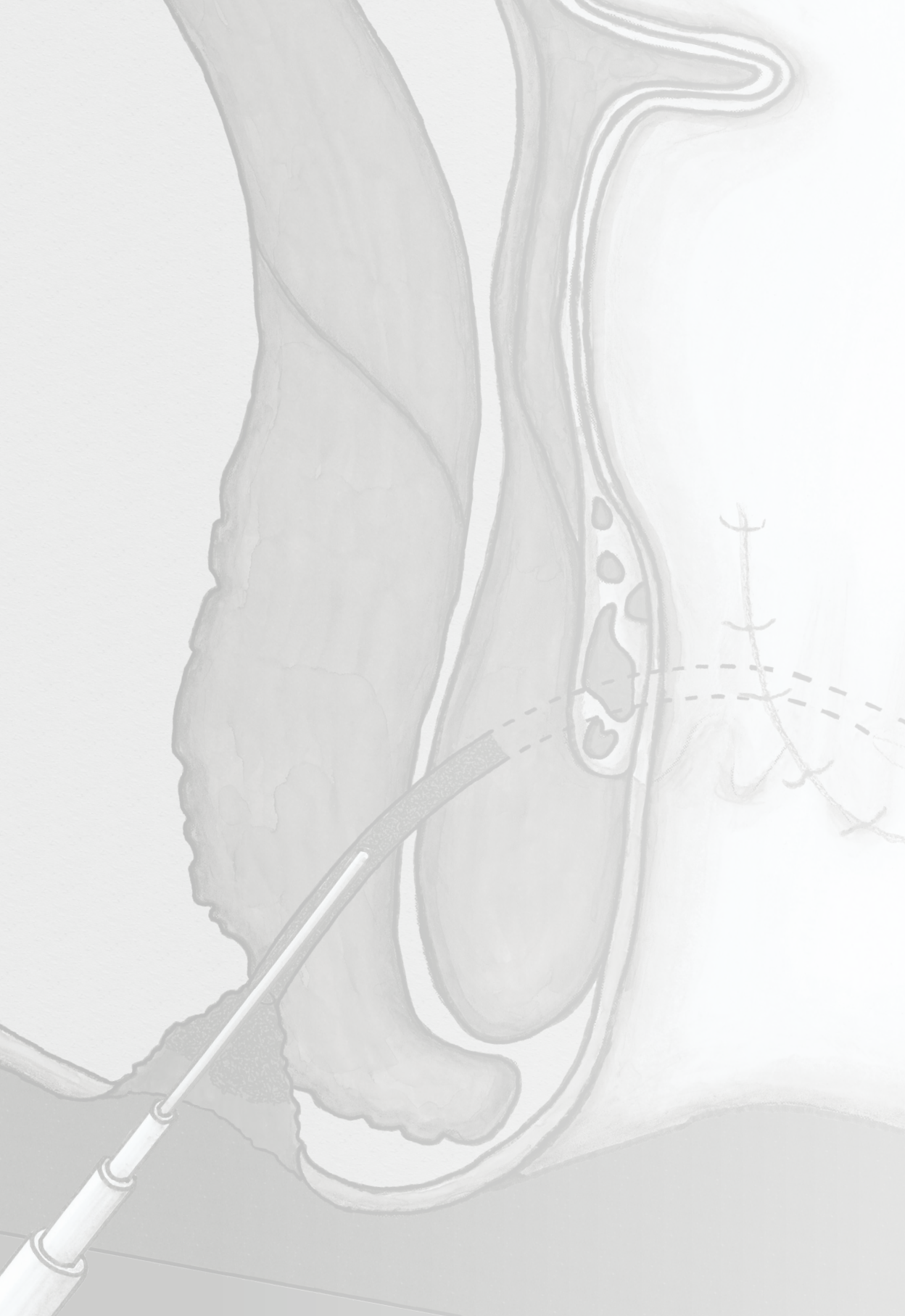

7 Rectovaginal fistula: A new technique and preliminary results using collagen matrix biomesh

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Abstract

Background

A rectovaginal fistula (RVF) is a debilitating condition that is difficult to treat. Many available techniques are invasive and involve extensive surgery. A local procedure with good closure rates would be preferable as a first step in the treatment of RVF. The aim of this study was the development of a local technique for the closure of RVF with good closure rates to prevent the use of more invasive procedures.

Methods

This was a pilot study. Patients with RVF who had undergone multiple operations in the pelvic area, local radiotherapy, chemotherapy or had been diagnosed with Crohn's disease were included in the study. All had a history of surgery for RVF A cross-linked collagen matrix biomesh was placed in the rectovaginal septum using a transperineal or a transvaginal approach. The main outcome measure in this study was the closure rate reported as absence of the fistula at one year.

Results

Twelve patients were included in the study. Absence of fistula at one year was 0.64 (95% confidence interval [CI] 0.30 – 0.85). Three patients (25.0%) developed a recurrence, 2 were reoperated on with a gracilis flap transposition, and 1 was treated with laparoscopic ligation. In 1 patient (8.3%) the fistula failed to close within 3 months after the mesh placement.

Conclusions

Our technique shows promising results. A local and simple technique with acceptable closure and morbidity rates, like our local repair with biomesh, would be ideal as a first step in treating rectovaginal fistulas. Long-term results are needed.

Introduction

A rectovaginal fistula (RVF) is an extremely debilitating condition. Symptoms include gas and stool passage vaginally, irritation and inflammation, and dyspareunia[1]. Besides these physical symptoms, RVF has a significant negative influence on the patient's quality of life and causes social embarrassment.[1]

The reasons for developing a RVF vary. RVF are often the result of trauma during childbirth, especially in developing countries. It can be caused by Crohn's disease, or develop as a result of cryptoglandular disease. Iatrogenous fistulas can also develop after complicated rectal or gynaecologic surgery. Besides these benign causes, RVF are seen in women that have previously been treated for malignant diseases in the pelvic area. These malignancies in the pelvis are often treated by radiotherapy resulting in tissue damage and poor healing.

The currently available operations for RVF are often extensive and invasive. They include several types of muscle flaps,[2-7] transabdominal approaches,[8] resections,[9] and endoscopic repairs.[10, 11] The success rates of the different muscle flap or transposition procedures vary widely from <50% to a 100%. Transabdominal approaches are nowadays usually performed laparoscopically and include fistula resection with or without omentumplasty and a diverting stoma, reporting a closure rate of up to 95%.[8] Although the success rates of these transabdominal approaches are high, the risk for complications and postoperative morbidity seems higher than that for local techniques. Endoscopic repairs are fairly new and still under development, and use histoacryl (glue) and clips to close the RVF.[10]

Less invasive local techniques include rectal,[12] or vaginal,[13] advancement flaps, and fistula plugs.[14] Advancement flaps are still seen as the gold standard by many surgeons although the closure rate averages around 60%.[12, 13, 15-18] None of the invasive and less invasive techniques have so far been studied in a randomized and controlled setting. A simple local procedure with acceptable closure and morbidity rates would be an ideal first step in a treatment algorithm for RVF. In this way, more invasive techniques, most likely associated with a higher morbidity rate, could be avoided in many patients, but are still available if the local technique fails. This retrospective study shows the first results using the Permacol biomesh (Covidien, Dublin, Ireland), a cross-linked collagen matrix mesh, for RVF.

Materials and methods

Patients

Between 2009 and 2012, 12 consecutive patients were treated in in 3 different surgical centres. All patients had a rectovaginal or pouch-vaginal fistula, confirmed clinically and by magnetic resonance imaging (MRI). Both low and high fistulas were included. Low fistulas were treated with a transperineal approach. High fistulas were treated with a transvaginal approach. Low fistulas were defined as involving the lower half of the rectovaginal septum, and high fistulas as involving the upper half of the rectovaginal septum, determined by the vaginal side.

Written informed consent was obtained from all patients before they underwent this new experimental treatment and long-term follow-up in the outpatient clinic. The study was conducted according to national medical ethical laws and guidelines.

Procedure

The whole procedure is performed with the patient under general or spinal anaesthesia in the lithotomy position. Prophylactic intravenous cefazolin (2000mg) and metronidazole (500mg) were administered 15-30 minutes prior to incision according to the local hospital gastrointestinal surgery protocol. Antibiotics were not continued postoperatively.

A 2- to 3-cm incision was made, either transperineally (Figure 1) or in the posterior wall of the vagina in a cephalad direction was made for a low rectovaginal fistula or a high rectovaginal fistula respectively (Video presented on the journal website, Supplemental Digital Content 1: Transvaginal approach with opening of the rectovaginal septum). After the incision the plane between the rectum and vagina was developed (Figure 2), and the fistula excised. The fistula opening in the rectum was closed with absorbable sutures. Then, the biomesh was placed, non-folded, in the developed plane and sutured in place on the anterior rectal wall using a parachute technique, allowing at least an overlap of 2 cm over both fistula openings (Figure 3; Video presented on journal website, Supplemental Digital Content 2: Placement of the biomesh). In the transvaginal approach the fistula opening and the dorsal vaginal wall were closed after placing the mesh (Video presented on journal website, Supplemental Digital Content 3: Closure of the rectovaginal septum and the fistula opening in the vaginal wall). In the transperineal approach the vaginal fistula opening was closed before mesh placement, and finally, the perineal incision was closed. No drainage was used. The costs for the biomesh are €380 or $530.

Follow-up

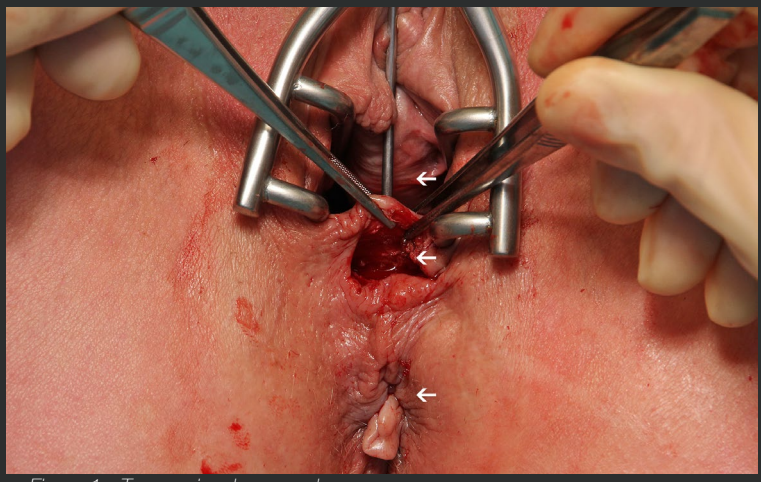
Regular follow-up visits were scheduled for all patients. Outpatient clinical follow-up was up to 1 year. All patients with follow-up over 1 year were contacted by telephone to assess recurrence of the fistula. A fistula was considered closed if the patient reported and no more passing of gas or liquid/solid stool via the vagina, and if the fistula openings were found to be closed during rectal and vaginal examination. An MRI scan was performed if it was not certain whether the fistula was closed.

If clinical or radiological findings showed that the fistula remained open 3 months after the operation the treatment had failed. A new fistula occurring after a symptom-free period was defined as a recurrence.

Results

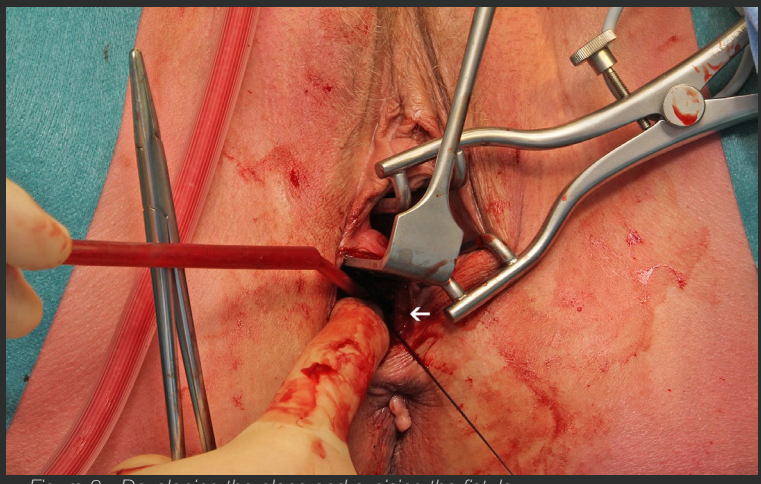
Twelve patients were included in this study between 2009 and 2012 in 3 proctology centres. The median number of previous fistula operations was 1.0 (range 1–3 operations). The median number of previous abdominal, perineal or vaginal operations was 1.0 (range 0–4 operations). All patients had an extensive history of treatment in the pelvic area or of Crohn's disease. Previous treatment history included several colorectal or gynaecological operations, local radiotherapy or chemotherapy, and previous operations for closure of the fistula. Four patients (33.3%) had previous local radiotherapy, 3 (25.0%) had previous chemotherapy, and 2 (16.7%) had a history of Crohn's disease (Table 1).

Ten patients (83.3%) were operated on using the transperineal incision. Median duration of follow-up was 22 months (range 2-45 months). Median time to closure of the fistula was 51 days (range 14.0-114.0 days). Reason for the closure at 114.0 days was unclear, and might not be related to our treatment. A Kaplan-Meier curve was created to show



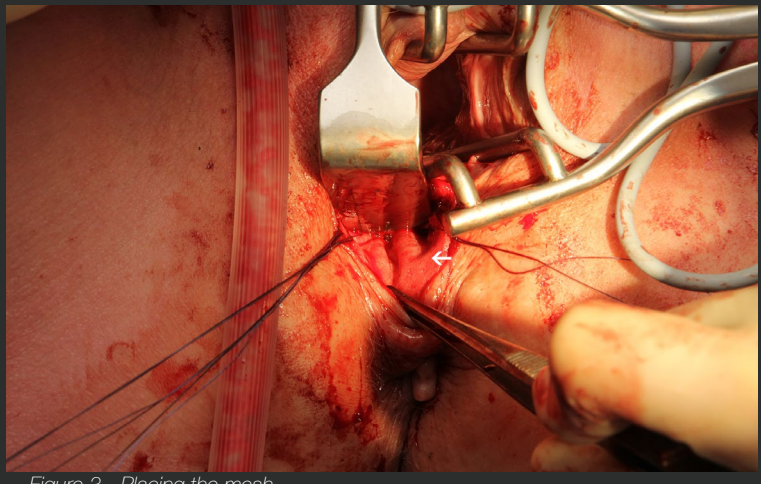
Arrows:
- Vagina
- Perineal incision
- Anus

Figure 1 - Transperineal approach



Arrow:
- Plane between the vagina and the rectum

Figure 2 - Developing the plane and excising the fistula



Arrow:
- Biomesh

Figure 3 - Placing the mesh

Table 1 - Aetiologies and previous treatments

Patient	Disease	Operations before fistula occurrence	Previous fistula treatment	Access	Stoma	Closure of fistula
1*	Cervical cancer: Resection and RTx.	Cervicectomy, hysterectomy, diagnostic laparoscopy complicated by iatrogenic perforation resulting in diverting ileostomy. Sigmoid resection with colostomy after sigmoid ischaemia.	Ligation	TV	Yes (pre-existent), closed after treatment	No
2	Episiotomy during vaginal birth.	Episiotomy	Ligation; Transperineal mesh (material unknown); Stoma	TP	Yes (pre-existent), closed after treatment	Yes
3	Crohn's disease	None	Stoma	TP	Yes (pre-existent), not closed	Yes
4	Ulcerative colitis	Restorative proctocolectomy, adhesiolysis for ileus, laparoscopic cholecystectomy + adhesiolysis	Ligation	TV	No	Yes
5	Crohn's disease + 4th degree child birth perineal laceration	Repair of child birth laceration	ERF; Stoma	TP	Yes (pre-existent), closed after treatment	Yes
6	Rectal carcinoma: RTx + resection + CT	LAR + diverting colostomy	Ligation	TP	Yes (pre-existent), not closed	No, persistent after laparoscopic ligation
7	Rectal carcinoma: RCt + resection	LAR + resection of posterior vaginal wall	Stoma	TP	Yes (pre-existent), closed after second treatment	Yes, after secondary rectus abdominal transposition
8	Cryptoglandular	None	Omental interposition; Labial fat interposition; Stoma	TP	Yes (pre-existent), not closed	No, persistent after gracilis transposition
9#	Rectal carcinoma: RTx + resection	Laparoscopic rectosigmoid resection	Stoma; Ligation	TP	Yes (pre-existent), closed after treatment	Yes
10	Cryptoglandular	None	Ligation	TP	No	Yes
11	Rectal polyp	TEM	ERF	TP	No	Yes
12	Ulcerative colitis	Restorative proctocolectomy	Ligation	TP	No	Yes

** Lost to follow-up; RTx: neo-adjuvant Radiotherapy; ERF: Endorectal advancement flap; LAR: Low-anterior resection; CT: (Adjuvant) chemotherapy; RCt: Neo-adjuvant chemo-radiation; TP: Trans-perineal; TV: Trans-vaginal; #: Died two months after treatment; TEM: Trans-anal endoscopic microsurgical resection*

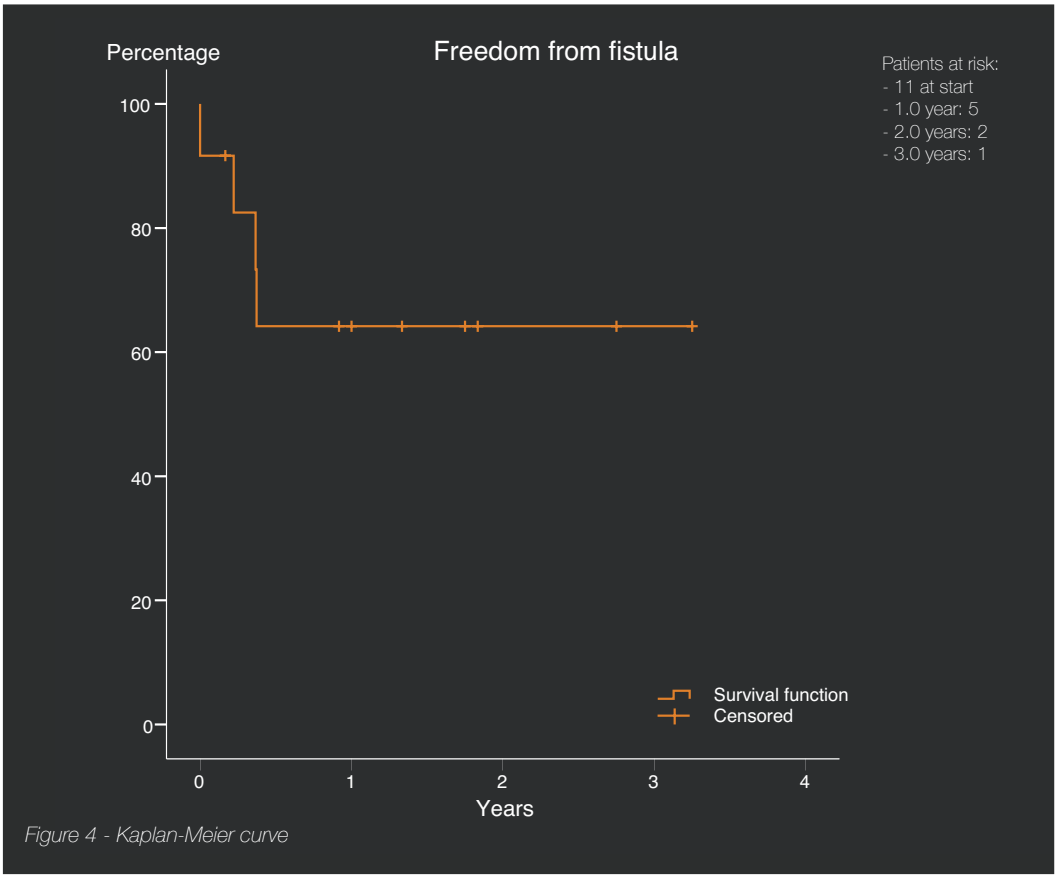


Figure 4 - Kaplan-Meier curve

freedom from fistula (Figure 4). Full recovery from fistula at 1 year was 0.64 (95% confidence interval 0.30–0.85). In 1 patient (8.3%) the fistula never closed. Median time until recurrence was 50 days (range 44-83 days). Of the 3 patients (25.0%) with a recurrence, 1 (33.3%) was treated with a rectus abdominis muscle transposition and closed afterwards, 1 (33.3%) underwent gracilis muscle transposition and the third (33.3%) patient underwent laparoscopic ligation. The latter 2 fistulas are still not closed. The last patient was lost to follow-up. One patient (8.3%) died 2 months after the operation of an unrelated cause (myocardial infarction), which explains the wide range in follow-up duration. Her fistula was closed at the time of death.
No changes in continence status were seen in any of the patients. The complications registered were 1 urinary tract infection, 1 labial abscess and 2 wound infections. The labial abscess was the only complication in a patient with a recurrence. None of the meshes needed to be removed.

Discussion

Our goal was the development of a local approach, easy to learn and perform, and associated with low recurrence rates and minimal complications, which could be a good first option in a treatment algorithm. The muscle flap or transposition techniques are based on the hypothesis that good vascularized tissue needs to be moved to or implanted in the RVF area. We describe a technique using a cross-linked collagen matrix mesh (Permacol). The collagen allows neovascularisation and healthy tissue to

grow into the mesh,[19] mimicking placement of healthy tissue. Resistance to infection is high, since it is a biological cross-linked collagen matrix mesh. The cross-linking resists degradation by host or bacterial collagenases and should insure durability of the mesh.[20] The first treatment of RVF with placement of a mesh was by Moore et al who describe the placement of an acellular porcine dermal graft in only 2 patients.[21] Later, articles appeared describing placement of a mesh consisting of porcine small intestine mucosa[16, 22, 23] and human acellular dermal matrix.[24] Only 2 patients were treated with human acellular dermal matrix mesh. The porcine small intestine mucosa showed closure rates of 71-81.5%, which seem to be reasonably good. This mesh will be completely replaced by the patients' tissue,[23] compared to the Permaco mesh, which allows healthy tissue to grow into it. The follow-up duration in these studies varied between 12 and 22 months. There is a slight difference in closure rate between our results and these studies. This might be explained by the difference in operative technique, the mesh itself, or patient populations included.

More invasive techniques like muscle flaps and transpositions were developed to introduce healthy tissue into the area of the RVF to allow for better healing conditions. These techniques show better closure rates (50-100%),[2-7] but none of them have been studied in a randomized and controlled setting. It is hypothesized that these techniques are associated with high morbidity rates and lower quality of life and impaired sexual function.[6] Only 1 article, describing a series of patients treated with a Martius procedure, reports morbidity levels based on the Clavien-Dindo classification of postoperative complications.[7] The authors do not take into account the results of various factors such as scarring, pain, dyspareunia or sexual dysfunction. The short-term morbidity level was 15%. Furthermore, options after a failed muscle flap may be very limited, while if our technique fails other procedures can still be performed.

Four of our 12 patients did not have a stoma before the mesh was placed. The other 8 patients had pre-existent stomas. Six of them had diverting stomas for the RVF and 2 had stomas placed during operations before the fistula developed (Table 1).

The 2 patients with a restorative proctocolectomy developed a spontaneous RVF without previous pouchitis or anastomotic leakage. Since these 2 RVF occurred spontaneously we did not see an indication for a diverting stoma. Both patients healed after treatment. The other 2 patients without a diverting stoma had a cryptoglandular RVF and a fistula after a transanal endoscopic microsurgical polypectomy. Both were healed after treatment.

Four patients had a history of malignant disease (cervical cancer (N=1), rectal cancer (N=3)), and all had been treated with radiotherapy. The radiotherapy most likely resulted in scarred and hypovascularized tissue in the pelvic area making healing more difficult.[25] Only 1 patient healed using our new technique although this patient died 2 months after surgery. These results seem to indicate that our local technique might not be successful in patients with a history of malignant disease and radiotherapy, even though all had a diverting stoma. A procedure introducing healthy tissue might be more appropriate.

Two patients had a RVF related to Crohn's disease and one of them also had a fourth degree childbirth laceration. Both had pre-existing diverting stomas due to active inflammatory disease, and both healed using our technique. In 1 patient the stoma was reconnected afterwards at the patient's request.

One patient developed a RVF after an episiotomy during childbirth. Several attempts to close the fistula were made in another centre, and finally, a diverting stoma was created. Our technique was successful in this patient and the stoma was later reversed.

The second patient with a cryptoglandular RVF had undergone several previous attempts at closure without success. We did not manage to close this fistula with our

technique, or with a secondary gracilis muscle transposition. Presently, this fistula is still recurrent and the diverting stoma was not closed. The patient decided not to undergo another attempt at closure.

Although only about two-thirds of our patients healed after treatment, we believe our new technique is promising. Almost, all of our patients suffered from inflammatory bowel disease, had undergone pelvic surgery more than once, or had radio/chemotherapy, and still healed after undergoing this local approach. Muscle flaps or transpositions were avoided in these patients. Our proposed technique seems to have a low complication and morbidity rate, is easy to learn and is less invasive than muscle flap techniques.

Some limitations of our study have to be addressed. First of all, this is only a pilot study of a new technique, although data was collected prospectively. Using telephone interviews for some of the patients in follow-up, we may have missed some complications. Selection bias might have occurred during the inclusion period, although consecutive patients were treated. Besides, we did not include preoperative data on quality of life, sexual function and pain, making it difficult to assess the morbidity associated with our procedure. Finally, the number of patients treated in our study is small, but comparable to many other studies in this field because of the low incidence rate of RVF.

Conclusion

We believe our local procedure using a cross-linked collagen biomesh for the treatment of RVF, especially in patients who had undergone extensive previous treatment in the pelvic area, shows promising results with low complication rates. Using this technique as the first step in a treatment algorithm for RVF, more invasive techniques might be avoided in a large number of patients, but are still available after using our technique. Randomized controlled trials with longer follow-up and larger patient numbers are needed, but not likely to materialize due to the low incidence of RVF.

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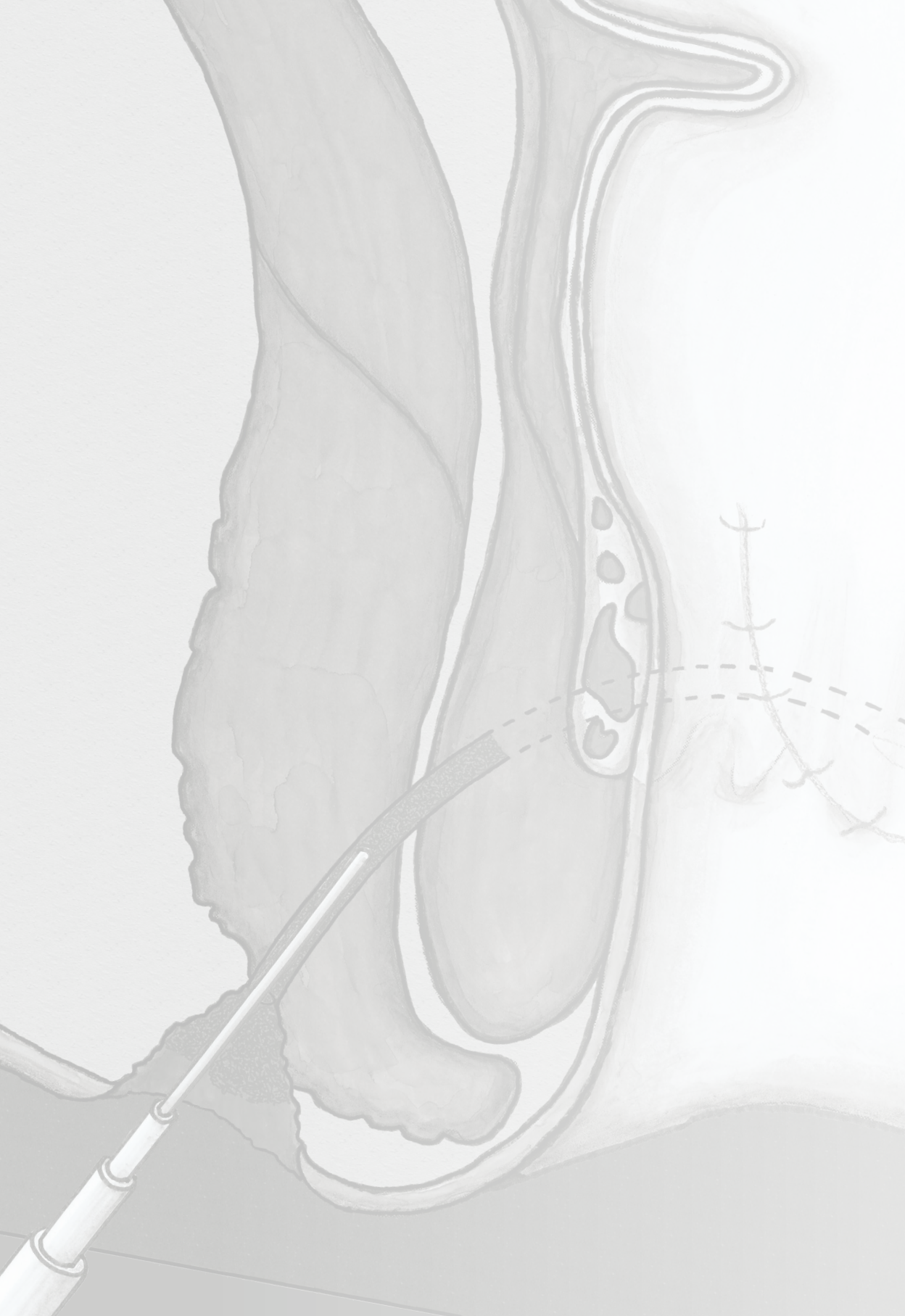

8 Muscle flaps and transpositions for recurrent perianal and rectovaginal fistulas: Fiction or feasible last resort option?

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In preparation

Abstract

Background

Both perianal and rectovaginal fistulas are known to have high recurrence rates after surgical treatment. Muscle flaps and transpositions are by many surgeons seen as a last resort in treatment.

Objective

To evaluate our results using muscle flaps and transpositions in multiple recurrent perianal and rectovaginal fistulas.

Design

A retrospective database study was performed.

Setting

The study was performed in a tertiary referral hospital.

Patients

All patients with multiple recurrent perianal and rectovaginal fistulas treated with any type of muscle flap or transposition in the last decade were included.
Interventions: Any type of muscle flap or transposition.

Main Outcome Measures

The main outcome measures were healing rate and recurrence rate. Secondary outcome measures were time to healing and recurrence, and complications.

Results

Twenty patients were treated in the last 10 years. 10 (50.0%) had a perianal fistula, five (25.0%) a rectovaginal fistula and five (25.0%) a combined perianal and rectovaginal fistula. The median number of previous operations for the fistula was 7.0, ranging from 2 to 12. Median follow-up was 68.5 months (Range 4.1 – 114.8). Fourteen (70.0%) patients healed postoperatively and six had a persisting fistula. Ten of the fourteen (71.4%) healed patients developed a recurrence. At one year the cumulative healing was 0.39 (95% CI 0.14 – 0.63). In one patient the muscle transposition became dehiscent after trauma, one patient developed a superficial wound infection and one a wound abscess.

Limitations

The retrospective design and the use of telephone interviews.

Conclusion

The use of muscle flaps and transpositions in the worst-case recurrent perianal and rectovaginal fistulas does not result in favourable results. The development of new surgical techniques and the evaluation of these techniques in large randomized controlled trials are needed to improve outcome.

Introduction

Many articles discussing surgical treatment of perianal (PF) and rectovaginal fistulas (RVF) start with reports of high recurrence rates and how difficult treatment therefore can be. The vast amount of different procedures that have been developed in the last decades to treat these two conditions seem to prove the above statement. It shows that the best treatment has yet to be developed.

Despite the different aetiology between PF and RVF there is also a resemblance: If all other techniques fail and the fistulas do not heal, muscle flaps or transpositions are by many seen as one of the last resorts of treatment for these conditions. The most used are the gracilis muscle transposition and the Martius procedure,[1, 2] but many others have been described.[3-7] Results for these techniques might not be as favourable as believed by many. Described closure rates for rectovaginal fistulas using the gracilis muscle transpositions and the Martius procedure are as low as 40 and 60% respectively, but some authors report rates up to 100%.[2, 8-10] These numbers appear to be reasonable. However, higher closure rates would be preferable for a last resort treatment, and therefore these results are not so ideal. Secondly, muscle transpositions or flaps are highly invasive techniques that might result in serious morbidity and aesthetic issues. Data on morbidity and aesthetic issues are unfortunately not available, apart from one study describing a postoperative morbidity of 15% based on the Clavien-Dindo classification.[9]

We reserve procedures with muscle transpositions or flaps for the most difficult cases in which other treatments have repeatedly failed or fistula complexes are so complex no other closure options are available. In this paper we present recurring PF and RVF from the last ten years that needed treatment with these invasive procedures in our practice to evaluate our results.

Materials and Methods

We retrospectively searched our database of patients with PF and RVF. All patients treated with any type of muscle flap or transposition for a recurring PF or RVF between 2004 and 2014 in our tertiary referral hospital were included in this study. Only high PF were treated with these techniques, resulting in the exclusion of all low PF.

The criteria for the use of a muscle flap or transposition were the impossibility of performing another local procedure, due to the morbidity of previous interventions, previous complications or fistula anatomy, and if a local procedure was determined not to be useful anymore by the treating surgeon.

Primary outcomes of this study were the healing and recurrence rates after treatment. If the fistula did not close after treatment this was defined as a persisting fistula. Secondary outcomes were time until healing and time until. Prior fistula surgery was defined as any type of surgery for the fistula, including seton treatment. However, seton treatment was not included in the number of previous surgical interventions (Table 1) as no actual closure of the fistula is performed. Drainage of a perianal abscess was not included.

Closure of the PF is defined as a visibly closed external fistula opening without discharge at palpation and compression. Closure of a RVF is defined as closure of the fistula openings during rectal and vaginal exam, and if the patient reports no more fluids, stool or gas leakage vaginally. An MRI-scan was performed if closure of the fistula was unclear.

Table 1 - Patient characteristics

	Value
Male	49.5 years (16.5)
Age	62.7% female
BMI	42.5%
Smoking	37.7 years (15.9)
Previous number of operations	8.7 years (5.7)
Type of fistula - Perianal fistula - Rectovaginal fistula - Combined perianal and rectovaginal fistula	 10 (50.0%) 5 (25.0%) 5 (25.0%)

** Mean, ^ median*

Operations that were performed were gracilis muscle transpositions,[11] Martius procedures,[9] Limberg flaps[12] or gluteal fold VY transposition flap (Figure 1).[13] The choice for one of these types of operations depended on the location and size of the fistula complex.
Patients that were not in outpatient follow-up anymore underwent telephone interviews to evaluate the current status of their fistula, and to find out if and how they were treated for a recurring fistula in another clinic. This study was performed according to national and local medical and ethical laws and guidelines. The local medical ethical committees approved this study.

Results

In total 20 patients were treated with a muscle flap or transposition for a recurring PF or RVF in de last decade in our hospital. Patient characteristics can be seen in Table 1. Ten (50.0%) patients had a PF, 5 (25.0%) patients had a RVF and 5 (25.0%) patients had a combined PF and RVF. The median number of previous operations for the fistula was 7.0, ranging from 2 to 12. The median follow-up was 68.5 months (Range 4.1 – 114.8). Only 14 (70.0%) patients healed after surgery, resulting in 6 persisting fistulas. Four of the persisting fistulas were PF, one was a RVF and one was a combined fistula. Of the 14 patients that healed after surgery 10 (71.4%) later presented with a recurrence. This resulted in a primary success percentage of 20.0%. Median time to healing of the fistula was 2.4 months (Range 1.5 – 6.3). Median time until recurrence was 5.2 months (Range 2.4 – 37.7). Results per patient are shown in Table 2. Cumulative healing was calculated with a Kaplan Meier analysis and is shown in Figures 2 and 3. At one year cumulative healing was 0.32 (95% CI 0.13 – 0.52).
Three complications occurred, all in separate patients. In one patient the muscle flap became dehiscent after a fall out of bed. This was one of the patients with a persisting fistula. In two other patients a wound infection occurred. One was treated with antibiotics, the other had a wound abscess drained.
In the patients with a PF three of the six (50.0%) healed fistulas resulted in a recurrence. Four out of 5 RVF (80.0%) healed after treatment, but three out of the four (75.0%) developed a recurrence. In the patients with a combined PF and RVF four out of five healed (80.0%), but all (100.0%) developed a recurrence. However, in one of these patients the recurrence was only a PF while the RVF stayed closed.
Some of the recurring fistulas after gluteal fold flaps eventually closed, but only after at least 2 or more extra surgical interventions. In two of these cases the gluteal fold

Figure 1 - Gluteal fold VY transposition flap

flap was moved to cover a new small fistula opening, but only after several smaller interventions were performed. In two other cases several interventions (laser ablation, mucosal advancement flap, seton treatment, etc) were needed to close the fistula.

Discussion

Our results after treatment of multiple recurrent PF and RVF with muscle flaps or transpositions are disappointing. Cumulative healing after one year was merely 0.32 (95% CI 0.13 – 0.52).

Although this study was only a retrospective analysis of patients we treated in the last 10 years in our clinic, it shows that treatment of PF and RVF can be very difficult, even with the amount of different techniques that are at our disposal. The results described in other studies show healing rates between 40 and 100%.[2, 8-10] Our results are less favourable and this may be related to our policy of reserving these flaps and transpositions for last resorts in patients with many previous operations, complications or large fistula complexes. This was often not the case in other studies. This raises the question on the usefulness of these techniques in patients with multiple recurrent

Table 2 - Results

Patient	Fistula	Aetiology	Previous types of operations	Previous operations (n)	Diverting stoma	Treatment	Fistula healed	Fistula recurrent	Time until recurrence (months)	Current status	Follow-up (months)
1*	Perianal	C	F, MAF	2	No	Limberg flap	Yes	No	-	Healed	26.5
2*	Perianal	C	St, MAF, FP	9	Yes	VY	No	Yes	-	Recurrent $	4.2
3*	Perianal	C	F, St, MAF	9	No	VY	Yes	Yes	3.2	Recurrent $	8.7
4	Perianal	Cr	St, FG, gluteal transposition flap	5	No	GT	No	Yes	-	Recurrent $	17.5
5*	Perianal	C	F, St, MAF	10	Yes	VY	Yes	No	-	Healed	71.6
6	Perianal	Cr	F, St, MAF, gracilis transposition	12	Yes	VY	Yes	Yes	3.0	Healed $	104.2
7*	Perianal	T	F, St, FG, MAF, J-pouch excision	8	Yes	VY	No	Yes	-	Recurrent $	62.7
8*	Perianal	C	F, St, MAF, ^	7	Yes	VY	Yes	No	-	Healed	85.7
9*	Perianal	C	F, St, ^	5	Yes	Limberg flap	Yes	Yes	4.4	Recurrent $	84.9
10*	Perianal	C	F, St, MAF, FI	7	Yes	VY	No	Yes	-	Closed $	92.7
11	Rectovaginal	T	MAF, FG	3	Yes	GT	Yes	Yes	0.3	Unknown	114.8
12	Rectovaginal	C	MAF	2	Yes	Martius procedure	Yes	Yes	3.0	Recurrent $	72.9
13	Rectovaginal	T	MAF	3	Yes	GT	Yes	No	-	Healed	33.5
14	Rectovaginal	T	MAF	4	Yes	GT	Yes	Yes	3.1	Unknown	67.0
15	Rectovaginal	Cr	FI, MAF, PRP,	5	Yes	GT	No	Yes	-	Recurrent $	48.0
16	Perianal + Rectovaginal	C	St, Mesh repair, F, O, MAF, unknown muscle transposition	8	Yes	GT	Yes	Yes (perianal)	15.9	Recurrent $ (perianal)	28.5
17	Perianal + Rectovaginal	Cr	St, MAF, unknown rotation flap	7	Yes	GT	Yes	Yes	9.4	Recurrent $	113.8
18	Perianal + Rectovaginal	Cr	St, MAF, FG	6	Yes	Martius procedure + MAF	Yes	Yes	31.4	Recurrent $	113.5
19	Perianal + rectovaginal	Cr	St, F, MAF, ^	7	Yes	VY	No	Yes	-	Recurrent $	70.1
20	Perianal + rectovaginal	Cr	St, F, MAF, LAR, O	10	Yes	VY	Yes	Yes	2,63	Recurrent $	49.5

** Male patient, ^ unknown technique, C: Cryptoglandular, Cr: Crohn's disease, T: Traumatic, F: Fistulotomy, St: Seton treatment, MAF: Mucosal advancement flap (endorectal in patients with rectovaginal fistula), FP: Fistula plug, FG: Fibrin glue, FI: Fistulectomy, PRP: Platelet-rich plasma, O: Omentoplasty, LAR: Low anterior resection, VY: Gluteal fold VY transposition flap, GT: Gracilis transposition, $: After further treatment*

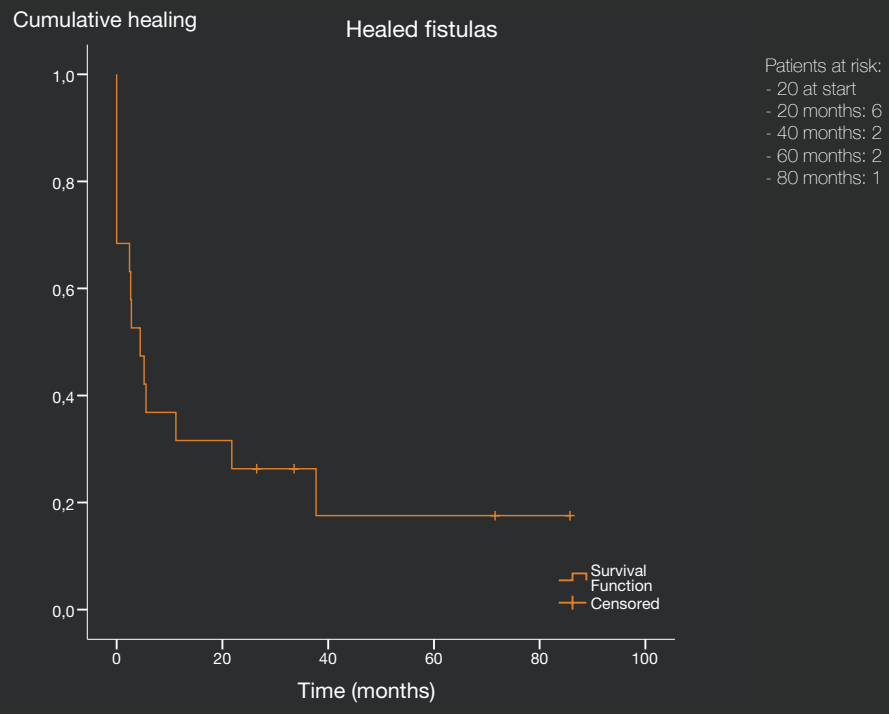

Figure 2 - Kaplan Meier curve for healing of fistulas

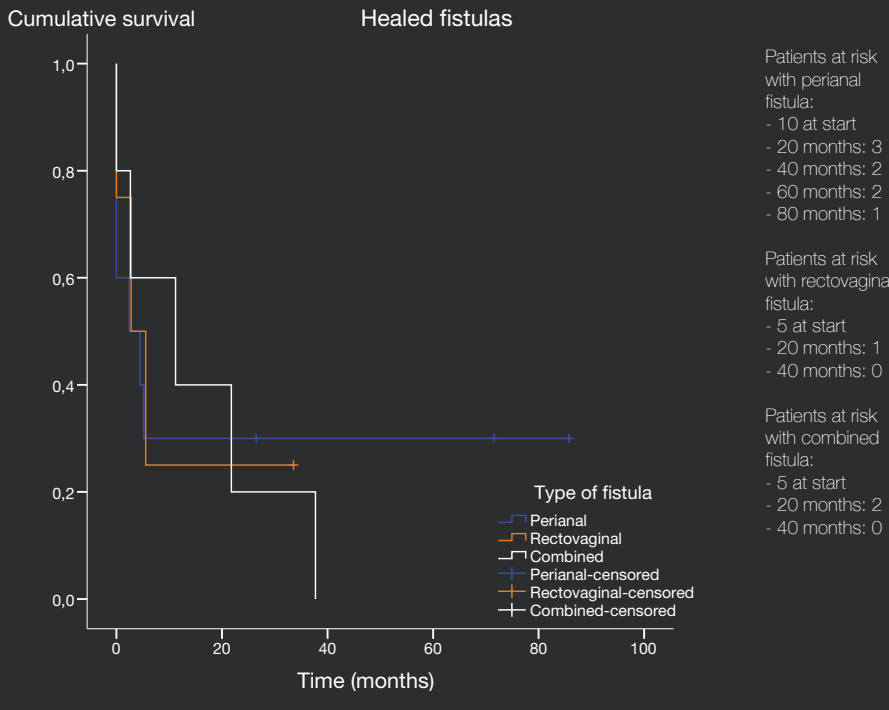

Figure 2 - Kaplan Meier curve for healing of fistulas

fistulas, especially since often extra interventions are needed to heal the patients, and whether or not these techniques should be used as a last resort or in an earlier stage. The gluteal fold flap is an extra option if a muscle flap or transpositions is considered, but as shown several extra interventions are often needed to heal the patient. The downside of all these techniques is that they are considered as more invasive with impaired aesthetic results, although data supporting this are lacking.With, for instance, the introduction of the Ligation of the Intersphincteric Fistula Tract (LIFT) for PF,[14] or placement of biomeshes or laparoscopic omentoplasty for RVF,[15, 16] good attempts were made to improve outcomes. However, now after reasonable time after introduction of these techniques, results are just as disappointing as with previous techniques with closure rates of around 60%.[15, 17] Muscle flaps and transpositions do not seem to be the solution either, and it might be better to focus on the reason for failure of all our surgical techniques.

This reason remains unclear, but the aetiology of the fistulas probably plays a large role. For instance, a RVF occurring after treatment for malignancy with radiotherapy is difficult to treat due to poorly vascularized and scarred tissue.[18] Fistulas related to Crohn's disease are notorious for having a worse outcome than cryptoglandular fistulas with many techniques.[19-22] A specific reason why some cryptoglandular or traumatic/iatrogenic fistulas have a persistent risk for recurrence after surgical treatment is unclear. It has been suggested that epithelialization of fistulas interferes with healing after surgical treatment if the epithelium is not removed before closure of the fistula.[23, 24] Another study disproves this theory and suggests epithelialization does not occur in all fistulas and does not influence healing.[25] The same authors suggest that the actual problem is more likely an on-going inflammation rather then epithelialization of the tract. Altogether, our knowledge regarding fistula aetiology and healing is inadequate and might prevent us from developing better treatments.

This study has of course several limitations. It is a retrospective analysis of operations performed in a selected patient category. Because of this retrospective aspect we might not have included all consecutive patients, but we believe this will probably not influence the shown results much. Telephone interviews are always prone to missing some information or recurrences.

Conclusion

We have now shown that our results are not as good as we expected. Muscle flaps and transpositions can still be used as last resort options, but should probably only be used in selected patients willing to undergo extra operations afterwards if needed. The fact remains that we still do not have ideal treatments for either PF or RVF. We would therefore like to make a plea for both basic research into fistula aetiology as well as the development of new techniques, and maybe more importantly, the evaluation of these techniques in randomized controlled trials. The low incidence of these disorders will call for large and probably international multi-centre studies, which in combination with better insight into fistula aetiology, will hopefully result in the better treatments for PF and RVF.

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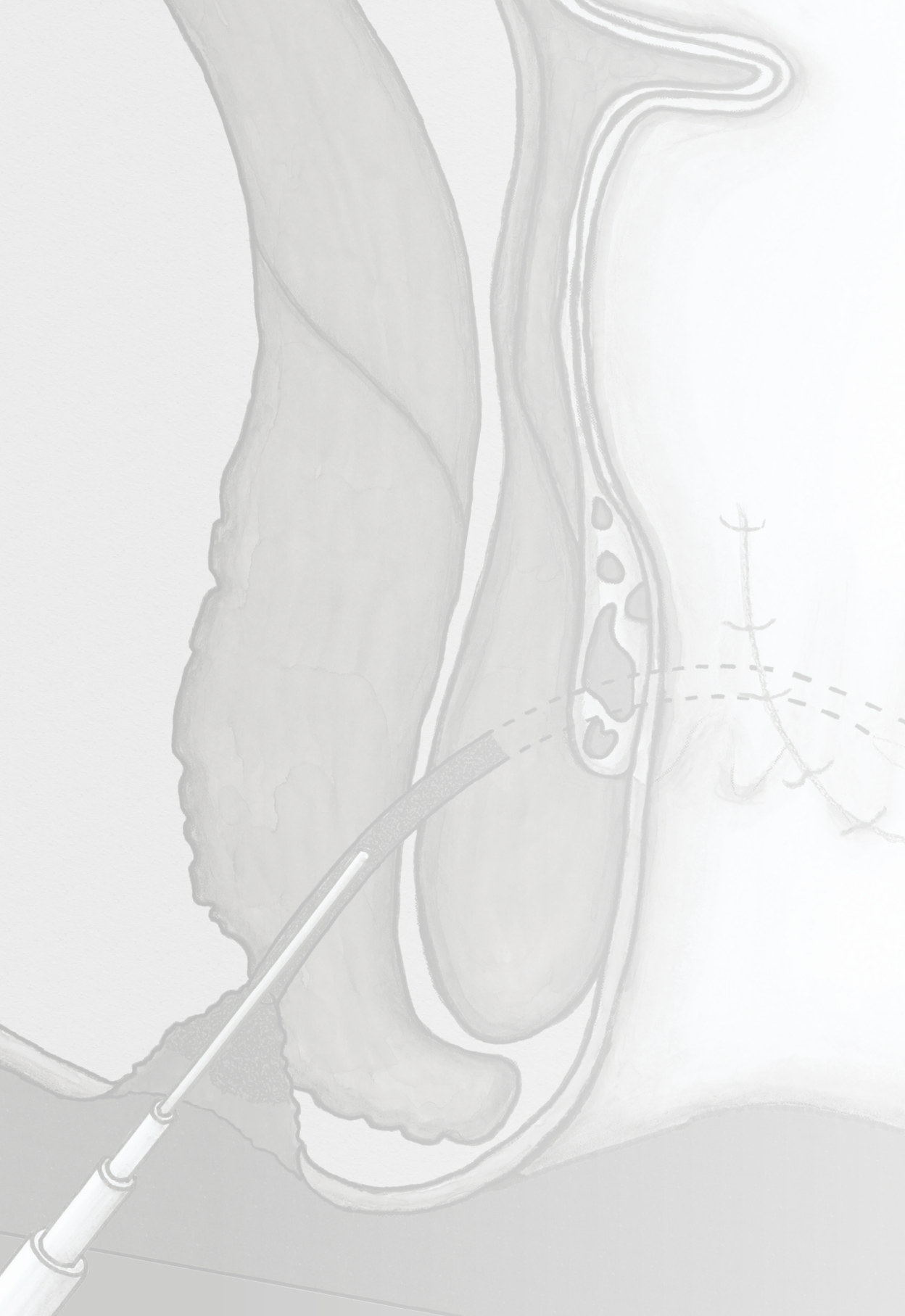

9 The disappointing quality of published studies on operative techniques for rectovaginal fistulas: A blueprint for a prospective multi-institutional study

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Abstract

Background

Treatment of rectovaginal fistulas is difficult, and many surgical interventions have been developed. The best surgical intervention for the closure of these fistulas is still unclear.

Objective

A systematic review was performed reporting the outcomes of different surgical techniques for rectovaginal fistulas.

Data sources

Medline (PubMed, Ovid), Embase (Ovid), and The Cochrane Library databases were searched for eligible articles as well as the references of these articles.

Study selection

Two independent reviewers analysed the search results for eligible articles based on title, abstract, and described results.

Intervention(s)

Any surgical intervention for the closure of rectovaginal fistulas was included.

Main outcome measures

The main outcome was closure rate. Secondary outcomes were quality of life, morbidity, and the effect on sexual functioning.

Results

Many articles with different operative techniques were identified and classified in the following categories: Advancement flaps (endorectal and endovaginal), transperineal closure, Martius procedure, gracilis muscle transposition, rectal resections, transabdominal closure, mesh repair, plugs, endoscopic repairs, closure with biomaterials, and miscellaneous techniques. Results vary widely with closure rates between 0% and >80%. None of the studies were randomized. Because of the poor quality of the identified studies, the comparison of results and performance of a meta-analysis were not possible. Data regarding the secondary outcomes were mostly unavailable.

Limitations

The major limitation of this review was the limited availability of high-quality prospective studies, making it impossible to perform a meta-analysis.

Conclusions

No conclusion about the best surgical intervention for rectovaginal fistulas could be formulated. More large studies of high quality are needed to find the best treatment for rectovaginal fistulas. A design for these high-quality studies was formulated.

Introduction

Rectovaginal fistulas (RVF) can be caused by childbirth trauma (up to 88% of all RVFs, with an incidence of 0.5% after childbirth).[1, 2] They can also be related to Crohn's disease, occur after complicated rectal or gynaecologic surgery or be the result of cryptoglandular disease. RVF may also occur after the treatment of malignant disease in the pelvic area with radiotherapy. Radiotherapy is known to cause tissue damage and poorly vascularized tissue,[3] making the treatment of the RVF even more difficult.
The treatment of these fistulas is also known to be complicated by recurrence ranging between 0% and >80%.[4, 5] Nowadays, many surgical treatments are available, ranging from minimallly invasive laparoscopic techniques,[6] to muscle transpositions and even rectal resections.[7, 8] There is currently no surgical intervention that is widely accepted to be the first and best choice for the treatment of RVFs. The choice for a surgical procedure may also depend on the cause of the RVF making it even more difficult to define the optimal treatment. For example, a RVF occurring after childbirth trauma could possibly be treated with a local surgical procedure only, such as an advancement flap.[9] A RVF after radiotherapy in an oncology patient might only heal after the introduction of healthy tissue as in muscle transpositions.[10]
The objective of this study was to perform a systematic review of available surgical interventions for the closure of RVFs, trying to identify the best intervention(s) and, if possible, to define an optimal treatment algorithm.

Materials and methods

This systematic review was conducted according to the guidelines of the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) group.[11]

Literature search

Medline (Pubmed, Ovid), Embase(Ovid) and Cochrane Library database were searched for relevant studies on surgical treatments for RVFs. No timeframe limitations were used. We used the following text words and MeSH items: Rectovaginal; Rectovag*; Fistula; Fistulas; Fistul*, "Rectovaginal Fistula"[Mesh]; Surgical Procedures, "Operative"[MesH]; Surgery; Surgical procedure; Surgical intervention; Operation; and Closure. All abstracts and studies were reviewed and references in the articles were searched. The final search for this review was conducted on July 14, 2013.

Inclusion criteria

Due to the known limited availability of high-quality studies for surgical treatments of RVFs all published studies describing a surgical intervention for RVFs, and reporting at least closure rates as outcome, were included in this review. All causes were included.

Exclusion criteria

Studies were excluded if the study was conducted in children, if the patient population and results overlapped with another more informative article, if the article was a review, or if the surgical intervention was not clearly described.

Outcomes

The main outcome investigated was the closure rate of the surgical interventions. A fistula was considered closed if no more symptoms (fluids, gas or stool loss vaginally) were reported, and if fistula openings were closed during rectal and vaginal examination. In the case of doubt regarding closure, endoscopy or imaging may be used. If available, secondary outcomes were morbidity, continence, quality of life and sexual functioning.

Data extraction

Two independent reviewers extracted data from the included studies. The data recorded were first author, year of publication, study design, number of patients undergoing the intervention, follow-up duration, and the described outcomes. Studies with fewer than 5 patients were considered to be case reports, and were reported as such.

Study quality

It was decided not to assess the quality of the studies with any scale due to the low availability of studies. Included articles are described in the Results, including study design, number of patients, etc.

Results

The search resulted in 84 citations. Figure 1 shows the results of the search strategy. Wide search criteria were used to avoid missing relevant studies, but this resulted in the exclusion of a large number of studies, mostly because a different disease was investigated in these studies (ie, enterocutaneous fistula, perianal fistula). Studies regarding congenital fistula in children were the second most common reason for exclusion.

Many surgical procedures were identified. We divided the procedures into the following categories: Advancement flaps (Endorectal and endovaginal), transperineal closure, Martius procedure, gracilis muscle transposition, rectal resections, transabdominal closure, mesh repair, plugs, endoscopic repairs, and closure with biomaterials. Techniques not fitting these categories were classified as miscellaneous techniques. We did not find any randomized controlled trials, most likely because of the low incidence numbers of RVF and the diversity of the cause, clinical impact and treatment modalities of the fistulas. An overview of the closure rates per group is presented.

Advancement flaps

Two general categories of advancement flaps were found: Endorectal advancement flap and endovaginal advancement flap. The endorectal flaps consist of the mucosal advancement flap, anocutaneous advancement flap, full-thickness flaps and some variations on these techniques. In total, 22 studies with 533 patients investigating endorectal advancement flaps and 6 studies with 41 patients investigating endovaginal advancement flaps were found (Table 1).[9, 12-33] Of these studies, one was a case report and is not shown in Table 1.[34] The comparison of studies is difficult. Most have low numbers of patients and surgical techniques vary. Some combine the different endorectal techniques and show only total results. All mentioned studies are retrospective. In general, the success rates of these advancement flaps averaged 60%,

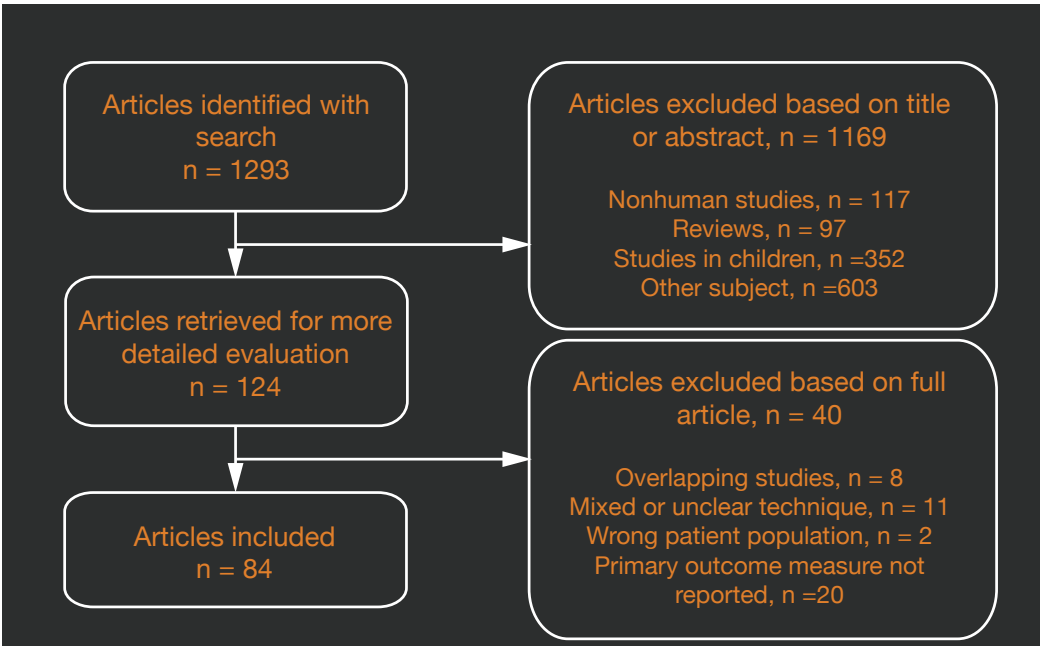

Figure 1 - Search Strategy

although some show closure rates >90%. The rates of continence impairment and sexual functioning are not reported in most studies, nor are morbidity rates. Follow-up in these studies varied between 7 and >40 months, but many studies failed to report follow-up duration altogether.

Transperineal closure

The transperineal closure technique is based on developing the plane between the rectal and vaginal wall through the rectovaginal septum followed by subsequently closing the fistula openings and the developed plane.35 Sphincter defects could be closed using this technique. Mainly retrospective studies with low patient numbers were available for analysis. Only 1 prospective study was identified. A total of 5 articles described the transperineal closure with a total of 82 patients (Table 2).[4, 35-38] Closure rates varied between 64.7% and 100%, although several articles did not describe closure rates. Follow-up varied, roughly, between 3 months and 10 years.

Martius procedure

The Martius procedure places well-vascularized tissue in the plane of the RVF. Usually, adipose tissue from the labia majora is used, but the actual Martius procedure uses the bulbocavernosus muscle and the adipose tissue for the interposition. The number of studies using this technique is very limited. A total of 12 articles were identified with 108 patients (Table 3).[7, 39-46] This included 3 case reports, which are not shown in the table.[47-49] In selected (retrospective) groups, success rates of >90% have been described, and rates seem to vary between 60% and 100%.[42-45, 48] Actual closure rates are difficult to estimate because of the small number of patients. Only 1 article specifically described morbidity levels based on the Clavien-Dindo classification

Table 1 - Advancement flaps

Author	Year of publication	No. of patients	Type of study	Follow-up (mo)	Results (Closed)	Disease cause	Fistula anatomy	Fecal diversion	Secondary outcomes reported
Rothenberger[12]	1982	ERF: 35	Retrospective	Unclear	ERF: 91%	C + T	Low	Unclear	None
Jones[13]	1987	ERF: 23	Retrospective	25	ERF: 68,5%	Cr + T	Low	Some	None
Lowry[14]	1988	ERF: 81	Retrospective	Unclear	ERF: 83%	C + T	Low	Unclear	None
Radcliffe[15]	1988	ERF: 8; EVF: 4	Retrospective	Unclear	ERF: 75%; EVF: 50%	Cr	Unclear	Unclear	None
Sher[16]	1991	EVF: 14	Retrospective	55	EVF: 92.9%	Cr	Unclear	All	None
Wise[17]	1991	ERF: 40	Retrospective	Unclear	ERF: 95%	T	Low	Unclear	Continence*
Kodner[18]	1993	ERF: 71	Retrospective	7	ERF: 93%	C, Cr, T	Low	Some	Continence*
Makowiec[19]	1995	ERF: 12	Retrospective	19.5	ERF: 41.7%	Cr	Unclear	Unclear	Continence*
Hull[20]	1997	ERF: 35	Retrospective	35	ERF: 54.3%	Cr	Low + high	Some	None
Joo[21]	1998	ERF: 20	Retrospective	17.3	ERF: 75%	Cr	Unclear	Some	None
O'Leary[22]	1998	ERF: 6; EVF: 1	Retrospective	38	ERF: 50%; EVF: 0%	Cr	Unclear	Some	Continence*
Hyman[23]	1999	ERF: 12	Retrospective	39	ERF: 91.7%	C, Cr, T	Low	None	Continence*
Milito[24]	1999	ERF: 21	Retrospective	Unclear	ERF: 85.7%	Unclear	Unclear	Unclear	None
Willis[25]	2000	ERF: 15	Retrospective	Unclear	ERF: 86.7%	C, Cr, T	Unclear	Unclear	None
Windsor[26]	2000	ERF: 9; EVF: 4	Retrospective	30	ERF: 33.3%; EVF: 75%	Cr	Low + High	Some	None
Penninckx[27]	2001	ERF: 11; EVF: 13	Retrospective	40.4	ERF: 54.5%; EVF: 53.8%	Cr	Low + high	Some	Continence*
Zimmerman[28]	2002	ERF: 9	Retrospective	15	ERF: 44%	C, T	Low	Some	Continence, sexual functioning*
Athanasiadis[29]	2007	ERF: 7	Retrospective	Unclear	ERF: 57.1%	Cr	Low	Some	Continence
Ellis[30]	2008	ERF: 44	Retrospective	10.5	ERF: 65.9%	C, T	Unclear	Unclear	None
Rodriguez-Wong[9]	2009	ERF: 16	Retrospective	Unclear	ERF: 87.5%	T	Low	Unclear	Sexual functioning*, Continence*
De Parades[31]	2011	ERF: 23	Retrospective	14	ERF: 65%	C, Cr, T	Unclear	Unclear	Continence
Jarrar[32]	2011	ERF: 15	Retrospective	Unclear	ERF: 46.7%	C, Cr	Unclear	Some	Continence*
Queralto[33]	2012	EVF: 5	Retrospective	30.3	EVF: 60%	Cr	Low + high	Unclear	Sexual functioning, continence
Total		ERF: 515; EVF: 41			ERF: 68.8%; EVF: 55.3%				

*ERF: Endorectal advancement flap; EVF: Endovaginal advancement flap; C: Cryptoglandular; Cr: Crohn's disease; M: Malignant. T: Traumatic / Obstetric / Iatrogenic; *: No standardized questionnaire / Unclear*

Table 2 - Transperineal procedures

Author	Year of publication	No. of patients	Type of study	Follow-up (mo)	Results (Closed)	Disease cause	Fistula anatomy	Fecal diversion	Secondary outcomes reported
Russell[35]	1977	21	Retrospective	>10 years	Unclear, multiple operations	C, Cr, T	Low	Unclear	None
Wiskind[4]	1992	21	Retrospective	3 months – 8 years	100% closed	C, Cr	Low	Unclear	None
Athanasiadis[36]	1995	12	Prospective	3 months – 9 years	64.7% closed	C, Cr, T	Unclear	Unclear	Continence*
Athanasiadis[37]	1996	11	Retrospective	Unclear	Not specified	Cr	Low	Unclear	Continence*
Chew[38]	2004	7	Retrospective	24	100% closed	T	Unclear	Some	Continence
Total		72			Calculation not possible				

*C: Cryptoglandular; Cr: Crohn's disease; M: Malignant; T: Traumatic / obstetric / iatrogenic; *: No standardized questionnaire / Unclear*

Table 3 - Martius procedure

Author	Year of publication	No. of patients	Type of study	Follow-up (mo)	Results (Closed)	Disease cause	Fistula anatomy	Fecal diversion	Secondary outcomes reported
White[7]	1982	14	Retrospective	Unclear	92% closed	M	Unclear	Unclear	None
Aartsen[39]	1988	14	Retrospective	10 years	93% closed	M	Unclear	Unclear	None
Elkins[40]	1990	6	Retrospective	Unclear	Not specified	T, M	Unclear	Unclear	None
Pinedo[41]	1998	6	Retrospective	23	Not specified	C, Cr, T	Unclear	All	Continence*
McNevin[42]	2007	16	Retrospective	75 weeks	94% closed	C, Cr, T	Unclear	Some	Continence*, Sexual functioning*
Sogne[43]	2007	14	Retrospective	40	93% closed	Cr, M, T	Unclear	Unclear	Continence*, Sexual functioning*
Cui[44]	2009	6	Retrospective	14	100% closed	M, T	Unclear	Some	Continence*, Sexual functioning*, Quality of life*
Pitel[45]	2011	23	Retrospective	35	65% closed	C, Cr, T	Low	Some	Morbidity, Continence, Sexual functioning, Quality of life
Kin[46]	2012	5	Retrospective	26	100% closed	C, Cr, T	Unclear	Some	Continence*, Sexual functioning*
Total		104			Calculation not possible				

*C: Cryptoglandular; Cr: Crohn's disease; M: Malignant; T: Traumatic / Obstetric / Iatrogenic *: No standardized questionnaire / unclear*

of postoperative complications.[45] This short-term morbidity level was 15%. Other secondary outcomes were reported in several studies. However, the method of reporting these outcomes was disappointing. Only 1 study used standardized questionnaires and reported no continence, quality of life or sexual functioning issues.[45] Follow-up duration is relatively good, ranging between 14 months and 10 years.

Gracilis muscle transposition

This technique uses the gracilis muscle as interposition between rectum and vagina. Available results seem comparable to the Martius procedure with >90% closure.50-52 Again numbers are low, and most data is retrospective. In total, we identified 15 studies with 108 patients (Table 4), including 5 case reports that are not shown in the table.[10, 50-63] Morbidity levels are not clearly described, but quality of life and sexual activity seem to remain abnormal even after the healing of the fistula,[52] although another study shows the opposite.[59] Reported follow-up durations are reasonably long between 14 months and >3 years.

Rectal resections

A more invasive procedure is partial rectal resection with anastomosis.[64] A newer technique is the stapled transanal rectal resection, which is described in a case report (not shown in Table 5).[8] Another possibility is transanal endoscopic microsurgery (TEM), which is described in only 1 retrospective study with 13 patients.[65] Because of the low numbers and low evidence, we cannot define closure rates for these techniques (Table 5). Morbidity levels are not reported in these articles.

Transabdominal procedurres

For high rectovaginal fistulas, a transabdominal approach can be used. Nowadays, these are most commonly performed laparoscopically and include ligation of the fistula with or without interposition of omentum. We found only 1 study with a reasonable amount of patients (N = 40) describing results using this laparoscopic technique. The closure rate was 95%. The number of studies describing transabdominal procedures was 4 with a total patient number of only 52 (Table 6), 2 of which were case reports (not shown in the table).[6, 66-68] Morbidity levels were not described. The reported follow-up durations were 22 and 28 months.

Mesh repair

Several types of meshes were used as interposition in the rectovaginal septum (Table 7). The first mesh repair described was by Moore et al in a case report.[69] They use Acellular porcine dermal graft (Pelvicol) in 2 patients. Later, other meshes used were porcine small intestinal submucosa (Surgisis),[30, 70, 71] and acellular human matrix (Alloderm).[72] Porcine small intestinal submucosa showed closure rates of 71% to 81.5% in 48 patients. Acellular human matrix was only described in a case-report (2 patients). Morbidity levels were not specifically reported. Reasonable follow-up durations of 12 and 22 months were described.

Table 4 - Gracilis muscle transposition

Author	Year of publication	No. of patients	Type of study	Follow-up (mo)	Results (Closed)	Disease cause	Fistula anatomy	Fecal diversion	Secondary outcomes reported
Obrink[53]	1978	16	Retrospective	Unclear	43%	M	Unclear	Unclear	None
Rius[54]	2000	3	Retrospective	18	66%	Cr	Unclear	Unclear	None
Rabau[55]	2006	6	Retrospective	Unclear	Not specified	C, Cr, M	Unclear	Yes	Morbidity*
Zmora[50]	2006	6	Retrospective	14	100%	Cr, M, T	Unclear	Yes	None
Fürst[51]	2008	12	Retrospective	3.4 years	92%	Cr	Low + high	Yes	Continence*
Wexner[56]	2008	17	Retrospective	Unclear	88%	Cr, M, T	Unclear	Yes	None
Lefevre[52]	2009	8	Retrospective	28	60%	Cr, T	Unclear	Yes	Sexual functioning*, Quality of life
Ulrich[57]	2009	9	Retrospective	28	Not specified	Cr, M	Unclear	Yes	None
Nassar[58]	2011	11	Retrospective	35	100%	M, T	Low + high	Yes	Morbidity*
Chen[59]	2013	11	Prospective	18	Not specified	Unclear	Unclear	Unclear	Continence, Sexual functioning, Quality of life
Total		99			Calculation not possible				

*C: Cryptoglandular; Cr: Crohn's disease; M: Malignant; T: Traumatic / obstetric / iatrogenic; *: No standardized questionnaire / Unclear*

Table 5 - Rectal resections

Author	Year of publication	No. of patients	Type of study	Follow-up (mo)	Results (Closed)	Disease cause	Fistula anatomy	Fecal diversion	Secondary outcomes reported
Kux[$64]	1986	7	Retrospective	Unclear	100% closed	Unclear	High	Unclear	None
D'Ambrosio[^65]	2012	13	Retrospective	25	92.3% closed	M, T	Unclear	Yes	Continence*

*$ Anterior resection; ^ Transanal Endoscopic Microsurgery resection; M: Malignant; T: Traumatic / Obstetric / Iatrogenic * No standardized questionnaire / Unclear*

Table 6 - Transabdominal procedures

Author	Year of publication	No. of patients	Type of study	Follow-up (mo)	Results (Closed)	Disease cause	Fistula anatomy	Fecal diversion	Secondary outcomes reported
Van der Hagen[6]	2011	40	Prospective	28	95%	Cr, M, T	High	No	Quality of life, Continence
Schloericke[66]	2012	9	Retrospective	22	100%	C, Cr, M, T	Low	Some	None

C: Cryptoglandular; Cr: Crohn's disease; M: Malignant; T: Traumatic / Obstetric / Iatrogenic

Plugs

Fistula plugs are well described for the treatment of perianal fistulas.[73] Less information is known for the treatment of RVFs. Our search returned only four studies investigating fistula plugs.[5, 30, 74, 75] All of these studies used plugs made from porcine small intestine mucosa (Surgisis). In total, 49 patients treated with these plugs were described (Table 8). Results seem to be disappointing with closure rates of 20%. Morbidity levels were not clearly described. Follow-up duration varies widely between 15 weeks and >2 years.

Endoscopic repair

Three endoscopic repair techniques were found. One technique is the well-known transanal endoscopic microsurgery, which was used to make a mucosal advancement flap under better vision.[76] Two other techniques use Resolution clips; in 1 study combined with histoacryl glue.[77, 78] All 3 articles are case reports with only 1 patient treated.

Biomaterials

Several biomaterials have been used for closure of RVFs. Fibrin glue was injected in the fistula resulting in a closure rate of 60%; however, the number of patients was low (Table 9).[79] The follow-up duration in this study was 26 months. A case-report describes successful injection of platelet-rich plasma in the RVF.[80] Garcia-Olmo et al described a case that was treated with autologous stem cells.[81] Another case-report describes 1 case with the injection of purified bovine serum albumin + glutaraldehyde (Bioglue) into the fistula.[82] Because of the different treatments described, and because 3 of 4 studies were case reports, no conclusions regarding closure rates can be formulated.

Miscellaneous techniques

Some techniques could not easily be classified in the other categories and were therefore mentioned here (Table 10).[83-86] Most of these techniques consist of other types of muscle transpositions and are case reports.[87-90] Schouten and Oom described rectal sleeve advancement in which the distal rectum is circumferentially mobilized and the most distal part resected.[85] The fistula is resected, and a new rectal anastomosis is made at the dentate line. The procedure is invasive, but seems to have reasonable closure rates (62.5%) and low morbidity levels. Hull et al perform closure of the fistula with episioproctotomy, in which they create a situation similar to a fourth-degree perineal childbirth laceration while resecting the fistula.[86] Then they closed the rectal mucosa, the overlying sphincter muscle, the vaginal mucosa, and finally the perineal skin. Closure rates of approximately 62% were reported. This is one of the few studies reporting data on quality of life, faecal function, and sexual functioning, although these data were only collected at the end of follow-up. They show better sexual and faecal function for episioproctotomy than for endorectal advancement flaps.

Discussion

To our knowledge, our systematic review is the only review trying to compare all surgical techniques for closure of RVFs and identified many techniques used to treat this disorder. The large amount of available techniques indicates the optimal treatment for RVF has not yet been found. New techniques are still being developed, because no standard treatment has been identified.

Table 7 - Mesh repair

Author	Year of publication	No. of patients	Type of study	Follow-up (mo)	Results (Closed)	Disease cause	Fistula anatomy	Fecal diversion	Secondary outcomes reported
Ellis[$30]	2008	27	Retrospective	22	81.5%	C, Cr	Unclear	Unclear	None
Schwandner[$70]	2009	21	Retrospective	12	71%	C, Cr, M, T	Low	Some	None
Total		48			76.3%				

$ Porcine small intestine mucosa (Surgisis); C: Cryptoglandular; Cr: Crohn's disease; M: Malignant; T: Traumatic / Obstetric / Iatrogenic

Table 8 - Plugs

Author	Year of publication	No. of patients	Type of study	Follow-up (mo)	Results (Closed)	Disease cause	Fistula anatomy	Fecal diversion	Secondary outcomes reported
Ellis[$30]	2008	7	Retrospective	22	85.7%	C, Cr	Unclear	Unclear	None
Goncalves[$74]	2009	12	Retrospective	15 weeks	58%	Cr, T	Unclear	Unclear	None
Thekkinkattil[$75]	2009	10	Retrospective	47 weeks	20%	C, Cr	Low + high	Unclear	None
Gajsek[$5]	2011	20	Prospective	118 weeks	20%	C, T	Unclear	Unclear	None
Total		49			45.9% closed				

$ Porcine small intestine mucosa (Surgisis); C: Cryptoglandular; Cr: Crohn's disease; T: Traumatic / Obstetric / Iatrogenic

Table 9 - Other biomaterials

Author	Year of publication	No. of patients	Type of study	Follow-up (mo)	Results (Closed)	Disease cause	Fistula anatomy	Fecal diversion	Secondary outcomes reported
Venkatesh[$79]	1999	8	Prospective	26	75%	C, Cr	Unclear	Unclear	None

$ Fibrin glue; C: Cryptoglandular; Cr: Crohn's disease

It was not possible to perform a meta-analysis on any of the techniques found because of the limited amount of studies and the low quality of all studies. Prospective studies were rare, and number of patients in all studies was low. Hence, it is difficult to draw conclusions on which technique should be preferred for the surgical closure of RVF. Closure rates described for the available techniques vary not only widely between the different techniques, but also between articles describing the same techniques. Whether these differences in closure rates for the same techniques can be attributed to a specific reason remains unclear. It is possible that the dedication and experience of the surgeons or even the actual operative technique varied between studies, possibly explaining the variation of reported results.

It could be discussed that local techniques like advancement flaps, fistula plugs or mesh repairs should be used as a first treatment option, because they are less invasive than muscle transpositions and resection. In this way, invasive procedures will not be necessary for all patients. In general, it could be defended that the local techniques result in less wound surface. This might result in a lower risk of infections, apart from the fact that less scaring results in a better cosmetic outcome. Unfortunately, there is no data supporting this.

Additionally, the cause of the RVF is not taken into account in many studies, and, if it is, numbers are too low to make comparisons. It is reasonable to believe that different causes require different surgical techniques, although there are no data supporting this. It is, for instance, common to treat active Crohn's disease first, before attempting any surgical intervention for a RVF. We believe, therefore, that it is not possible to advice a certain procedure over the other procedures, and surgical technique should be chosen case by case.

Another important outcome after treatment of a RVF is quality of life. Many of the developed techniques are invasive, and could, in theory, result in high postoperative morbidity levels and possibly lower quality of life. However, studies reporting these outcomes are rare, and often no standardized questionnaires are used. Similar reasons for lack of validated data are seen regarding continence status and sexual functioning. Data about these outcomes are therefore limited.

The major limitation of this study is the limited availability of prospective and high-quality studies. We would therefore like to suggest a standard design for future studies. Hopefully, this will result in high-quality studies making the quest for the best surgical treatment easier and more productive.

The low incidence of RVF is the main cause of low quality studies. Prospective trials should be randomized, and, to make this possible, it will most likely be necessary to start multicentre trials to reach the needed inclusion numbers.

The causes of RVF are mixed in many studies. We would like to suggest aiming a study for specific disease cause, or at least reporting the results per cause, allowing for better comparison between studies. This should give more insight in best treatment per caus. In our opinion 4 main categories might be best: Cryptoglandular disease, Crohn's disease, postmalignancy (with and without previous radiotherapy) and traumatic (including traumatic fistula, obstetric fistula, and iatrogenic fistula after interventions).

Fistula anatomy should play an important role in future studies. It is reasonable to believe that high RVF might be better treated with transabdominal procedures compared to low RVF, which might be better treated with anorectal, transvaginal or transperineal approaches. Although this does not apply to all available procedures, we suggest authors report on the anatomy of the RVF. A useful classification could be the division of RVF in low (located in the lower half of the vaginal septum or lower one third of the rectum) or high (located in the upper half of the vaginal septum up to the posterior

vaginal fornix or the middle third of the rectum).[91]
Faecal diversion is unfortunately not described in many studies. The reason for diversion is sometimes the treatment of symptoms caused by the RVF but, most frequently, it is performed to enhance chances of closure of the RVF. The reason for diversion should be stated.
Regarding outcomes, the most important one is still the success rate of an intervention. What is not always taken into account, and even less often described, is the difference between treatment failure and the recurrence of a RVF. We believe this outcome should thus be reported as persisting fistula (or treatment failure) and recurrent fistula.
Although secondary outcomes are often not reported, and just as often not measured in the right way, they are as or maybe even more important than the success rate of a treatment. The closure of a RVF is the goal of a surgical procedure, of course, but this should not be at the cost of quality of life, incontinence, sexual dysfunctioning or high levels of morbidity. Therefore, we advise reporting these outcomes using standardized measurements. Quality of life can be measured and reported using, the validated SF-12.[92, 93] Continence levels can be measured using different tools like the Wexner continence score or the Vaizey score.[94, 95] Sexual functioning can be reported using the Female Sexual Function Index.[96, 97] To show the influence of the treatments on these outcomes, the tools should be used pre- and postoperatively.
Postoperative morbidity levels and complications can be reported systematically using the Clavien-Dindo classification.[98]

Conclusion

This systematic review did not result in a treatment algorithm for RVF owing to the many available surgical techniques, disease causes, types of fistula anatomy, and, most importantly, the low level of evidence in the available literature. We hope that our plea for multi-institutional studies, specific disease cause categories, categories of fistula anatomy, and systematic reporting of all important outcomes will result in high-quality studies finally showing us the Holy Grail of RVF treatment.

Table 10 - Miscellaneous techniques

Author	Year of publication	No. of patients	Type of study	Follow-up (mo)	Results (Closed)	Disease cause	Fistula anatomy	Fecal diversion	Secondary outcomes reported
Kosugi[±83]	2005	5	Retrospective	Unclear	100%	M	Low + high	Some	Continence*
Oom[=84]	2006	26	Retrospective	14	62%	C, Cr, T	Low	Unclear	Continence, Sexual functioning*
Schouten[#85]	2009	8	Retrospective	12	62.5%	C, T	Unclear	Some	Continence*, Sexual functioning*
Hull[§86]	2011	50	Retrospective	49.2	62.2%	C, T	Unclear	Some	Continence, Sexual functioning, Quality of life

*± Gluteal-fold flap; = Puborectal sling interposition; # Rectal sleeve advancement; § Episioproctotomy; C: Cryptoglandular; Cr: Crohn's disease; M: Malignant; T: Traumatic / Obstetric / Iatrogenic * No standardized questionnaire / Unclear*

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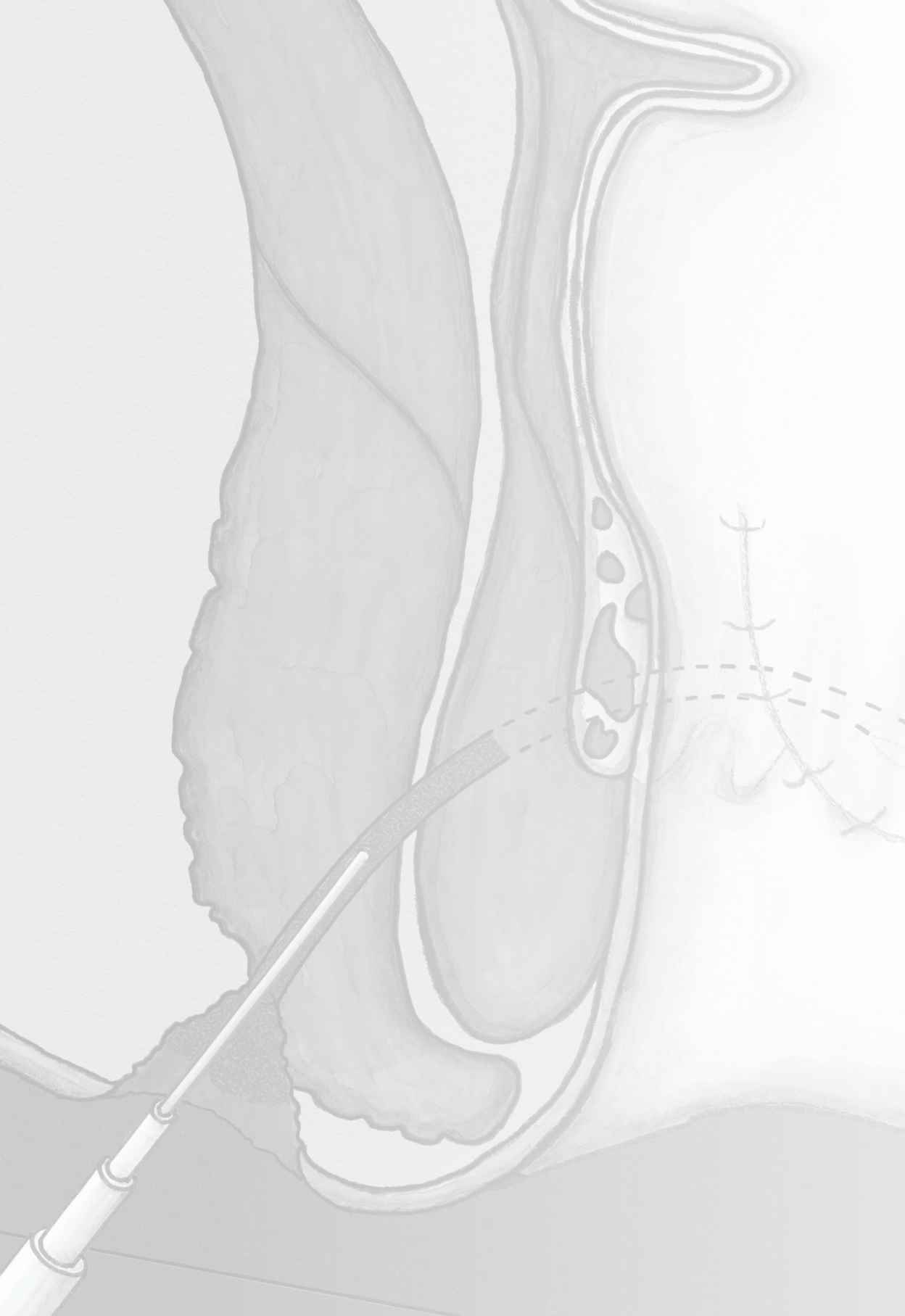


10 General discussion

Current status

Perianal fistulas

As previously described, perianal fistulas (PF) are nowadays mostly divided in low and high PFs, but the classification according to Park's is also still used.[1] To define the best treatments for these fistulas the classification in low and high is often the most useful. Low PFs are commonly treated with fistulotomy. Closure rates described are high with some authors even reporting rates up to a 100%.[2-5] The findings in ***chapter 2*** however show a lower healing rate of 0.81 (95% CI, 0.71-0.85). In this study a long follow-up of 5 years was achieved. Even though we do not reach a 100% healing rate in our patients, these results seem comparable to many other studies. Moreover, ***chapter 2*** of this thesis focussed specifically on several secondary outcome measures after performing fistulotomy. The postoperative continence scores found make it debatable if fistulotomy is a good treatment. Unfortunately it is about the only definitive treatment available for low PFs. Some have tried other techniques like the Ligation of the intersphincteric fistula tract (LIFT) for low PF to avoid sphincter damage,[6] but more data is needed to show the benefit of this technique, making the fistulotomy still the golden standard for low PF treatment.

High PFs are more difficult to treat compared to low PFs. In ***chapter 3*** it is shown that many techniques are available, and that most of these techniques have not been investigated in randomized controlled trials (RCTs). This makes it difficult to advise a certain technique over any other technique. For a long time the mucosa advancement flap (MAF) was seen as the golden standard for closure of a high PF, but even though the technique is known by many surgeons, it is not the most easy technique to master. It seems that the LIFT is gaining more supporters, because it is easy to learn and perform, and results seem comparable to the MAF.[7] It might not be unlikely that in the near future many will see this technique as the new golden standard.

A suggestion, not evidence-based, for a treatment algorithm might be the following (Figure 1). It could be useful to start with a technique that is little invasive, but that complies with the general idea that closure of the internal fistula opening is the preferred repair mechanism. Hopefully, we can prevent the use of more invasive techniques in as many patients as possible.

Various techniques would then be suitable to start with, like the fistula plug,[8] but also techniques like fibrin glue[9] or stem cells[10] when they are not combined with a MAF.

For failures of these techniques a next step could be one of the nowadays well-known techniques like the MAF, combined or not with biomaterials like platelet-rich plasma (PRP) (***Chapters 4 and 5***), fibrin glue, stem cells or others, or one could use the LIFT.[11] Which to use depends mostly on the surgeon's experience, and on the fistula anatomy (course of fistula tract, side tracts, etc.) allowing for the technique to be used. Whether or not the techniques should be retried in case of failure can be discussed, because continence issues might be more likely to arise after multiple interventions. What would be more suitable is to switch techniques in case of failure, meaning the MAF should be followed by a LIFT, and the LIFT by a MAF.

What to do when these techniques fail is even more unclear. We do not know why surgical procedures fail, but one of the ideas is that the fistula tracts still contain much inflammation resulting in failure.[12] This could mean techniques like the video-assisted anal fistula treatment (electro-coagulation)[13] or laser ablation techniques[14] might be useful to clear the tracts of inflammation allowing for secondary healing after a MAF or LIFT.

If maximal invasive techniques like fistulotomy with sphincter reconstruction,[15] rectal wall advancement[16] or even rectal resections, are useful as a further step is not clear due to the low quality of data available. As a last resort, techniques using muscle flaps or transpositions may be used as described in ***chapter 8***, although the results are not as positive as hoped.
Faecal diversion could be useful during treatment or could be used as treatment for the fistula itself as one of the last options. It is usually not necessary to divert before treatment of the PF, but in some cases it might be beneficial as can be seen in ***chapter 8***.
Whether any of the previously mentioned options should be preceded by non-cutting seton drainage to clear inflammation also remains a matter of debate. Some authors report good results with the so-called two-stage technique,[17] but others show the addition of the seton treatment is not necessary.[18] Besides the usefulness of seton drainage prior to another technique, many more seton treatment variations are available and it is not clear which variation would be the best.[19] If none of the above described options result in healing or acceptable symptoms, a non-cutting draining seton can be used as definitive treatment.
The cause of the fistula is of course also important for PF. As was described in ***chapter 6***, PF incidence is high in patients with Crohn's disease and results of treatment are not good with high recurrence rates, which is also shown in other studies and in ***chapter 5***.[20-22] Unfortunately, it is not known if one specific technique should be used for Crohn's disease related fistulas, but we do know that we should only treat surgically when the intraluminal disease is in regression.
The aim of treatment of a benign disease like PF is to render the patient as symptom-free as possible. In other words: The patient should be aware as little as possible of the disease and its symptoms, and of the consequences of the treatment that was performed to cure it.

Rectovaginal fistulas

Defining the best treatment for rectovaginal fistulas (RVF) is currently not possible. It is unlikely that this will be the case in the near future. As was shown in ***Chapter 9***, many different techniques are available for the surgical repair of these fistulas, but the number of studies and the quality of available data are so low that using these data to define a treatment algorithm would eventually result in an opinion-based advice. In the future, next to options for better surgical treatments, secondary outcomes like quality of life and sexual function have to be taken into account.
The new technique described in ***chapter 7*** is not yet the ultimate solution for closing RVF, but it seems to be a good addition to the treatments we already have. About two-thirds of the patients treated using this technique healed. These results, when confirmed in other studies might justify the avoidance of much more invasive techniques in a large number of patients.[23, 24]
As stated before, any attempt to create an evidence-based treatment algorithm, would result in failure. An advice on a treatment strategy, however, although not evidence-based, could be useful in practice (Figure 2). Based on the fact that high recurrence rates are seen for RVF, often resulting in multiple operations for patients, it would be logical to start with the least invasive procedures. In this way, in case of failure, other techniques are still possible.
The treatment algorithm could therefore start with a transperineal or transvaginal approach,[25, 26] with or without mesh repair, plug repair,[27] or the use of some

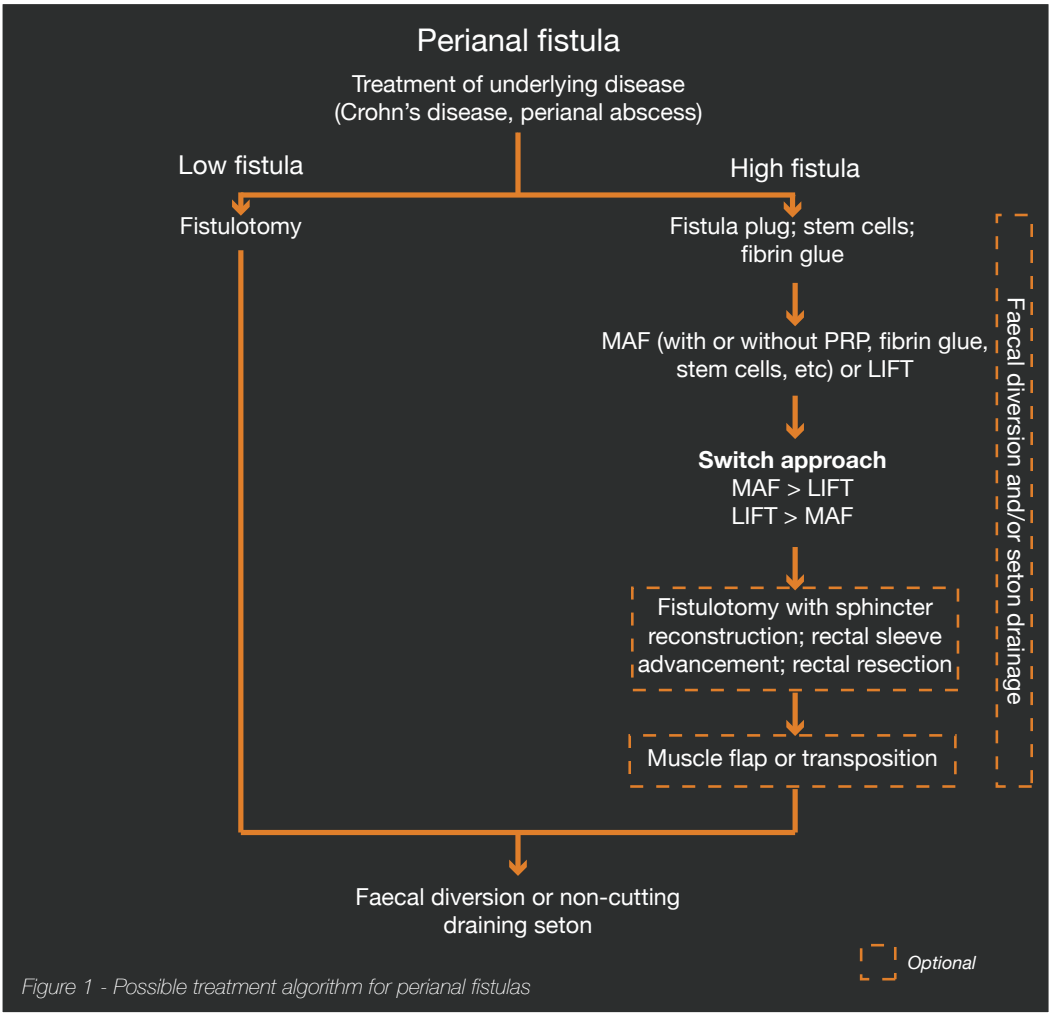


Figure 1 - Possible treatment algorithm for perianal fistulas

biomaterials.[28] What should be the next step in this algorithm is up for discussion. Advancement flaps, endorectal or endovaginal,[29, 30] or a laparoscopic repair with omentoplasty might be a good candidate.[31] The new endoscopic approaches, described in ***chapter 9***, might also be a good option in specialized centres.[32-34]
In case all these techniques fail a next step could be a muscle or transposition flap. The Gracilis muscle transposition and the (modified) Martius procedure are probably the best known of these techniques,[24, 35] but newer procedures could be used in specialized centres or in specific cases.[36, 37] It has always been believed that the muscle placing techniques are the best or last options in many cases. However, as shown in ***chapter 8***, the results of these techniques are not as good as we might hope, and if we can prevent their use with the techniques previously mentioned this would benefit our patient.
Although basically not techniques to repair a RVF, (partial) rectal resections could be the final option if all other treatments fail. These techniques range from a complete low anterior resection,[38] to the new transanal stapled rectal resection.[39] If these techniques should be used depends upon the specific patient, since these techniques are not without risk, although not much data is available for their use in RVF. Often patients will be faecally diverted at this point in the treatment, which could also be an option as final treatment.

Another issue, which has to be addressed regarding the treatment of a RVF, is the aetiology of the fistula. For a basic cryptoglandular or traumatic RVF this described algorithm might work well. However, for a malignancy related or Crohn's disease related RVF it might be better to start with a technique that introduces healthy tissue like a muscle transposition, because local techniques seem more likely to fail as was shown in ***chapter 7***.

Besides the type of fistula (Cause of the fistula; High vs. low), the specific choice for the treatment of a patient also depends on the experience of the surgeon and the clinic in which the procedure is performed. Importantly, the expectations of the patient need to be taken into account. The results of our studies add relevant information that can be used while counselling the patient. Does the patient want to be healed completely, with the risk of increased postoperative incontinence or impaired sexual function, or will she be satisfied with remaining symptoms and no deterioration in these other aspects, with for instance faecal diversion?

What treatment to use remains case specific for the reasons mentioned above. A general advice to start low invasive and work towards more invasive techniques is the most reasonable sequence. Whether or not these options should be preceded by or combined with faecal diversion, is also not clear and should also be case-specific.

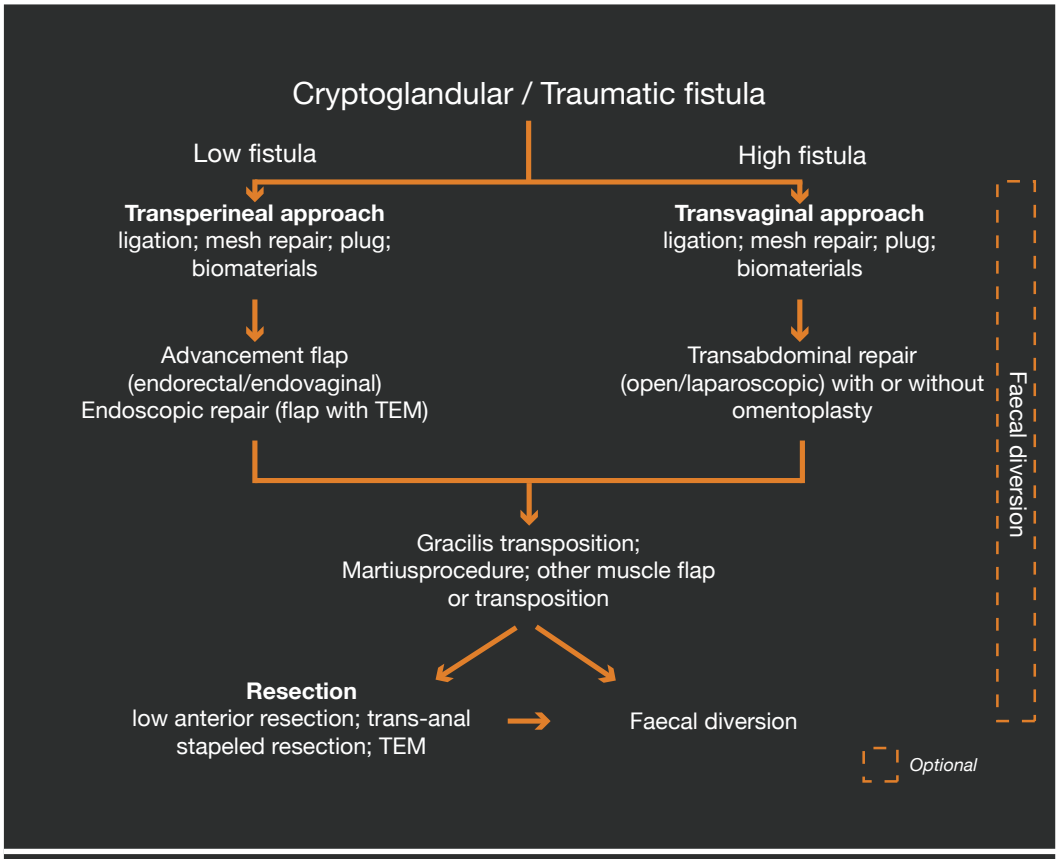
Perspectives for the future

Even though PF and RVF are two different entities, they do share some similarities. Both are not very common and both are difficult to treat. Evidence on how best to treat these diseases is limited, which applies for RVF even more than for PF. Only developing new surgical procedures might not be the best way to tackle this problem. Probably, it will be more productive if we try to figure out why our treatments fail.

Is it epithelialization that prevents our treated fistulas to heal,[40] or is this hypothesis wrong like some suggest?[12] Some suggest it might be the level of inflammation inside the fistula tracts.[12] However, it was already shown that drainage of inflammation with seton treatment before final closure does not seem to improve the outcome.[18] Although others have found clues that continuing inflammation prevents key cells in tissue healing, myofibroblasts, to migrate to and arrange at the disease site.[41]

The persistence of some fistulas might also be related to the bacterial flora inside the fistula tracts. Some authors have suggested that in patients with Crohn's disease bacterial antigens might trigger an abberant (probably genetically triggered) immune response, resulting in a proinflammatory reaction and finally in a PF.[42] This cascade might also be responsible for on-going inflammation inside the fistula tracts. The authors suggest antibiotics might therefore play a role in treatment and prevention of recurrence. For cryptoglandular PF studies have shown that neither type nor amount of bacteria influences the chronicity of the fistulas.[43, 44] Other authors have described a general low number of bacteria inside the fistulas, concluding that bacterial infection might not play a role in maintaining the fistula.[45] They do, however, find peptidoglycan in the fistula tracts, which is part of gram negative and positive bacterial walls, and that works as a powerful proinflammatory effector, which might suggest that bacteria do play an important role. We might even need to look into the tissues healing capabilities or the composition of the tissue itself to figure out why some fistulas do not heal.

In the meantime, we could further investigate the techniques already available to us instead of developing more and more new procedures. Specifically, we need to design trials that actually compare the techniques to find out which are the most useful, after which a true evidence-based treatment algorithm might be developed.



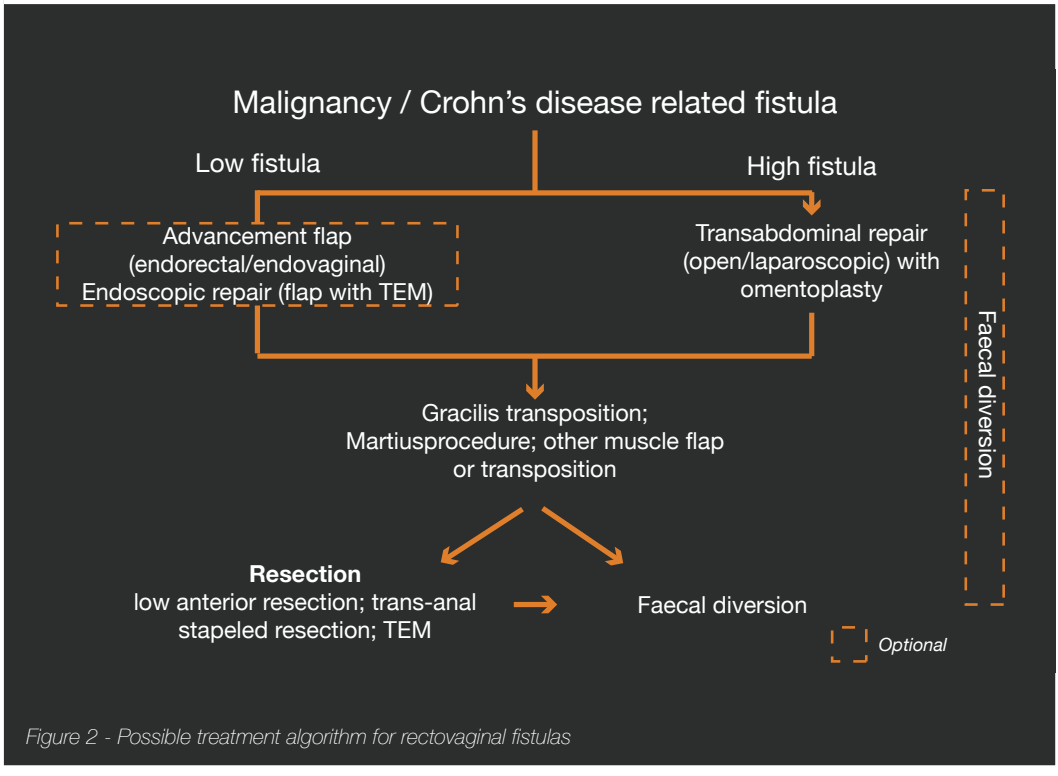


Figure 2 - Possible treatment algorithm for rectovaginal fistulas

Following better identification of the preferred technique(s) emphasis could be put on perfecting techniques and on uniform performance. Differences in outcome between centres and studies might in part be caused by difference in techniques and in indication.
The new techniques we developed and that were described in this thesis in ***chapter 4, 5 and 7***, will be further investigated. The MAF combined with PRP is already being investigated in a RCT, comparing it with the standard MAF. Additionally, we will need more basic research to find out why techniques fail in some patients and are successful in others. Is this due to the cause of the fistula (Cryptoglandular versus Crohn's disease), differences in thrombocyte function and number, differences in release or function of growth factors, differences in basic tissue composition (for instance collagens), epithelialization, inflammation, immune response, scarring, microbiotic flora in the fistula, etc?
About the same applies for our treatment for RVF. The biomesh treatment requires further investigation. However, RCTs remain unlikely to appear for treatment of RVF because of low incidence numbers. Basic research, beside the points described above, into the effect of Permacol and other biomesh treatments on the diseased tissue will also be necessary to figure out why it is successful in some, and not in others.
Another direction of research should be the reason why PF and RVF develop. The cryptoglandular hypothesis, as described in the Introduction, was one of the first theories developed.[46, 47] But the actual reason why this inflammation starts and subsequently results in fistulas is unknown. Another unknown issue that merits further study is why only half of the patients with a surgically drained perianal abscess develop a fistula and the other half not.
As a final conclusion, it is still unknown why PF and RVF develop and why they persist in some and heal in others, and what techniques are best used to treat them, ensuring enough material for study in the coming years.

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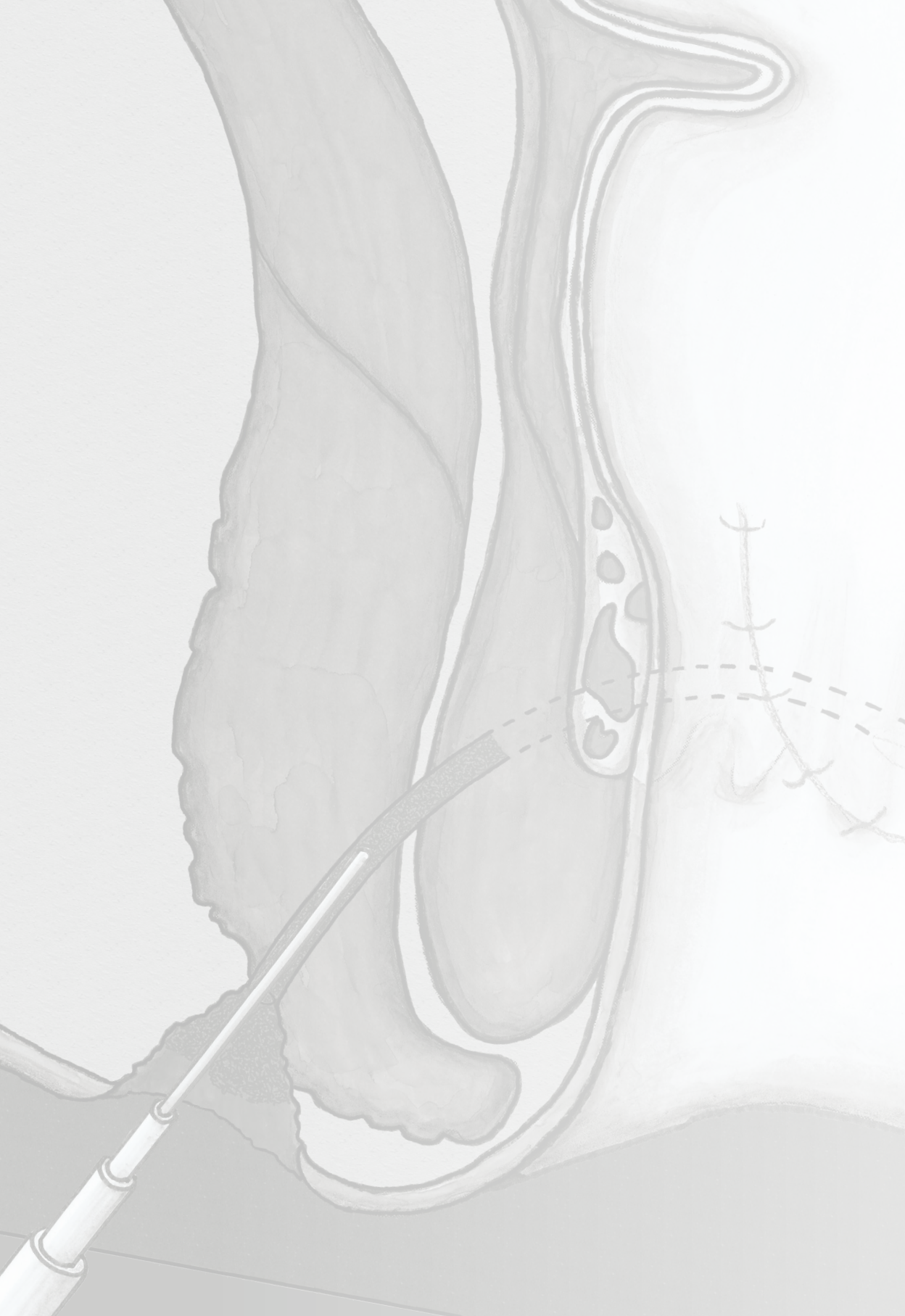

11 Summary

Summary

This thesis discusses both perianal fistulas (PF) and rectovaginal fistulas (RVF). Although these are different diseases and their aetiologies differ, there are also similarities. Already in the time of Hippocrates the diseases have been described, and up to the present day, for both, we still do not have definitive solutions.
The first real treatments for low PFs were described in the 14th century, and with some modifications this technique, the fistulotomy, is still used nowadays. The fistulotomy is still the golden standard for the treatment of low PFs today with healing rates of around 95%.[1] The best treatment for both high PFs and RVFs remains a subject of discussion among proctologists.
The large amount of different techniques for high PFs and RVFs shows the difficulty of treatment of these conditions.[2-10] Although many studies are published on the surgical treatment, the quality of these studies is unfortunately low. For RVF treatment no randomized controlled trials (RCTs) are available and prospective studies are rare with short follow-up.[3, 11-14] For high PF treatment more but often small, prospective trials have been published,[6, 8, 10] and some RCTs are available.[15-28] Comparison of all these studies remains difficult because of the many different techniques and different study designs. A clear suggestion what technique should be used for high PFs and RVFs is not possible, resulting in widely varying treatment algorithms between medical centres worldwide, nationally and even locally. A national Dutch guideline on PF treatment is currently being developed. That this guideline will result in an evidence-based treatment algorithm is unlikely, and many expect a consensus-based advice.

Chapter 2 is the result of a retrospective study on the outcome of fistulotomy for low perianal fistulas (LPF). The goal of this study was to evaluate the healing and recurrence rates of the fistulotomy. Also, the continence status postoperatively was evaluated to establish if the fistulotomy is successful in this secondary outcome as well.
In the last 10 years 537 patients were treated for a LPF. The fistulas were mostly of cryptoglandular origin (66.5%). The freedom from fistula after 5 years of follow-up was 0.81 (95% CI, 0.71-0.85). The secondary healing rate after re-treatment of recurrences was slightly better with 90.3% healing.
Although continence status was only evaluated postoperatively, the results are remarkably low with only 26.3% of patients reporting perfect continence status. Major incontinence, defined as a Vaizey score >6,29 was even seen in 95 patients (28.0%). Quality of life on the other hand was comparable to the general population.
We did not find a clear relationship between number of previous fistula operations and continence status, however it remains reasonable that patients with more previous operations have a higher risk of anal sphincter damage. Besides, it might also be true that some fistulas treated with a fistulotomy are actually high PFs, which will result in a higher risk of incontinence.
Fistulotomy for LPF results in high healing rates, however, perfect continence status is seen in about only one quarter of patients, and major incontinence is seen in as much as 28% of patients treated. For a treatment considered the golden standard for LPF, this secondary outcome is concerning. It might be necessary to improve treatment for LPF when this could lower major incontinence levels postoperatively. This could be accomplished by doing more preoperative imaging to identify the actual LPFs, by improving the fistulotomy or by developing a better surgical technique than the fistulotomy.

In ***chapter 3*** the aim is shifted to the treatment of high cryptoglandular perianal fistulas (HCPF). An overview is presented of the available randomized studies on the treatment of this kind of PF. The availability of RCTs is limited and comparison is severely impeded because so many different techniques are available. It was only possible to perform a meta-analysis for the mucosal advancement flap (MAF) and the fistula plugs (FP). This meta-analysis did not result in an outcome favouring either of these techniques.
The MAF seems to be the most investigated technique for HCPF. Whether it is the best technique to be used remains unclear. Other techniques studied in randomized trials were fibrin glue, autologous stem cells, island flap anoplasty, rectal wall advancement flap, ligation of intersphincteric fistula tract (LIFT), fistulotomy with sphincter reconstruction, sphincter preserving seton, and techniques combined with antibiotics. Only one other systematic review compares all available surgical techniques for high PFs. These authors were also not able to advice one technique over the others.[30] Some other reviews have appeared in recent years, most investigating one specific surgical intervention and including non-randomized studies.[31] We presented a review with only RCTs, and although this is the way to present a review with the highest level of evidence, it might not be the easiest way to identify the best technique for operating HCPF because of the low incidence numbers and many different techniques. A systematic review with all available results for all techniques might show us which techniques we should compare in RCTs, later hopefully resulting in the identification of the preferred technique in a meta-analysis.

The long-term results of a new technique for the closure of HCPFs are described in ***chapter 4***. This technique combines the MAF with platelet-rich plasma (PRP) in order to improve wound healing.10 The MAF is one of the oldest and well-known techniques for the closure of PF and was therefore chosen as the basis of this additional procedure. After two years we found a good freedom from recurrence of 0.83 (95% CI, 0.62-0.93). The short-term results were published previously and showed a better result after one year of follow-up.[10] Postoperative continence in the long-term showed good results with a median Vaizey score of 3.
The use of PRP has been shown useful in other fields of wound healing, like maxillofacial, plastic and orthopaedic surgery, and in the treatment of chronic wounds and ulcers.[32-37] Thrombocytes in PRP release growth factors when activated, which then cause improved tissue healing and regeneration, new capillary growth and acceleration of epithelialization in chronic wounds. These effects seem to result in better healing of PFs. The price of the preparation of PRP is about €700. If the treatment is cost-effective needs to be evaluated in future studies.
Even though the results of this study are favourable, the results of a RCT, investigating the combination of the MAF with PRP, will need to be awaited. This trial has already been started.

The first results of a pilot study investigating the use of PRP in patients with Crohn's disease (CD) related high PFs are discussed in ***chapter 5***. This pilot study was started after the first results of PRP in patients with HCPFs became available. The goal of this pilot study was to try and improve healing of high PFs in patients with CD. The technique used was the same as for cryptoglandular PFs. We combined the MAF with the injection of PRP into the fistula tract.
The first results show freedom from fistula at one year of 0.70 (95% CI, 0.33-0.89), which is less favourable than in cryptoglandular fistulas. However, we know that healing rates of CD related fistulas are worse compared to cryptoglandular fistulas.[38-41]

Two patients (20%) did not heal using our technique. One patient (10%) developed a recurrence after healing. Data on preoperative continence status were not available, but postoperatively the median Vaizey score was 8, which is reasonably high. This might be due to previous operations or because of CD itself that already results in a higher risk of faecal incontinence.[42]
It is unclear if the positive effect of PRP on wound healing is equal in patients with or without CD. Several growth factors and interleukins were shown to have impaired or different function in patients with CD.[43-45] Unfortunately, no other studies on the use of PRP in patients with CD are available up to now.
Whether or not PRP improves healing rates of high PFs in patients with CD will remain unclear until long-term results, and preferable, results of a RCT will become available.

Chapter 6 describes a study performed using the population-based cohort from the Southern Limburg region in the Netherlands (IBDSL). Incident inflammatory bowel disease cases in this area have been included since 1991. All patients with CD were included for study. Data on PF and RVF occurrence, fistula recurrence, and data on medical treatments and surgical treatments for fistulizing disease were extracted from patients' medical records. 1162 patients in the IBDSL database had CD. The absolute incidence of PF was 13.9%. 30.4% developed the PF before CD diagnosis. The PFs developed at a median time of 2.1 years after CD diagnosis. The 20-year cumulative probability of developing a PF was 21.5%. No significant difference in incidence was seen between the era before and after introduction of anti-TNF. Risk factors identified were colonic localization of the CD (adjusted HR 2.18; 95%CI 1.33-3.58) and development of a perianal abscess (adjusted HR 18.60; 95%CI 13.22-26.16). Specific medical and surgical treatments could unfortunately not be retrieved for most patients. Of the patients with a PF 36.6% developed a recurrence, corresponding to a cumulative probability of 73.2% after 20 years. The recurrence rate of PFs was higher in the group after introduction of anti-TNF (45.2% versus 30.0%, $p<0.05$), but the reason is unclear. The absolute incidence of RVF was 2.3%, corresponding to a cumulative probability of 3.9% after 20 years. The incidence of RVF was significantly lower in the era after introduction of anti-TNF (1.4% versus 5.1%, $p<0.05$). If this can be contributed to this therapy is unclear. The only risk factor identified was occurrence of a perianal abscess (HR 8.59; 95%CI 3.30-22.36). Specific medical and surgical treatments could also not be extracted for RVF.
This population-based study showed that the incidence of RVF decreased over time, while PFs are still common and often recur, despite changes in CD management. The findings of the present study underline the importance of improving medical and surgical treatment strategies for these invalidating conditions.

Chapter 7 the first results of a local transperineal or transvaginal treatment for RVF repair were presented, using a collagen matrix cross-linked biomesh (Permacol). The results of this new technique are reasonable with freedom from fistula at 1 year of 0.64 (95% CI, 0.30-0.85), but compared to all the techniques described in ***chapter 9***, this outcome does not seem superior. However, it is a local and low invasive technique, which allows other techniques to be performed if it fails. If two-thirds of patients are healed, only few need to be exposed to more invasive techniques like muscle flaps or transpositions.
Some other studies with mesh placement are available and all use different types of biomeshes.[5, 46-49] The main difference with the Permacol mesh is that the other meshes dissolve while Permacol first allows tissue to grow into it, before it is completely

replaced by the patients tissue.
Whether this technique is useful for RVFs of all causes is not yet clear. The patients with post-malignancy RVFs did not seem to heal well with our local technique. Fistulas of this cause might be better treated with the placement of healthy tissue like a Martius procedure, gracilis muscle transposition or any other type of transposition (***chapter 8 and 9***), because of the impaired healing tendency of scar tissue and post-radiotherapy tissue.[50]
Results on long-term outcome, and especially on secondary outcomes like continence status, sexual functioning and quality of life, need to be awaited to see if this new technique is a useful addition to our range of available surgical options.

In ***chapter 8*** results of muscle flaps and transpositions for PF, RVF and combined fistulas were presented. These techniques (Martius procedure, gracilis muscle transposition, Limberg flap[51] and Gluteal fold VY transposition flap[52]) were reserved for worst-case scenarios. All patients treated with these techniques had multiple previous operations without success.
In total 20 patients were treated with one of these techniques in the last decade. Ten (50.0%) had a PF, 5 (25.0%) a RVF and 5 (25.0%) a combined fistula. The number of previous fistula operations ranged between 2 and 12 with a median of 7.0. Merely 14 (70.0%) healed after treatment, resulting in 6 (30.0%) persisting fistulas. Of the 14 healed patients 10 (71.4%) developed a recurrence. This results in a primary healing rate of only 20.0%. Cumulative healing of the fistulas one year after surgery was 0.32 (95% CI 0.13 – 0.52). The median time until recurrence was 5.2 months (range 2.4 – 37.7).
This study makes it doubtful that the mentioned muscle and transposition flaps are a feasible option as a last resort surgical intervention for PF, RVF or combined fistulas. They can of course still be used in selected cases, and in patients willing to undergo further treatment afterwards because often small(er) recurrent fistulas seem to occur. The fact remains that we still do not have ideal treatments for any of these fistulas. Further basic research into fistula aetiology, further development of techniques and, just as important, good comparison of currently available surgical techniques is needed.

Chapter 9 provided an overview of the literature on surgical treatment for RVFs. We identified many different techniques, which were classified into several groups: advancement flaps; transperineal closure; Martius procedure; gracilis muscle transposition; rectal resections; transabdominal closure; mesh repair; plugs; endoscopic techniques; closure with biomaterials; and miscellaneous techniques. This large amount of categories presents the wide range of treatments available and indirectly explains the difficulty proctologist encounter when treating a RVF.
Even though a reasonable amount of studies were found, the quality of the studies was low. RCTs were not available as mentioned above and exactly 5 prospective studies could be identified making it impossible to present a decent conclusion on which technique should be preferred when treating a RVF. What seemed comparable between studies of all the different techniques was that the healing rates appear to decline with the publication of further studies. The reason for this decline in outcome remains unclear, but several options are suggested: selection bias in earlier studies; publication bias; better designed studies today; or because of differences between surgeons performing the operations. In general, healing rates seem to average 66% for techniques that are relatively well studied.[13, 53-55]
Apart from the discussion on which techniques result in the best healing rates, more attention should be given to secondary outcomes like postoperative continence status,

sexual function and quality of life. While the amount of good research on surgical treatment is rare, studies presenting standardized results on these secondary outcomes are extremely rare.[11, 12, 54, 56] It is imperative that studies include these secondary outcomes, because a decline in these outcomes might not make a treatment successful even though the fistula remains closed. Especially in cases when the fistulas do not close, we do not want to worsen the accompanying symptoms.
Suggestions on systematic reporting of trials and their outcomes were given, which will hopefully result in RCTs, or at least better comparable studies, in the near future, to make it possible to find out what treatment is best for RVF repair.

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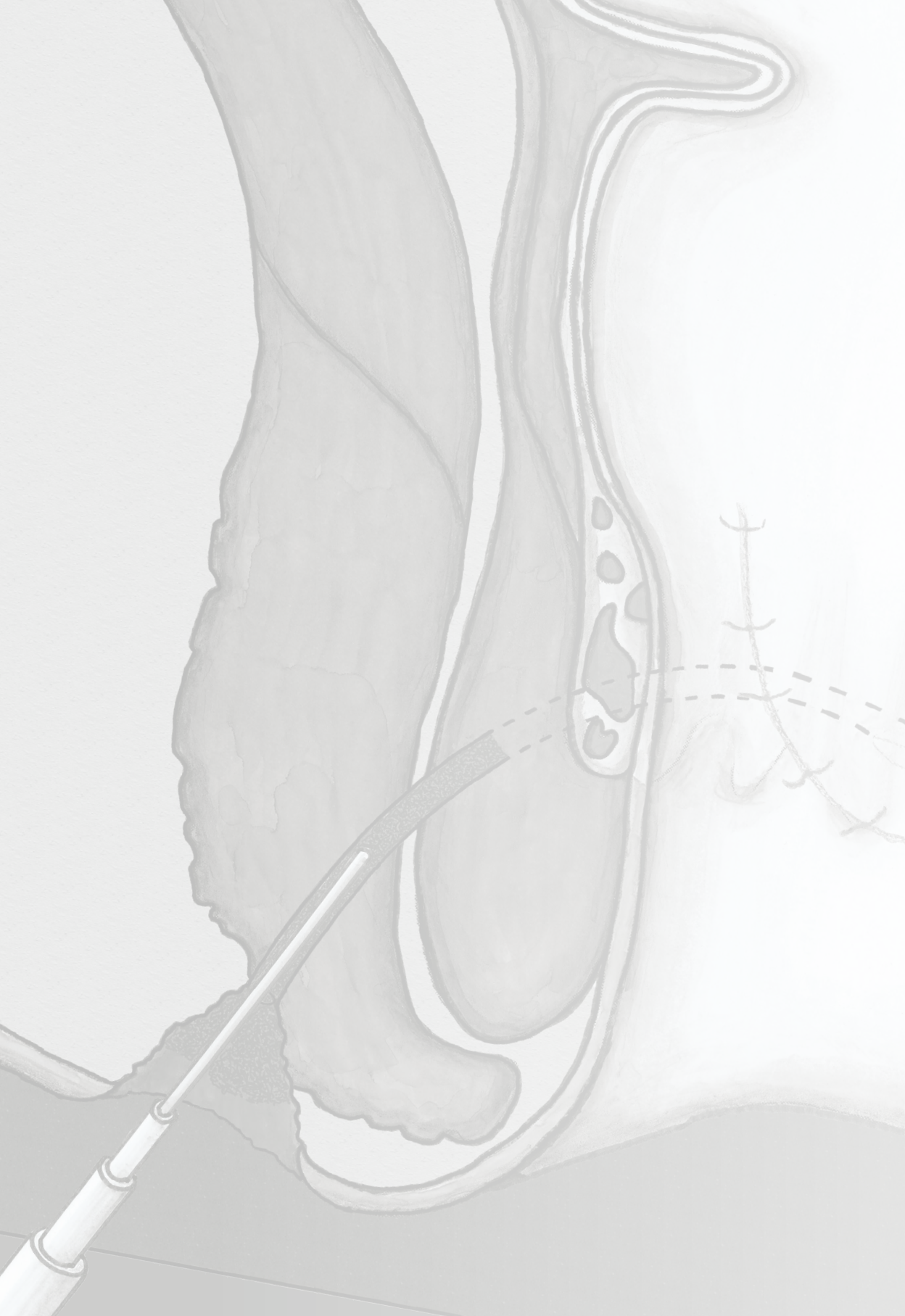

12 Samenvatting

Samevatting

Dit proefschrift beschrijft zowel de behandeling van perianale fistels (PF) als van rectovaginale fistels (RVF). Fistels zijn niet-anatomische kanaaltjes die vormen tussen twee holle organen. PF beginnen in het rectum, ook wel de endeldarm genoemd, en komen uit in de huid rondom de anus. RVF lopen zoals de naam al zegt tussen het rectum en de vagina. Het zijn twee verschillende aandoeningen die echter toch veel overeenkomsten hebben. Beiden zijn al lang geleden beschreven door Hippocrates, ver voor onze jaartelling, en voor beiden hebben we tegenwoordig nog geen behandeling met voldoende goed resultaat.
De behandeling van de lage vorm van PF is al beschreven in de 14e eeuw en wordt tegenwoordig, met enige aanpassingen, nog steeds gebruikt. Dit is de fistulotomie, waarbij de fistel en alle tussen de huid en fistel inliggend weefsel, in de lengte opengesneden wordt. Deze behandeling wordt nog steeds gezien als de gouden standaard waarbij genezingspercentages rond de 95% worden beschreven.[1] Hoge PF kunnen niet zomaar met een fistulotomie behandeld worden, omdat hiermee de anale sluitspier volledig doorgesneden wordt en incontinentie voor ontlasting het gevolg is. De behandelingen voor de hoge vorm van PF en voor RVF blijven een onderwerp van discussie.
De grote hoeveelheid aan verschillende technieken voor de behandeling van hoge PF en RVF geeft aan hoe moeilijk het is om deze aandoening te behandelen.[2-10] Ondanks dat er veel studies zijn gepubliceerd over deze chirurgische technieken, blijft de kwaliteit van de studies laag. Er zijn geen gerandomiseerde studies naar de behandeling van RVF beschikbaar en prospectieve studies zijn erg zeldzaam.[3, 11-14] Meer prospectieve studies, meestal klein, zijn gepubliceerd betreffende de behandeling van hoge PF,[6, 8, 10] en tevens zijn er enkele gerandomiseerde studies beschikbaar.[15-28] Het vergelijken van al deze studies blijft moeilijk door het grote aantal verschillende technieken dat wordt gebruikt en het verschil in studieopzet. Een goed advies over welke techniek gebruikt moet worden voor hoge PFs en RVFs is niet mogelijk, waardoor er grote verschillen zijn in behandelalgoritmes tussen verschillende centra wereldwijd, nationaal en zelfs regionaal. Een nationale richtlijn voor Nederland over behandeling van PF wordt op dit moment ontwikkeld. De verwachting is niet dat deze richtlijn een evidence-based behandelalgoritme zal voortbrengen, maar vooral een advies op basis van consensus zal geven.

Chapter 2 is het resultaat van een retrospectieve studie naar de resultaten van de fistulotomie bij lage PF (LPF). Het doel van de studie was het evalueren van de genezings- en recidiefpercentages van de fistulotomie in een regionale setting, met als specifiek doel het evalueren van de postoperatieve continentiestatus om te zien of de techniek ook goed is met betrekking tot deze secundaire uitkomstmaat.
In de laatste 10 jaar zijn 537 patiënten behandeld voor een LPF. De fistels waren grotendeels cryptoglandulair (66,5%). Vrijheid van de fistel na 5 jaar follow-up was 0,81 (95% betrouwbaarheidsinterval (BI), 0,71-0,85). Het secundaire genezingspercentage, na een tweede behandeling voor een recidief, was iets beter met 90,3%.
Alhoewel de continentiestatus alleen postoperatief werd geëvalueerd, lijken de resultaten zorgelijk met slechts 26,3% van de patiënten die een normale continentiestatus rapporteren. Hoge incontinentie, geduid als een Vaizeyscore >6,29 werd gezien in 95 patiënten (28,0%). De kwaliteit van leven was gelijk aan de normale populatie.
Ondanks deze relatief hoge incontinentiegetallen die werden gevonden, leek er geen invloed te zijn op de kwaliteit van leven. Er werd geen duidelijke relatie gevonden

tussen het aantal eerdere fisteloperaties en de continentiestatus. Desondanks blijft het denkbaar dat multipele operaties de kans op sfincterschade groter maken. Daarnaast blijft het ook mogelijk dat patiënten die behandeld zijn met een fistulotomie mogelijk een hoge PF hadden, wat een groter percentage aan incontinentie kan opleveren.
De fistulotomie geeft hoge genezingspercentages, echter wordt er maar bij ongeveer een kwart van de patiënten een normale continentiestatus gevonden en bij zelfs 28% van de patiënten was sprake van hoge incontinentie. Voor een behandeling die wordt gezien als de gouden standaard voor LPF, is deze secundaire uitkomst erg zorgelijk. Het is nodig om de behandeling voor LPF te verbeteren als dit het percentage aan hoge postoperatieve incontinentie kan verlagen. Dit kan bereikt worden door meer preoperatieve diagnostiek om de echte LPFs aan te tonen, door het verbeteren van de fistulotomie of door het ontwikkelen van een betere chirurgische techniek dan de fistulotomie.

In chapter 3 wordt de blik verschoven naar de behandeling van hoge cryptoglandulaire perianale fistels (HCPF). Een overzicht wordt gepresenteerd van de beschikbare gerandomiseerde studies naar de behandeling van deze vorm van PF.
De beschikbaarheid van gerandomiseerde studies is beperkt en vergelijking wordt bemoeilijkt door de hoeveelheid aan verschillende technieken die worden vergeleken. Hierdoor was het alleen mogelijk om de verschuivingsplastieken (MAF) te vergelijken met fistelpluggen (FP) in een meta-analyse. Deze meta-analyse liet geen voordeel zien voor een van beide technieken.
De MAF lijkt wel de meest onderzochte techniek te zijn voor HCPF. Of dit dan ook de beste techniek is blijft onduidelijk. Andere technieken die gerandomiseerd onderzocht zijn, zijn fibrinelijm, autologe stamcellen, de island flap anoplastiek, de verschuivingsplastiek van de volledige rectale wand, de ligatie van het intersfincterische fistelkanaal (LIFT), fistulotomie met sfincterreconstructie, sfincter sparende seton, en technieken gecombineerd met antibiotica.
Slechts een andere systematische review vergelijkt alle beschikbare chirurgische technieken voor hoge PF, en de auteurs achten het ook hier niet mogelijk om een techniek te adviseren boven elke andere.[30] Er zijn nog enkele andere reviews verschenen in de afgelopen jaren, die voornamelijk een specifieke techniek bekijken en vaak ook niet-gerandomiseerde studies includeren.[31] Wij presenteren een review met alleen gerandomiseerde studies, en alhoewel dit het meest betrouwbare bewijs oplevert, is het in dit geval misschien niet de beste manier om de juiste techniek te identificeren voor behandeling van HCPF. Een studie met alle beschikbare resultaten van alle technieken laat ons misschien zien welke technieken het best gerandomiseerd bekeken kunnen worden, wat later hopelijk wel resulteert in de identificatie van de beste techniek.

De lange termijn resultaten van een nieuwe techniek voor het sluiten van HCPFs wordt beschreven in chapter 4. De MAF wordt hierbij gecombineerd met trombocytenrijk plasma (PRP) om te proberen de wondgenezing te verbeteren. De MAF is een van de oudste en meest bekende technieken voor het sluiten van een PF en is daarom gekozen als basis voor deze operatieve techniek met het idee dat dit de beste resultaten oplevert met de kortste leercurve.[10]
Twee jaar na operatie vinden we een goed resultaat met vrijheid van de fistel van 0,83 (95% BI, 0,62-0,93). De korte termijn resultaten die eerder zijn gepubliceerd laten een jaar na operatie iets betere resultaten zien, zoals verwacht.[10] Postoperatieve incontinentie op de lange termijn laat goede resultaten zien met een mediane Vaizeyscore van 3.

Het gebruik van PRP is al aangetoond nuttig in andere vormen van wondgenezing, zoals maxillofaciaal, plastische chirurgie, orthopedische chirurgie, en in de behandeling van chronische wonden en ulcera.[32-37] Uit de trombocyten in de PRP komen groeifactoren vrij als ze geactiveerd worden, die zorgen voor verbeterde wondgenezing en regeneratie van weefsel, nieuwe capillaire groei en versnelling van epithelialisatie in chronische wonden. Deze effecten lijken ook een verbeterde heling te geven in PF, waarbij de prijs van het maken van de PRP ongeveer € 700,- is. Of de behandeling kosteneffectief is zal moeten blijken uit verder onderzoek.
Ondanks dat de resultaten van deze studie goed zijn, moet de techniek toch onderzocht worden in een gerandomiseerde studie. Deze studie is reeds gestart en de resultaten zullen afgewacht moeten worden.

De eerste resultaten van een pilotstudie naar het gebruik van PRP bij patiënten met Crohnse hoge PF worden beschreven in ***chapter 5***. Deze pilotstudie is gestart nadat de eerste resultaten van de techniek bij HCPF bekend werden. Het doel van de pilotstudie was om ook verbeterde heling van hoge PF te bewerkstelling bij patiënten met de ziekte van Crohn. De techniek die gebruikt werd is gelijk aan de techniek voor HCPF. We combineerden de MAF met het injecteren van PRP in het fistelkanaal.
De eerste resultaten laten een vrijheid van de fistel zien, 1 jaar na operatie, van 0,70 (95% BI, 0,33-0,89), wat minder goed is dan bij de cryptoglandulaire fistels. Echter, we weten dat de genezingspercentages lager zijn bij fistels gerelateerd aan de ziekte van Crohn.[38-41] Twee patiënten (20%) genazen niet met onze techniek. Eén patiënt (10%) ontwikkelde een recidief na eerdere heling. Data betreffende preoperatieve continentiestatus waren niet beschikbaar, maar postoperatief was de mediane Vaizeyscore 8, wat redelijk hoog is. Dit komt mogelijk door eerdere operaties, of omdat, zoals bekend is, de kans op incontinentie bij patiënten met de ziekte van Crohn over het algemeen groter is.[42]
Het is onduidelijk of PRP dezelfde verbetering in wondgenezing geeft bij patiënten met de ziekte van Crohn. Verschillende groeifactoren en interleukines lijken een veranderde of verminderde functie te hebben bij de ziekte van Crohn.[43-45] Helaas zijn er tot nu toe geen andere studies bekend die PRP gebruiken bij patiënten met deze ziekte.
Of PRP nuttig is voor het verbeteren van de genezingspercentages bij hoge PF bij patiënten met de ziekte van Crohn blijft onduidelijk totdat lange termijn resultaten, en zo mogelijk resultaten van een gerandomiseerde studie, beschikbaar komen.

Chapter 6 beschrijft een studie die gedaan werd met het populatie-gebaseerde IBD cohort van Zuid Limburg in Nederland (IBD-ZL). Alle gevallen van inflammatoire darmziekten zijn sinds 1991 geregistreerd in dit cohort. Alle patiënten met de ziekte van Crohn zijn gebruikt voor deze studie. Gegevens over incidentie van PF en RVF, recidieven en gegevens over medicamenteuze en chirurgische behandelingen zijn uit database en medische statussen gehaald. In totaal hadden 1162 patiënten uit het cohort de ziekte van Crohn. De absolute incidentie van PF was 13,9%. Hiervan ontwikkelde 30,4% de fistel voor het stellen van de diagnose ziekte van Crohn. De mediane periode van het ontwikkelen van de fistel na diagnose was 2,1 jaar. De 20-jaars cumulatieve waarschijnlijkheid van het ontwikkelen van een PF was 21,5%. Er werd geen significant verschil in incidentie gezien tussen de periodes voor en na introductie van anti-TNF. Geïdentificeerde risicofactoren waren lokalisatie van de ziekte van Crohn in het colon (adjusted HR 2,18; 95%CI 1,33-3,58) en een perianaal abces (adjusted HR 18,60; 95%CI 13,22-26,16). Specifieke medicamenteuze en chirurgische behandeling konden helaas voor het overgrote deel van de patiënten niet worden geïdentificeerd. Bij 36,6% van de patiënten ontstond er een recidief, wat correspondeert tot een

cumulatief recidiefrisico van 73,2% na 20 jaar. De recidieven kwamen meer voor in de groep na introductie van anti-TNF (45.2% versus 30.0%, p<0.05), waarvoor geen goede verklaring is gevonden.
De absolute incidente van RVF was 2,3% wat correspondeert met een cumulatieve incidentie van 3,9% na 20 jaar. De incidentie van RVF lijkt significant lager te zijn na de introductie van anti-TNF (1.4% versus 5.1%, p<0.05). Of deze therapie hiervoor verantwoordelijk is, is onduidelijk. De enige risicofactor die werd aangetoond is het ontwikkelen van een perianaal abces (HR 8.59; 95%CI 3.30-22.36). Ook voor dit type fistel konden medicamenteuze en chirurgische behandelingen niet goed worden geïdentificeerd.
PF zijn veel voorkomend bij de ziekte van Crohn en, ondanks recente ontwikkelen en veranderingen in medicamenteuze behandelingen, lijkt de incidentie niet af te nemen. RVF komen minder vaak voor en hiervan lijkt de incidentie in de laatste 10 jaar af te nemen. De resultaten van deze studie onderstrepen de noodzaak van het verbeteren van zowel medicamenteuze als chirurgische behandelingen voor deze type fistels.

In ***chapter 7*** worden de eerste resultaten gepresenteerd van een lokale, transperineale of transvaginale, behandeling voor RVF, waarbij gebruik wordt gemaakt van een gecrosslinkte collagene matrix biomat (Permacol). Het resultaat van deze nieuwe techniek laat redelijke resultaten zien betreffende vrijheid van de fistel na 1 jaar van 0,64 (95% BI, 0,30-0,85). In vergelijking met de technieken die beschreven worden in ***chapter 9***, lijkt dit resultaat niet superieur. Echter, het is een lokale techniek die laag invasief is, wat er voor zorgt dat andere technieken nog uitgevoerd kunnen worden in geval van falen. Als tweederde van de patiënten genezen zijn, dan hoeft slechts een beperkt aantal blootgesteld te worden aan de meer invasieve operaties zoals spierflappen of -transposities.
Er zijn nog enkele andere studies beschikbaar die gebruik maken van matten, en allen maken gebruik van verschillende typen biomatten.[5, 46-49] Het grootste verschil met de Permacolmat is het feit dat de andere matten oplossen en dat Permacol het weefsel juist toelaat om erin te groeien waarbij het vervangen wordt voor stevig weefsel. De hypothese is dat Permacol op deze manier mogelijk een betere barrière vormt tussen de beide fistelopeningen.
Of deze techniek nuttig is voor RVF van alle typen is nog niet duidelijk. De patiënten met een fistel die ontstond na behandeling van een maligniteit leken niet te helen met deze lokale techniek. Fistels van deze oorzaak zouden mogelijk beter behandeld kunnen worden met het plaatsen van gezond weefsel zoals een Martius procedure, een gracilis spiertranspositie of een andere vorm van spiertranspositie, vanwege de bekende beperkte genezingsmogelijkheid en littekenvorming van weefsel na radiotherapie.[50]
De lange termijn resultaten, en specifiek de secundaire uitkomsten zoals continentiestatus, seksueel functioneren en kwaliteit van leven, moeten afgewacht worden om te zien of deze techniek een nuttige aanvulling is op ons scala aan operatieve opties.

In ***chapter 8*** worden resultaten gepresenteerd van spierflappen en transposities voor PF, RVF en gecombineerde fistels. Deze technieken (de Martius procedure, transposities van de gracilis spier, de Limberg flap[51] en de gluteale VY transpositie flap[52]) zijn gereserveerd voor de meest ernstige casussen. Alle patiënten die door middel van deze technieken geopereerd zijn hadden al multipele andere operaties ondergaan zonder succes.
In totaal zijn 20 patiënten door middel van deze technieken geopereerd in de laatste

10 jaar. Tien (50.0%) hadden een PF, 5 (25.0%) hadden een RVF en 5 (25.0%) had een gecombineerde PF en RVF fistel. Het aantal eerdere fisteloperaties varieerde tussen de 2 en 12 met een mediaan van 7.0. Slechts 14 (70.0%) genas na de operatie, wat betekent dat er 6 (30.0%) een persisterende fistel hadden. Van de genezen patiënten ontwikkelde 10 (71.4%) een recidief fistel. Dit betekent dat het primaire succespercentage slechts 20.0% was. Eén jaar postoperatief was de cumulatieve genezing 0.32 (95% BI 0.12 – 0.52). De mediane tijd tot het ontstaan van een recidief was 5.2 maanden (2.4 – 37.7).
Deze studie laat zien dat de beschreven technieken waarschijnlijk geen goede laatste optie zijn voor PF, RVF en gecombineerde fistels. Het is natuurlijk wel mogelijk om in geselecteerde patiënten deze technieken te gebruiken, waarbij patiënten wel bereid zouden moeten zijn tot vervolgoperaties gezien er regelmatig kleine(re) recidieven optreden. Het wordt in deze studie wederom duidelijk dat we nog geen goede definitieve chirurgische opties hebben voor deze fistels. Het blijft nodig om meer basaal onderzoek naar de etiologie van de fistels te doen, chirurgische technieken verder te ontwikkelen, en om de huidige beschikbare technieken goed met elkaar te vergelijken.

In ***Chapter 9*** van dit proefschrift wordt een overzicht gegeven van de literatuur die beschikbaar is over de chirurgische behandeling van RVF. Er zijn veel verschillende technieken geïdentificeerd, waarbij deze ingedeeld zijn in de volgende groepen: Verschuivingsplastieken, transperineale sluitingen, de Martius procedure, transposities van de gracilis spier, resecties van de endeldarm, transabdominale procedures, reparatie met een mesh (mat), pluggen, endoscopische technieken, sluiting met biomaterialen, en overige technieken. Deze grote hoeveelheid aan categorieën geeft op zichzelf al aan hoeveel opties er zijn en indirect welke problemen proctologen tegenkomen bij de behandeling van een RVF.
Ondanks dat er een behoorlijk aantal studies zijn geïdentificeerd, was de kwaliteit van de literatuur laag. Gerandomiseerde studies waren niet beschikbaar zoals uitgelegd, en slechts 5 prospectieve studies zijn gevonden. Dit maakt het onmogelijk om aan goede conclusie te trekken over welke techniek gebruikt moet worden om een RVF te behandelen. Wat wel duidelijk werd uit meerdere studies over verschillende technieken, was dat het genezingspercentage lijkt af te nemen naarmate er meer studies over een techniek gepubliceerd worden. Over het algemeen lijkt de genezingstendens rond de 66% van alle patiënten te liggen op het moment dat er voldoende literatuur over een techniek beschikbaar is. [13, 53-55] De reden voor deze afname in genezing blijft onduidelijk, maar verschillende redenen zijn mogelijk: Selectiebias in de eerdere studies, publicatiebias, beter opgezette nieuwere studies, of omdat er verschillen zijn in uitvoering van de technieken tussen chirurgen.
Losstaand van de discussie welke techniek nu resulteert in de beste genezingspercentages, is het feit dat er meer nadruk gelegd moet worden op de secundaire uitkomsten van de behandelingen zoals postoperatieve incontinentie, seksueel functioneren, en kwaliteit van leven. Terwijl goede studies naar de chirurgische behandeling zeldzaam zijn, zijn de resultaten met betrekking tot deze secundaire uitkomsten vrijwel niet bestaand.[11, 12, 54, 56] Het is noodzakelijk dat nieuwe studies deze secundaire uitkomsten bekijken, want een verslechtering in deze uitkomsten kan een behandeling toch onsuccesvol maken, ondanks dat de fistel dicht blijft.
Suggesties zijn gegeven over hoe resultaten van trials systematisch te rapporteren, wat er hopelijk voor zorgt dat er uiteindelijk gerandomiseerde studies volgen, of in ieder geval beter vergelijkbare studies, zodat we kunnen uitvinden welke behandeling voor RVF het beste is.

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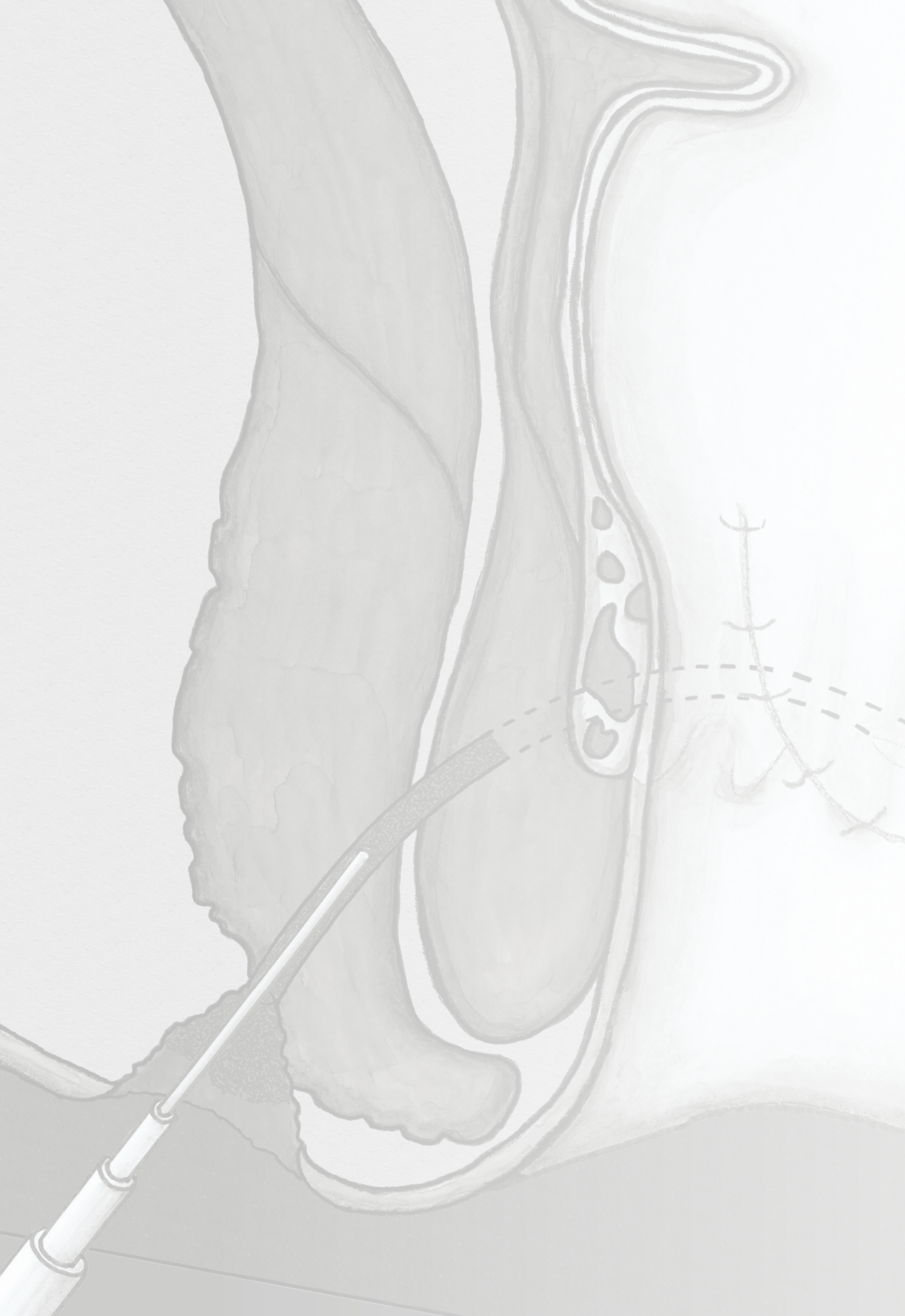


Valorisation

Valorisation

Introduction

This thesis describes available evidence and outcomes of (new) surgical treatments for both rectovaginal and perianals fistulas. Nowadays, medical professionals, insurance companies and patients demand the use of evidence-based medical treatments. Specifically for the treatment of these two types of fistulas the treatments are far from evidence-based. Low incidence numbers and the many available surgical techniques make it difficult to start and compare high quality studies. The data regarding best treatment options are therefore still lacking. However, patients need to be treated for these conditions and available data will need to suffice for now in clinical practice, even though this data consists mostly of case series.
The new techniques described in this thesis showed improvement of closure rates of the fistulas. Data regarding secondary outcomes has not been investigated thoroughly yet, but will be part of future research. ***Chapters 3 and 9*** confirm that the data we have on our surgical treatments are not of high quality, and suggest ways of improving our research. ***Chapter 6*** shows that the number of patients with Crohn's disease developing fistulas is high and that this number will probably rise in the future with more interest being shown for these fistulas. As a result it is likely that more patients will require treatment making it even more import to improve our treatments to prevent recurrences and re-treatments.

Economical relevance

The results of this thesis will hopefully result in future improvement of treatment of both rectovaginal and perianal fistulas. The improvement of these treatments will not only need to improve the outcome for patients, but will also need to result in a decrease of costs of treatment.
The goal within the surgical community is to improve operative techniques for the treatment of these two types of fistulas. Nowadays often more than one procedure is needed to reach the desired result, closure of the fistula. In many cases this result will not be reached, viewing the success rates reported in this thesis. The development of new operative techniques will hopefully reduce the number of re-operations. This will consequently lower overall costs.
Besides costs related to the operations, other profits can be achieved. Many patients with persisting fistulas have to use many types of bandages, medication and other supporting materials. In time these costs can increase and could be lowered by improving surgical treatment.
Other outcome measurements of fistula treatment that we use nowadays, are faecal incontinence and quality of life. In case a patient becomes faecal incontinent as a result of our surgical treatment this can result in extra operations, or the long-term use of dressings and medication with of course financial consequences. The use of colon irrigation to clean the intestines and the long-term use of stool thickening medication are some of the solution for this problem, but when symptoms are not controlled satisfactory continence restoring operations might be the next step.

Social relevance

Regarding quality of life mostly psychosocial functioning is impaired in patients with rectovaginal or perianal fistulas. The fistulas often cause unwanted odours and the loss

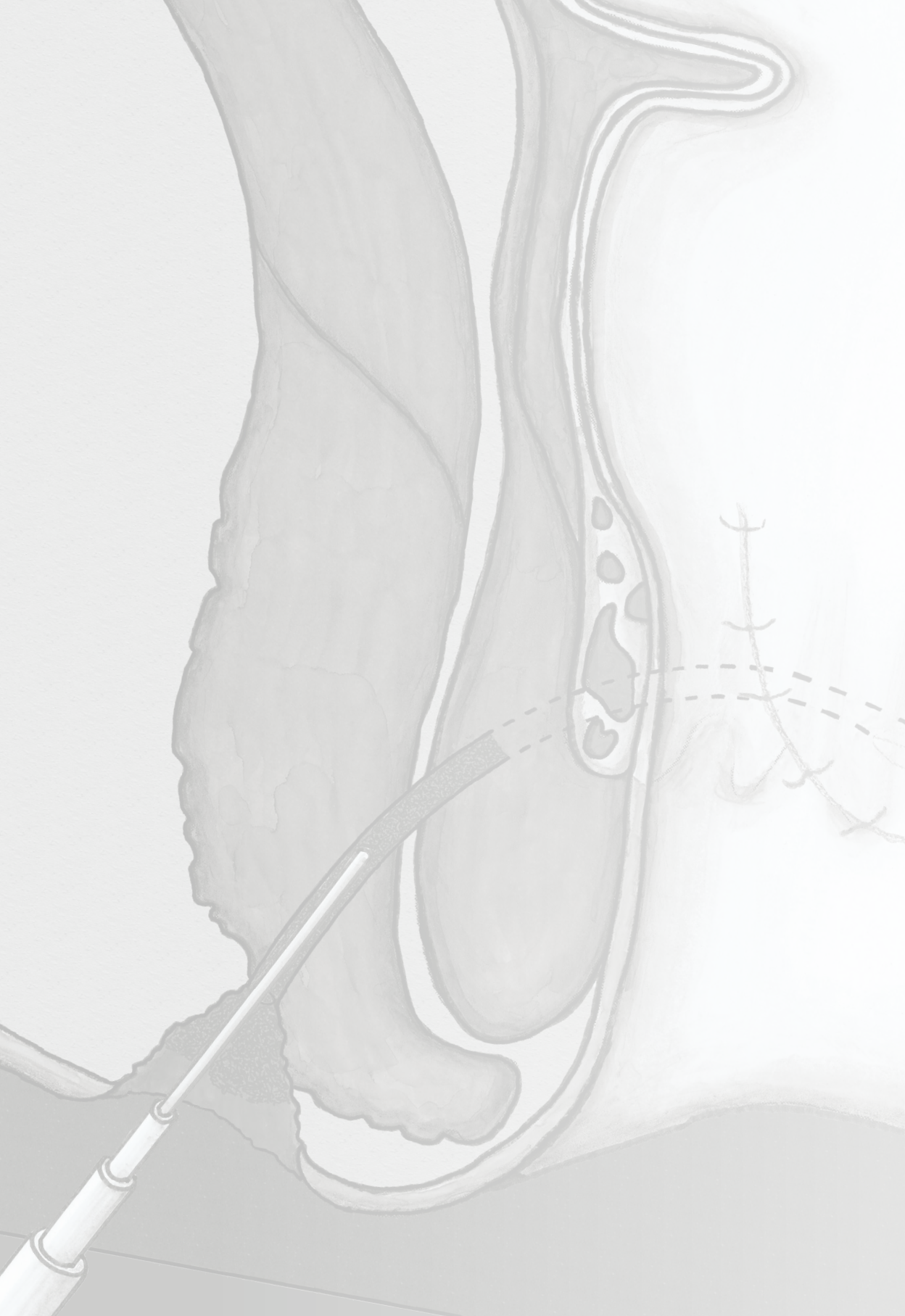
of faeces or fluids. Regularly this will result in patients avoiding socials contacts and becoming isolated. Besides issues with personal contact, uncontrolled loss of odours and fluids may cause problems in the working atmosphere. Long-term absence from work is often seen. By improving these secondary outcomes of our treatments, we can possibly reduce the socials consequences of the diseases.

Implementation and innovation

The new techniques described in ***chapters 4, 5 and 7*** are still experimental. The current costs for the materials used in these new surgical procedures are still relatively high because a limited number of companies develop and produce them. Improvement of these materials, the user-friendliness and the lowering of production costs can result in both improvement of surgical outcome and more cost-effective treatment.
For this thesis specifically we need to think of improvements in producing platelet-rich plasma (PRP), and the manner of introduction of the PRP in the fistula tract. Besides this, the development of techniques and devices that preoperatively predict the chances of success of the procedure by counting blood platelets, growth factors, and the quality of the PRP seem areas of interest for future research and development.
Regarding the mesh we used in ***chapter 3***, many improvements are possible for the production of the mesh. Further research will be needed to show if improvement of the material could further improve the closure rates of the rectovaginal fistulas.
Although the new materials and techniques described in this thesis are already used and shown useful in other medical areas, these are the first results of studies investigating rectovaginal and perianal fistulas. The use of the materials is therefore not new, but the way they are used is. Innovation in the treatment of these fistulas is needed, because of the previously described unsatisfactory results of current treatments, and further research into the new techniques described in this thesis will be part of this.

Future research

Parts of this thesis have already resulted in the start of a randomized controlled trial investigating the use of PRP of perianal fistulas. For this trial, and also for the further use of the mesh described in ***chapter 3***, we work closely together with several biomedical companies. The experiences we gain by doing clinical research will result in further development and improvement of products we use.
Additionally, steps are being taken to simplify treatments of these fistulas to lower costs of standard treatment. An example is the development of materials to easily probe fistulas resulting in shorter operating times and lower costs. Furthermore, diagnostics are being developed to explain and eventually hopefully predict why some patients do and others do not develop fistulas, which can result in more specific treatments for patients. Currently steps are taken to start these studies, which will be part of the future research into rectovaginal and perianal fistulas.



Dankwoord

Dankwoord

Dit proefschrift, hoe mooi het uiteindelijk ook geworden is, stond aan het begin van mijn opleiding tot chirurg niet in de planning. Wat specifieker gezegd, het proefschrift met dit onderwerp stond niet in de planning. Toen ik een half jaar aan mijn opleiding bezig was ben ik in dit onderzoekstraject gerold, omdat een collega besloot een andere richting te kiezen. Maar zoals gezegd was het plan om te promoveren tijdens mijn opleiding wel degelijk aanwezig voor ik aan dit traject begon. Tijdens mijn sollicitatiegesprek bij de regionale opleidingscommissie heb ik heel stellig gezegd dat ik voor het afronden van mijn opleiding gepromoveerd zou zijn. Zo stellig dat dr. Ton Hoofwijk mij verzekerde dat hij mijn C-formulier in beslag zou nemen als ik dit niet zou waarmaken. Met het afronden van dit proefschrift is dit obstakel in ieder geval overwonnen. Dus, beste Ton, hartelijk dank voor de extra stimulans om dit waar te maken.

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hoofdstuk in dit boekje opgeleverd en ik ben er van overtuigd dat het een mooie publicatie zal opleveren. Bedankt voor de fijne samenwerking. Ik weet zeker dat onze afdelingen in de toekomst nog meer goed onderzoek samen zullen doen en presenteren.

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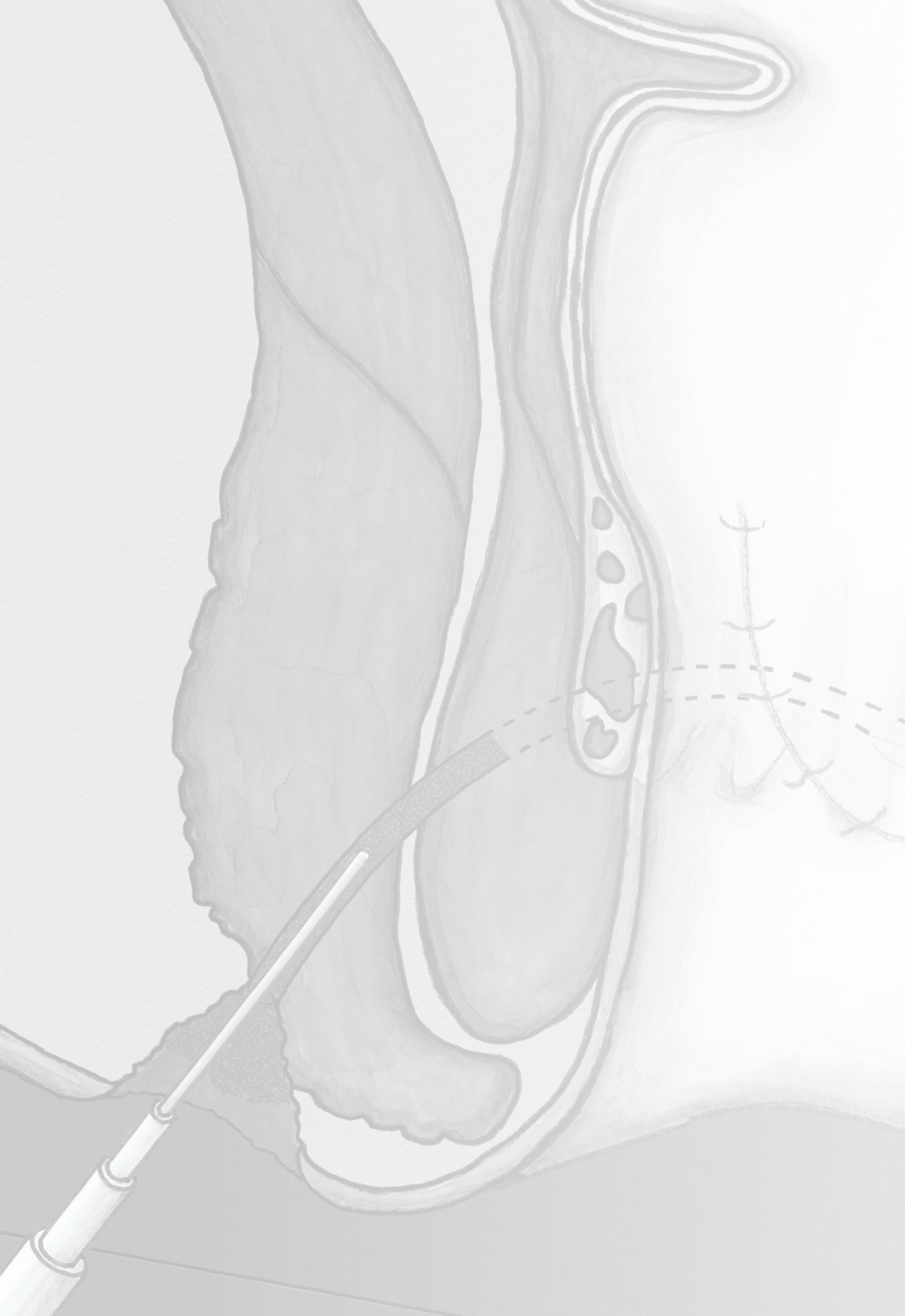

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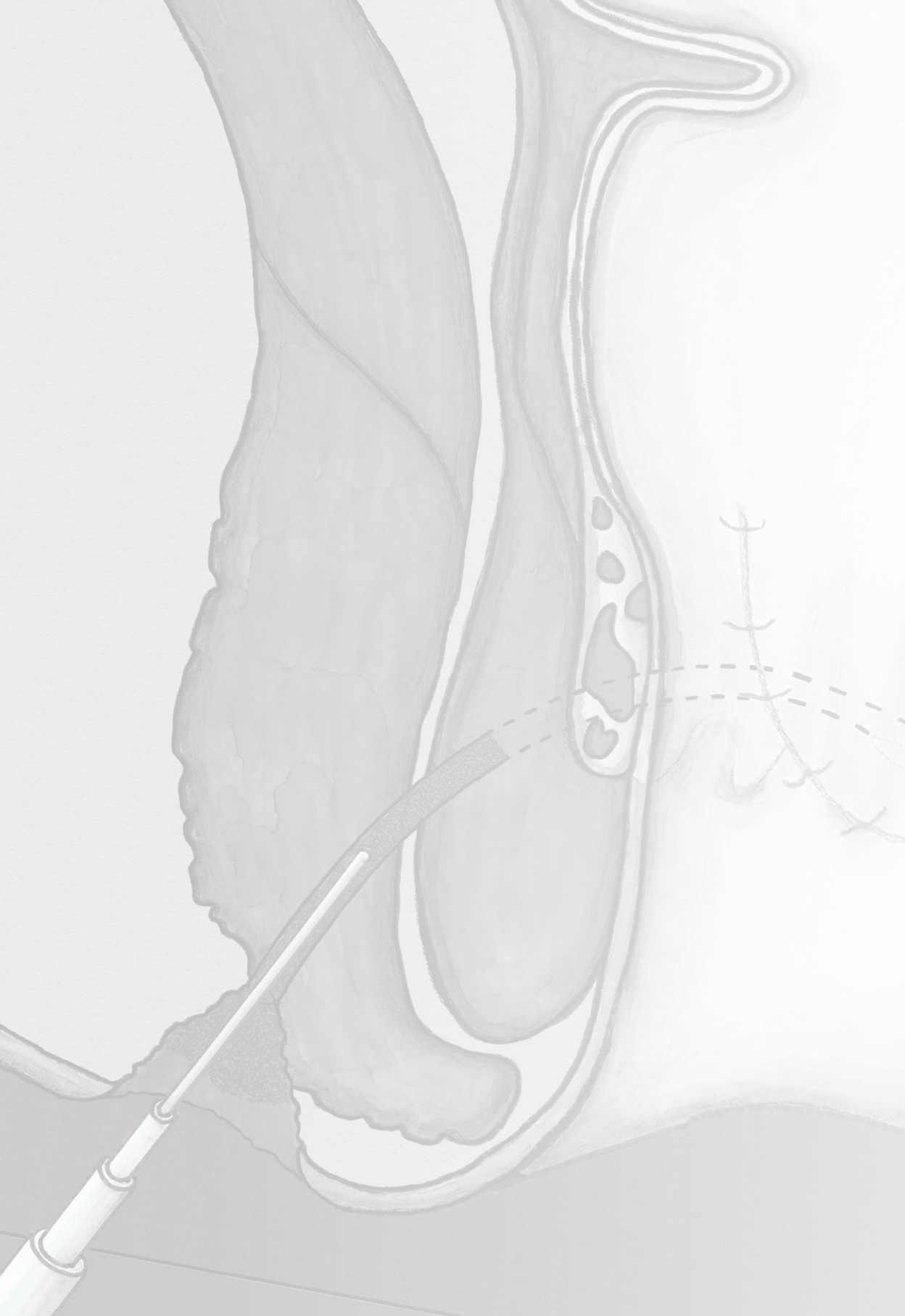
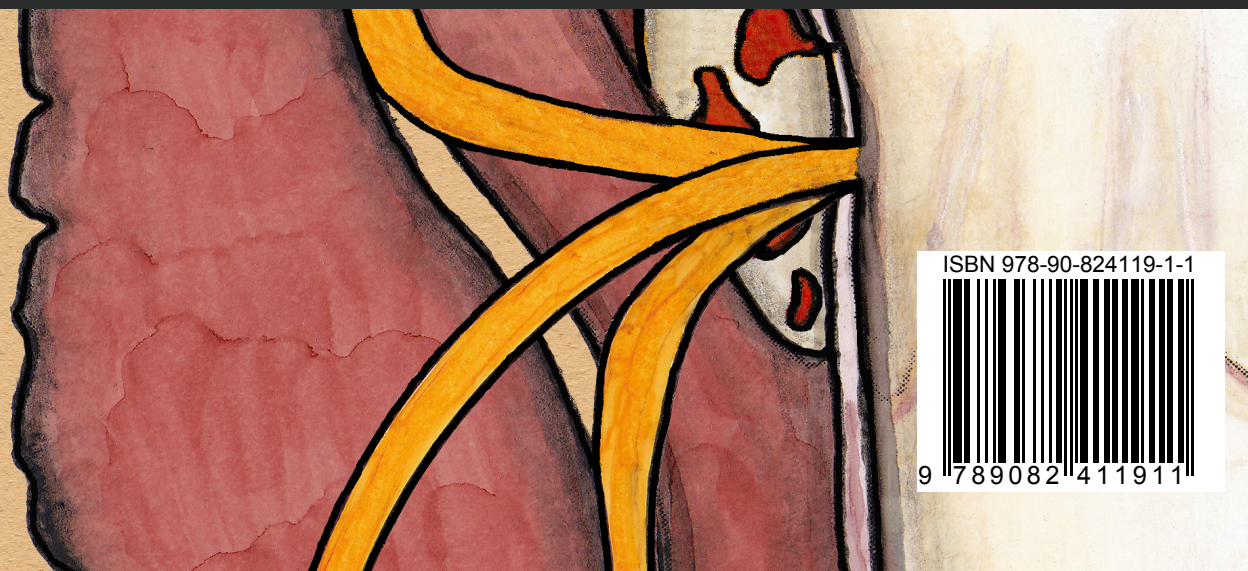


Curriculum Vitae

Curriculum Vitae

Kevin Willem Antonius Göttgens was born on December 18 1985 in Heerlen, The Netherlands. After graduating cum laude for his gymnasium degree at the Bernadinus College in Heerlen, he started his medical studies at Maastricht University in 2004. In 2010 he received his medical degree and started work as resident in general surgery at the Maastricht University Medical Center (MUMC+). After applying in 2011, his surgical training started on January 1st 2012 at the MUMC+ and he completed his first 3 years in this hospital. Half a year into his training, he started working on this Ph.D. thesis supervised by dr. S.O. Breukink and Prof. dr. L.P.S. Stassen. He is currently finishing the last 3 years of his training at the Catharina hospital in Eindhoven.

Kevin Willem Antonius Göttgens is geboren op 18 december 1985 te Heerlen. Na zijn cum laude afstuderen aan het Bernardinus College te Heerlen is hij gestart met zijn studie geneeskunde aan de Universiteit Maastricht in 2004. In 2010 heeft hij zijn Master in Medicine gehaald, waarna hij als assistent niet in opleiding tot specialist (ANIOS) begonnen is in het Maastricht Universitair Medisch Centrum (MUMC+). Na in 2011 gesolliciteerd te hebben voor de opleiding chirurgie, is hij hiermee gestart op 1 januari 2012 in het MUMC+, waar hij de eerste 3 jaren van deze opleiding heeft afgerond. Ongeveer een half jaar nadat hij is gestart met zijn opleiding tot chirurg is hij begonnen aan dit proefschrift, gesuperviseerd door dr. S.O. Breukink en Prof. dr. L.P.S. Stassen. Op dit moment werkt hij in het Catharina Ziekenhuis te Eindhoven waar hij de laatste drie jaar van zijn opleiding zal afronden.



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